No. 2017-1153, -2048, -2049, -2050

In the
United States Court of Appeals
for the Federal Circuit

GRUNENTHAL GMBH, DEPOMED, INC.,

Plaintiffs-Cross-Appellants,

v.

ALKEM LABORATORIES LIMITED, WEST-WARD PHARMACEUTICALS INTERNATIONAL LIMITED, WEST-WARD PHARMACEUTICALS CORP,

Defendants-Appellants,

ACTAVIS ELIZABETH LLC,

Defendant-Appellee,

ACTAVIS, INC., ACTVAIS LLC, ACTAVIS LABORATORIES UT, INC.,

Defendants.

Appeal from the United States District Court for the District of New Jersey,
Case Nos. 2:13-cv-04507-CCC-MF, 2:13-cv-06929-CCC-MF, 2:13-cv-07803-CCC-MF, 2:14-cv-03941-CCC-MF, 2:14-cv-04617-CCC-MF, and 2:15-cv-06797-CCC-MF.
The Honorable **Claire C. Cecchi**, Judge Presiding.

ALKEM LABORATORIES' OPENING BRIEF

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September 7, 2017

CERTIFICATE OF INTEREST

I, Imron T. Aly, Counsel for Defendant-Appellant Alkem Laboratories Limited, certify the following:

1. The full name of every party or *amicus* represented by me is:

Alkem Laboratories Limited

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

Alkem Laboratories Limited, as named in the caption, is the real party in interest.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

Alkem Laboratories Limited has no parent corporation and no publicly traded company owns more than 10 percent of its stock.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

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TABLE OF CONTENTS

Page

CERTIFICATE OF INTEREST i
TABLE OF AUTHORITIES v
STATEMENT OF RELATED CASES 1
JURISDICTIONAL STATEMENT 2
STATEMENT OF THE ISSUE 3
INTRODUCTION 4
STATEMENT OF THE CASE 7
I. The Asserted Claims Relate to Form A tapentadol hydrochloride 8
II. The Prior Art Disclosed Crystalline Tapentadol Hydrochloride 8
III. The Prior Art Taught Routine Crystal Polymorph Screening 10
IV. Grünenthal Hired A Polymorph Screening Lab To Do The Routine Crystal Polymorph Screening 12
V. Grünenthal's Patent Application Misrepresented That It Started With Form B To Make Form A, When In Reality It Started With Form A 14
SUMMARY OF THE ARGUMENT 16
STANDARD OF REVIEW 18
ARGUMENT 19
I. The District Court Created An Improper Rule That Polymorph Patents Can Never Be Obvious 19
II. The District Court Committed Legal Error by Requiring Absolute Predictability To Show Obviousness 22
A. Obviousness Requires a Reasonable Expectation of Success, Not Absolute Predictability 23
B. Using Routine Published Prior Art Crystallization Techniques Results In Form A, Rendering The Claimed Invention Obvious 27

1. A person of ordinary skill had a reasonable expectation of success in conducting a routine polymorph screen published by Byrn.....28

2. Following the Byrn article would have provided Form A to any person of ordinary skill in the art.....30

3. The district court erroneously discounted the Byrn article by relying on other district court cases that never addressed the Byrn article.....36

4. The absence of any asserted secondary considerations further confirms obviousness of the polymorph claims.....38

C. Using Routine Published Prior Art Crystallization Techniques Results In Form A, Rendering The Claimed Invention At Least Obvious To Try.....39

CONCLUSION.....44

TABLE OF AUTHORITIES

CASES

Antares Pharma, Inc. v. Medac Pharma Inc.,
771 F.3d 1354 (Fed. Cir. 2014) 32

AstraZeneca LP v. Breath Ltd.,
603 F. App'x 999 (Fed. Cir. 2015) 6, 25, 26

Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.,
752 F.3d 967 (Fed. Cir. 2014) 19, 20

Cubist Pharms., Inc. v. Hospira, Inc.,
805 F.3d 1112 (Fed. Cir. 2015) 7, 26, 27

Graham v. John Deere Co. of Kansas City,
383 U.S. 1 (1966) 19

Howmedica Osteonic Corp. v. Zimmer, Inc.,
640 Fed.App'x. 951 (Fed. Cir. 2016) 23

In re Armodafinil Patent Litigation,
939 F. Supp. 2d 456 (D. Del. 2013) 36, 37

In re Kubin,
561 F.3d 1351 (Fed. Cir. 2009) ..... passim

In re O'Farrell,
853 F.2d 894 (Fed. Cir. 1988) 23, 42

KSR Int'l Co. v. Teleflex Inc.,
550 U.S. 398 (2007) ..... passim

McNeil-PPC, Inc. v. L. Perrigo Co.,
337 F.3d 1362 (Fed. Cir. 2003) 18

Medichem, S.A. v. Tolabo, S.L.,
437 F.3d 1157 (Fed. Cir. 2006) 23

Merck & Cie v. Watson Labs., Inc.,
125 F. Supp. 3d 503 (D. Del. 2015), *rev'd on other grounds*, 833 F.3d 1347 (Fed. Cir. 2016) 37

Pfizer, Inc. v. Apotex, Inc.,
480 F.3d 1348 (Fed. Cir. 2007) ..... passim

Richardson-Vicks Inc. v. Upjohn Co.,
122 F3d 1476 (Fed. Cir. 1997) 18

Sanofi-Synthelabo v. Apotex, Inc.,
470 F.3d 1368 (Fed. Cir. 2006) 23

Santarus, Inc. v. Par Pharms., Inc.,
694 F.3d 1344 (Fed. Cir. 2012) 35

SmithKline Beecham Corp. v. Apotex Corp.,
403 F.3d 1331 (Fed. Cir. 2005), *cert. denied* 126 S. Ct. 2887 (2006) 18

Takeda Pharm. Co. v. Handa Pharm., LLC,
Case No. C-11-00840, 2013 U.S. Dist. LEXIS 187604 (N.D. Cal. Oct. 17, 2013) 37

United States v. U.S. Gypsum Co.,
333 U.S. 364 (1948) 18

STATUTORY AUTHORITIES

28 U.S.C. § 1295(a)(1) 2

28 U.S.C. § 1338(a) 2

35 U.S.C. § 103 ..... 16, 18

35 U.S.C. § 271(e)(2)(A) 2

RULES AND REGULATIONS

Cir. R. 47.5 1

STATEMENT OF RELATED CASES

Pursuant to Federal Circuit Rule 47.5, Alkem Laboratories identifies as related cases, *Janssen Pharmaceuticals, Inc. et al. v. Sandoz Inc. et al.*, Case No. 2:13-cv-06929-CCC-MF; *Grünenthal GmbH et al. v. Alkem Laboratories Limited*, Case No. 2:13-CV-07803-CCC-MF; *Grünenthal GmbH et al. v. Roxane Laboratories, Inc.*, Case No. 2:14-cv-03941-CCC-MF; *Grünenthal GmbH et al. v. Actavis Laboratories UT, Inc.*, Case No. 2:14-cv-04617-CCC-MF, all in the United States District Court for the District of New Jersey and consolidated as *Grünenthal GmbH et al. v. Actavis Elizabeth LLC et al.*, Case No. 2:13-cv-04507, which cases have been consolidated with the present appeal.

JURISDICTIONAL STATEMENT

This Court has jurisdiction under 28 U.S.C. § 1295(a)(1), this being an appeal from a final judgment of the United States District Court for the District of New Jersey in a case arising under 28 U.S.C. § 1338(a) and 35 U.S.C. § 271(e)(2)(A). The district court's opinion with injunction issued on September 30, 2016, and Alkem filed a notice of appeal on October 28, 2016 which was deactivated pending the district court's entry of final judgment, which occurred on April 11, 2017. Following the district court's entry of judgment, this Court reactivated Alkem's appeal on May 25, 2017.

STATEMENT OF THE ISSUE

For claims to a polymorph of a known compound, did the district court err in applying an obviousness analysis that required absolute predictability of the polymorph's crystal structure, as opposed to applying the proper test requiring a reasonable expectation of success for the result of a routine polymorph screen?

INTRODUCTION

This case presents the question of whether a polymorph patent can ever be invalid as obvious, a question of law reviewed *de novo*. A "polymorph" is a chemical compound that can be packed into different three-dimensional crystalline structures. For example, crystals can be in the shape of a cube or other three-dimensional shape. (Appx44.) Pharmaceutical products are routinely screened to determine which polymorphs are readily obtained—in 1987 the FDA guided pharmaceutical companies to conduct screens for polymorphs, and in 1995 Dr. Stephen Byrn wrote the definitive publication ("the Byrn article") about how to perform the screens. (Appx138.) The Patent Office did not have the benefit of the FDA guidance or the Byrn article when issuing United States Patent 7,994,364 ("the '364 patent").

The '364 patent claims a polymorph of the chemical compound tapentadol hydrochloride. Tapentadol hydrochloride itself was already in the prior art, as was the fact that "tapentadol hydrochloride is made in crystalline form." (Appx138, Appx9714 at 77:3-6, Appx9648 at 3-7.) By the time of the claimed invention in 2004, polymorph screening was so common that it could simply be outsourced. The named inventors of the '364 patent sent a tapentadol sample to a vendor in order to perform a routine polymorph screen and identify the easy-to-find polymorphs for

the compound. That vendor was Dr. Byrn, the author of the 1995 Byrn article, who followed the established polymorph screen protocol published in that article.

Byrn's lab found that there were only two readily-available polymorphs for tapentadol: "Form A" and "Form B." Form A was found to be stable at room temperature and free of impurities. Form B was also created at times but only intermittently by using odd conditions, such as by raising the temperature to over 40ºC (over 100ºF) or by adding impurities. Even then, Form B began to revert to Form A because Form A is the only stable form. The '364 patent, not surprisingly, claims Form A—the only form that could be repeatedly prepared and stable at room temperatures.

Despite these facts, the district court found that claiming tapentadol hydrochloride Form A was not obvious because its specific crystalline structure was not predictable: "the results of the polymorph screen—*i.e.*, the determination of the structure and properties of the polymorph forms of tapentadol hydrochloride—would have been impossible to predict."[1] (Appx143-144.) This Court has repeatedly ruled that obviousness is not so exacting a standard as to require absolute

[1] While the district court also states that polymorphic screening consists of "unpredictable application of [] routine techniques," the facts relied on by the court relate only to the unpredictability of the resulting polymorph structure itself. (Appx143, Appx57384, Appx10921-10922 at 44:5-45:12, Appx10789-10791 at 213:20-215:8, Appx10794 at 218:20-24, Appx10795-10797 at 219:21-221:11.)

predictability, such as the particular crystal structure of a polymorph, which cannot be known before screening is done. Rather, the standard for obviousness is more flexible and requires only a reasonable expectation of success—here that a polymorph screen would result in the readily-available polymorphs. Further, as articulated by the Supreme Court, the "obvious to try" threshold merely requires that a person of ordinary skill in the art would pursue a routine polymorph screen with a reasonable expectation of success. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007).

This Court has applied these proper obviousness tests in several different contexts within the pharmaceutical field to underscore one basic principle: patent exclusivity rights should not be granted where a company does only what any person of ordinary skill in the art would have done to obtain the claimed result. In the salt context, patent claims are invalid as obvious where a company screens commonly known anions—even if 53 of them—using routine techniques and then claims one that works. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1367–69 (Fed. Cir. 2007). In the sterile compound context, patent claims are invalid as obvious where a company selects from known sterilization techniques which simply claims a particular result. *See AstraZeneca LP v. Breath Ltd.*, 603 F. App'x 999, 1002 (Fed. Cir. 2015). And in the purification context, patent claims are invalid as obvious where a company uses routine purification techniques to find one that works to

maximize purity. *See Cubist Pharms., Inc. v. Hospira, Inc.*, 805 F.3d 1112, 1127–28 (Fed. Cir. 2015).

The Supreme Court's *KSR* guidance is particularly applicable here. Polymorphs represent an area of science that may have been pioneering at one time, but, after the FDA guidance and the Byrn standard publication, polymorph screens became routine. The district court already made these findings. (Appx140 ("A POSA would have understood as of June 2004 how to conduct a polymorph screen and there were publications that provided guidance on how to do such a screen."); Appx141 ("The Byrn article explains steps to detect polymorphism.").) Now, these "advances, once part of our shared knowledge, defined a new threshold from which innovations start once more." *KSR*, 550 U.S. at 427. The asserted claims are unworthy of patent protection, as they are "the product not of innovation but of ordinary skill and common sense." *Id*. at 421. The asserted claims are obvious or obvious to try, and do not deserve patent protection that would unfairly extend Cross-Appellants' monopoly on tapentadol hydrochloride products for three years, from August 22, 2022 (when the compound patent expires) to June 27, 2025 (when the polymorph patent is due to expire).

STATEMENT OF THE CASE

Cross-Appellants Grünenthal GmbH ("Grünenthal") and Depomed, Inc. ("Depomed") brought suit against Alkem Laboratories Ltd. ("Alkem") for filing an

Abbreviated New Drug Application ("ANDA") by seeking to market a generic version of NUCYNTA®, the active ingredient of which is tapentadol hydrochloride.

I. The Asserted Claims Relate to Form A tapentadol hydrochloride.

The district court found the asserted claims of the '364 patent not anticipated and not obvious. Asserted claims 1, 2, 3 and 25 of the '364 patent each recite an X-ray powder diffraction result that the parties do not dispute corresponds to the "Form A" crystal of tapentadol hydrochloride. (Appx127.) Representative claim 1 reads:

> 1. A crystalline Form A of [tapentadol hydrochloride] exhibiting at least X-ray lines (2-theta values) in a powder diffraction pattern when measured using Cu Kα radiation at 15.1±0.2, 16.0±0.2, 18.9±0.2, 20.4±0.2, 22.5±0.2, 27.3±0.2, 29.3±0.2 and 30.4±0.2. (Appx405-406.)

The claimed X-ray lines correspond to the three-dimensional structure that is Form A. There is also no dispute that the particular values listed in the claim that correspond to Form A—and are derived from Form A's crystal structure—would not have been predictable before a polymorph screen was done. Such predictability is not the proper requirement for invalidity, and the district court should have found claims 1, 2, 3 and 25 invalid as obvious. Importantly, the claims do not have any purity limitation. The claims therefore cover any amount of Form A, even if combined with other polymorphic forms.

II. The Prior Art Disclosed Crystalline Tapentadol Hydrochloride.

Grünenthal, the assignee of the '364 patent, already had a prior art patent on tapentadol hydrochloride. That prior art patent, U.S. Patent 6,248,737 ("the '737

patent"), issued in 2001 and is assigned to Grünenthal. (Appx46497.) The '737 patent disclosed crystalline tapentadol hydrochloride as "Example 25" (Appx373, Appx138), its medical uses as a pain reliever, and the fact that it existed in crystalline form. (Appx63, Appx138.) It was not until three years later, in 2004, that Grünenthal filed an application that eventually resulted in the '364 patent. (Appx63.)

The district court agreed that the '737 patent had already disclosed tapentadol hydrochloride and that "the patent synthesis of tapentadol hydrochloride is disclosed in Example 25." (Appx63.) The '737 patent also expressly stated that the synthesis resulted in a crystalline form of tapentadol hydrochloride, though it did not identify the X-ray peaks corresponding to that form. As the district court agreed, "[w]hile Example 25 states that tapentadol hydrochloride 'crystallised out' at the end of the synthesis, the patent does not discuss the solid state crystal form of tapentadol hydrochloride." *Id*. (internal citation omitted).

Alkem also tested the prior art synthesis disclosed in Example 25 of the '737 patent—the results of which revealed mixtures of Form A and Form B—to show that the prior art inherently anticipated the later-claimed Form A polymorph. As the district court noted, "[i]n support of their inherent anticipation contention, Defendants commissioned scientists at the University of Wisconsin to perform a synthesis that Defendants contend is consistent with the procedure of Example 25."

(Appx130-131.) Alkem's expert witness Dr. Jonathan Steed reviewed the test results and concluded that following the prior art "produced some Form A tapentadol hydrochloride crystals and some Form B tapentadol hydrochloride crystals." (Appx131.) Because the claims have no purity threshold, any amount of Form A is enough to anticipate.

Cross-Appellants disputed inherent anticipation and argued that the University of Wisconsin scientists "only performed Step 3 of the synthesis and did not start at the beginning with Step 1" (*id*.) and that Grünenthal had done its own internal testing which "produced tapentadol hydrochloride samples that contained only Form B." (Appx133.) Though Alkem rebutted these issues, the district court ultimately found no inherent anticipation because the record "leaves this Court unconvinced that practicing the procedure of Example 25 will ***necessarily and inevitably*** result in Form A." (Appx137) (emphasis in original).) The prior art showed either Form A or Form B. Thus, it was undisputed that even just practicing the protocol in the '737 patent—without any further polymorph screen—resulted in either Form A or Form B tapentadol hydrochloride.

III. The Prior Art Taught Routine Crystal Polymorph Screening.

It was entirely routine by 2004 to screen drug candidates to determine readily-available polymorphs. In 1987—almost twenty years before the patent application for the '364 patent was filed—the Food and Drug Administration ("FDA") issued

guidelines instructing drug companies that "[a]ppropriate analytical procedures should be used to determine whether (or not) polymorphism occurs." (Appx57314, Appx9714 at 77:11-15, Appx139.) This was not surprising to Grünenthal; company scientist and named inventor, Dr. Helmut Buschmann, testified that "it was considered important also to take consideration of the so-called solid phase of the compound." (Appx8647 at 77:20-22.) As the court found, "[b]y 2000, Grünenthal generally understood that pharmaceutical companies 'take consideration of polymorphism when they are developing pharmaceutical compounds.'" (Appx140.)

There was also no secret about how to perform a polymorph screen, as that too had become standard and routine. As Grünenthal's own expert conceded, "[c]rystallization from solution is one of the first laboratory skills that chemists acquire, and applying variations to the conventional methods has been a traditional strategy in the search for polymorphs." (Appx59465.) In 1995, Dr. Stephen Byrn published the Byrn article entitled: "Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations." (Appx57372.) The publication explicitly acknowledges its link to the FDA's general guidance, recognizing that "[i]nterest in the subject of pharmaceutical solids stems in part from the FDA's drug substance guidelines." (Appx57372.) The Byrn article was intended to provide specific "analytical procedures" that "should be used to detect polymorphic, hydrated or amorphous forms of the drug substance." (*Id*.) The Byrn article goes on to explain

a basic set of experiments that a person of skill in the art would understand could be used to obtain and identify crystal forms:

> Solvents should include those used in the final crystallization step and those used during formulation and processing and may also include water, methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, ethyl acetate, hexane and mixtures if appropriate. New crystal forms can often be obtained by cooling hot saturated solutions or partly evaporating clear saturated solutions. (Appx57373.)

In sum, the Byrn article described crystallization procedures, well known by 2004, that involved dissolving a drug in the identified solvents (like methanol) and then cooling or evaporating to induce crystallization and obtain polymorphs. The district court agreed that "[t]he Byrn article explains steps to detect polymorphism" and that it "specifically lists certain solvents to use in the recrystallization experiments." (Appx141.) The district court also noted that Michael Gruss, another named inventor, "understood at that time that polymorph screening was a common technique that involved different common solvents and temperatures to test for polymorphs." (Appx140.) The Byrn article was not before the Patent Office during prosecution.

IV. Grünenthal Hired A Polymorph Screening Lab To Do The Routine Crystal Polymorph Screening.

Polymorph screening had become so routine by 2004 that companies outsourced the task, which is exactly what Grünenthal chose to do. Grünenthal reached out to SSCI, "a company founded by the same Dr. Byrn who authored the

Byrn article." (Appx142.) SSCI, in turn, simply did what was already published in the Byrn article—it "followed known procedures (including using eight of the nine solvents listed in the Byrn article and different cooling and evaporation conditions) to conduct the polymorph screen." (*Id*., Appx59447, Appx59454, Appx57791-92, Appx8536 at 236:12-24, Appx8537 at 237:18-22.) The result? Each and every solvent and condition that resulted in a crystal of any kind included at least some Form A, which is all that the asserted claims of the '364 patent require. (Appx57791-57792, Appx49395-49396, Appx9719 at 82:13-14, Appx11043 at 30:6-10.) It took SSCI about only three weeks to perform the screen and report those results to Grünenthal. (Appx57774, Appx59452.)

A person of ordinary skill in the art would not have done anything differently than what Grünenthal and SSCI did, *i.e.* using the published routine solvents to do the polymorph screen, and would have seen Form A present. As the district court summarized, "[a] POSA would have understood as of June 2004 how to conduct a polymorph screen and there were publications that provided guidance on how to do such a screen." (Appx140.) There is no dispute that this was an easy and fast procedure for third-party SSCI to conduct.

The fact that a person of ordinary skill in the art would have seen Form A present when doing a prior art polymorph screen is confirmed by the nature of tapentadol hydrochloride itself. It has only two polymorphs that have been

discovered to date: Form A and Form B. (Appx66.) Form A is the one which is ordinarily stable at room temperature (Appx146-147), whereas Form B requires special conditions like heating to over 40ºC (over 104ºF). (Appx148, Appx63384-63385 at 60:12-25, 61:1-5.) Grünenthal's temperature studies repeatedly confirmed that Form B reverts back to Form A when returning to room temperature. (Appx47379, Appx49619, Appx49397, Appx57774.) Grünenthal also confirmed that Form B can be formed when substantial impurities are added to tapentadol hydrochloride—and then still with Form A present. (Appx10848 at 272:3-14.) Grünenthal may argue that these properties of tapentadol hydrochloride were not published in the prior art, but that argument misses the point: these inherent properties of tapentadol confirm that ***any*** person of ordinary skill in the art would have happened across Form A; it would have taken luck or extreme and improbable conditions to obtain only Form B, without any trace of Form A. Here, SSCI followed the Byrn protocol and obtained Form A. No one from SSCI is named as an inventor.

V. Grünenthal's Patent Application Misrepresented That It Started With Form B To Make Form A, When In Reality It Started With Form A.

When applying for the '364 patent, Grünenthal made much of the claim that Form A was different than the prior art form found in the '737 patent: "The present invention provides a new form (Form A) of [tapentadol] hydrochloride which is different from the form already known (Form B) obtained by the procedure described in example 25 of U.S. Pat. No. 6,248,737." (Appx397 at 1:55-67.) The

examples that involve preparing Form A begin by stating that the starting material "[w]as prepared according to example 25," implying (in connection with its other statements) that Grünenthal started with Form B to make Form A. (Appx399 at Example 2, 5:35-51.) That connection was key to the Examiner's Reasons for Allowance: "The crystalline form recited in the instant claims and supported by the instant Figures and throughout the specification is novel and nonobvious over the closest prior art disclosed in United States Patent No. 6,248,737." (Appx57933.)

Yet at trial, Grünenthal admitted that the compounds supposedly "obtained by the procedure described in example 25 of U.S. Pat. No. 6,248,737" ***were in fact Form A tapentadol*** all along. Example 2 of the '364 patent states that the starting material used to obtain Form A was prepared according to example 25 of European patent 693,475, which is the same as example 25 in the prior art '737 patent. (Appx399 at 5:39-41, Appx8896 at 56:14-17, Appx9811 at 89:1-4, Appx46632.) Plaintiffs identified SSCI as the entity that performed the polymorph screening reflected in Example 2 of the '364 patent. (Appx48968, Appx48970, Appx57592.) The SSCI screen confirmed, however, that the starting material prepared according to example 25 of the '737 patent was, in fact, Form A. (Appx49384, Appx49392, Appx63720 at 50:18-52:7, Appx63721 at 57:14-58:9, 58:19-59:3, 59:9-10, 59:12-18, Appx63395 at 102:5-10, Appx6339 at 107:12-16.) This was proven at trial through the cross examination of named inventor Dr. Gruss, who confirmed

Grünenthal's discovery responses showed the examples in the '364 patent were done by SSCI. (Appx8900-901, Appx48968, Appx48970.) Dr. Gruss also confirmed that the SSCI report, in turn, showed that what Grünenthal sent as starting material for the examples in the patent was Form A. (Appx 8902-8903, Appx49384, Appx49392). Dr. Bernstein also agreed that "[f]orm A was also identified as the material received [by SSCI] from Grünenthal." (Appx10906 at 29:6-8.) Then when SSCI did its very first polymorph screen, all results had either "No Solid Present" or provided some Form A. (Appx8904, Appx49394.)

SUMMARY OF THE ARGUMENT

The district court applied the wrong legal standard in concluding that claims 1-3 and 25 of the '364 patent are not obvious under 35 U.S.C. § 103. The district court required that the result of a routine polymorph screen—the exact crystal structure resulting from the screening experiment—be entirely predictable. The district court erroneously relied upon a standard of absolute predictability to hold that "predictability is a touchstone of obviousness" and that "the determination of the structure and properties of the polymorph forms of tapentadol hydrochloride—would have been impossible to predict." (Appx144.) Strict predictability, however, is not the standard for obviousness. Under the proper analysis, the district court should have considered whether a person of ordinary skill in the art would have been motivated to follow the prior art combination or whether there was a limited number

of identified solutions, with a reasonable expectation of success. The district court recited the proper obviousness test in the legal background of the opinion (Appx89) but clearly did not apply that standard.

Under the proper obviousness analysis, the asserted claims of the '364 patent are invalid as obvious, because any person of ordinary skill in the art would have performed the routine polymorph screen for tapentadol hydrochloride, as specified in the prior art, and found Form A. The prior art '737 patent already disclosed tapentadol hydrochloride, a way of making it, and the fact that it formed crystals. The prior art Byrn article taught how to screen crystals for polymorphs, including the specific solvents to use. The FDA guidance and the Byrn article reference to the FDA guidance provided an express motivation to combine the references and conduct a standard polymorph screen on tapentadol. Though inherent anticipation in view of the '737 patent was factually disputed, there is no factual dispute that the '737 patent procedure resulted in either Form A or Form B, and that performing the standard Byrn screen would have resulted in at least some Form A (which is all that the claims require). And ***Cross-Appellants offered no evidence of any secondary considerations***, such as unexpected results that could show that Form A was the result of any innovation. Therefore, this Court should reverse the district court and find the asserted polymorph claims 1-3 and 25 obvious, or at a minimum remand for further findings under a proper obviousness analysis.

STANDARD OF REVIEW

"This Court reviews a district court's judgment following a bench trial for errors of law and clearly erroneous findings of fact." *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1337 (Fed. Cir. 2005), *cert. denied* 126 S. Ct. 2887 (2006). Obviousness is a legal conclusion based on underlying factual determinations. *See Richardson-Vicks Inc. v. Upjohn Co.*, 122 F3d 1476, 1479 (Fed. Cir. 1997). Accordingly, the ultimate determination of obviousness is reviewed *de novo*, while any underlying factual findings are reviewed for clear error. *See McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1368 (Fed. Cir. 2003). A factual finding is clearly erroneous if, despite some supporting evidence, the Court "is left with the definite and firm conviction that a mistake has been committed." *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948).

A patent is obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a [POSA] to which said subject matter pertains." 35 U.S.C. § 103(a). Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art are to be resolved. Against this background, the obviousness of the subject matter is determined and secondary considerations, if any, are utilized to give light to the

circumstances surrounding the origin of the subject matter sought to be patented. *See Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966).

The obviousness analysis entails "an expansive and flexible approach.…" *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 401 (2007). "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *Id*. at 417. Ultimately, "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *Id*. There need not be "precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id*. at 418.

ARGUMENT

I. The District Court Created An Improper Rule That Polymorph Patents Can Never Be Obvious.

The district court created a special exception for polymorph patents such that polymorphs can never be obvious because it is impossible to predict the specific crystal form that results from a routine polymorph screen. No other types of patentable subject matter enjoy such special treatment, nor should they. Even new chemical compounds—the hallmark of unpredictability—are subject to obviousness so long as there is "clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable

expectation of success from doing so." *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 973 (Fed. Cir. 2014) (internal citations omitted). This case presents the opportunity for the Federal Circuit to clarify that polymorph patents are not immune from obviousness.

Alkem cross-examined Cross-Appellants' polymorph expert, Dr. Joel Bernstein, who testified that no polymorph can ever be obvious, even if the prior art were to disclose specific screening instructions, because it is not possible to predict the crystal structure or a polymorph before doing the experiments:

> Q. And that's where I want to conclude with you, Dr. Bernstein. You believe that no polymorph patent can ever be obvious, right?
>
> A. Because it is not predictable. I agree, I would agree with that statement.

(Appx11043-11044 at 30:23-31:2.) The district court stated that it "does not speak on the hypothetical question of whether every polymorph patent is nonobvious," (Appx145), but in fact found that "the determination of the structure and properties of the polymorph forms of tapentadol hydrochloride—would have been impossible to predict" and "[a]s predictability is a touchstone of obviousness, Defendants have failed to meet their burden…." (Appx144 (internal citations omitted).) Because the results of a polymorph screen are unpredictable, the implication of the district court's opinion is that polymorphs are always patentable.

According to the district court, it was actually concerned about going too far in the opposite direction: "the Court notes that Defendants' argument appears to imply the opposite extreme—that every polymorph patent is obvious." (Appx145.) But that is not at all Appellant's view nor did Appellants argue that position at trial. Instead, the obviousness rule for polymorphs should be consistent with any other types of patentable subject matter: if the claimed invention would have been what any person of ordinary skill in the art would have done, following published prior art, then the invention is obvious. *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (upholding obviousness where "the prior art teaches a protein of interest, a motivation to isolate…and illustrative instructions"). There are many examples of polymorphs that might not fit within this category of obvious polymorphs, such as polymorphs discovered by using techniques which are not the routine published ones, or those that are difficult to obtain but were obtained anyway (such as if Grünenthal claimed Form B), or polymorphs for which there are supporting secondary considerations.

There is no reason to exempt polymorphs from obviousness. Requiring absolute predictability for polymorphs is anathema to the flexible obviousness analysis required by the Supreme Court and the law of this Circuit. The Supreme Court has instructed that the "overall obviousness inquiry must be expansive and flexible." *KSR*, 550 U.S. at 415, 419. "This court cannot, in the face of *KSR*, cling

to formalistic rules for obviousness, customize its legal tests for specific scientific fields in ways that deem entire classes of prior art teachings irrelevant, or discount the significant abilities of artisans of ordinary skill in an advanced area of art." *In re Kubin*, 561 F.3d at 1360.

A categorical rule exempting polymorphs from obviousness is also bad policy. Without an opportunity to show obviousness for polymorph patents—even where the patent shows the result of following express instructions from the prior art—drug companies will be encouraged to artificially extend patent protection. Just as Grünenthal did here, drug companies will patent a pharmaceutical compound, and then wait years before filing a new patent on an obvious polymorph. This Court should discourage practices which improperly extend the patent monopoly.

II. The District Court Committed Legal Error by Requiring Absolute Predictability To Show Obviousness.

Although the district court identified the proper legal standard, it certainly did not apply it to the '364 patent. In the legal background section of its opinion, the district court cited *Medichem* and the rule that "[o]bviousness does not require absolute predictability of success," but rather, requires "a reasonable expectation of success." (Appx89.) The district court used that test in connection with the '593 patent related to the tapentadol hydrochloride compound itself. (Appx97, Appx113, Appx119.) But it did not do so for the '364 polymorph patent; the "reasonable expectation" standard was nowhere addressed or applied to the '364 polymorph

patent. To the contrary, the district court concluded for the polymorph patent that "predictability is a touchstone of obviousness" and held that "the results of the polymorph screen—*i.e.*, the determination of the structure and properties of the polymorph forms of tapentadol hydrochloride—would have been impossible to predict." (Appx144.)

A. Obviousness Requires a Reasonable Expectation of Success, Not Absolute Predictability.

Absolute predictability is not the standard for obviousness. This Court has repeatedly stated that "[o]bviousness does not require absolute predictability of success . . . all that is required is a reasonable expectation of success." *See, e.g.*, *Howmedica Osteonic Corp. v. Zimmer, Inc.*, 640 Fed.App'x. 951, 962 (Fed. Cir. 2016) citing *In re Kubin*, 561 F.3d at 1360; *Medichem, S.A. v. Tolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988)). This Court has consistently applied the "reasonable expectation of success" standard to invalidate many different types of patents—including in the pharmaceutical field, where exact claimed results are unpredictable.

Chemical compound salts. For years, the "unpredictability of formation" deterred courts from finding pharmaceutical salts obvious as a nearly categorical rule. *See Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1379 (Fed. Cir. 2006). Requiring absolute predictability meant that a drug company could invent a compound, wait a few years, and patent a new salt even if it was a salt made by

following prior art guidance. Finally, in *Pfizer*, this Court rejected the proposition that salts could never be obvious:

> Indeed, a rule of law equating unpredictability to patentability, applied in this case, would mean that any new salt … would be separately patentable, simply because the formation and properties of each salt must be verified through testing. This cannot be the proper standard since the expectation of success need only be reasonable, not absolute.

Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1364 (Fed. Cir. 2007).

In *Pfizer*, one prior art reference disclosed the compound amlodipine and another disclosed commonly acceptable salts which included the claimed besylate salt. *Id.* at 1361. The salt reference did not disclose only besylate salts, but rather 53 different anions that could be tried. *Id*. at 1363. The patent owner and its expert argued that there were "unlimited" salt conditions that could be created, and the district court found there was "no reliable way to predict the influence of a particular salt species on the active part of the compound." *Id*. at 1362, 1364. This Court fully recognized that it could not "reject the district court's finding that in 1986, it was generally unpredictable as to whether a particular salt would form and what its exact properties would be." *Id*. at 1364.

But, as this Court ruled, there is no requirement to show predictability about whether a salt would form or what its exact properties would be, which is why using routine salts published in the prior art is not patentable without compelling secondary considerations. In *Pfizer*, the Court reviewed the inventor's own statements to

represent what any person of ordinary skill would have done: trying different salts to "show improved physicochemical characteristics." *Id*. at 1364-65. Because the prior art already disclosed the amlodipine compound and the besylate salt, combining the two was obvious even without any proof of predictability. This Court therefore held that "contrary to the district court's finding, a reasonable fact-finder could only conclude that the skilled artisan would have had a reasonable expectation of success with the besylate salt form of amlodipine." *Id*. at 1361. In addition, the *Pfizer* court held that "the optimization of the acid addition salt formulation for an active pharmaceutical ingredient would have been obvious where as here the acid addition salt formulation has no effect on the therapeutic effectiveness of the active ingredient and the prior art heavily suggests the particular anion used to form the salt." *Id*. at 1368.

Sterilized chemical compounds. Similarly, in *AstraZeneca LP v. Breath Ltd.*, this court found that sterilizing compositions was obvious where published prior art sterilization techniques were used, even though the prior art did not disclose the specific "sufficient purity and pharmaceutical acceptability" resulting from the sterilization. 603 F. Appx 999, 1002 (Fed. Cir. 2015). In that case, prior art disclosed "non-sterile budesonide compositions" and other prior art taught "sterile compositions of cortico-steroids other than budesonide, and five well-known sterilization techniques." *Id.* at 1001. The asserted claims specifically required

meeting "the criteria of sterility according to the US Pharmacopoeia 23/NF18," a result that could not have been predicted ahead of time. *Id.*

But this Court held that obviousness requires not absolute predictability but "a reasonable expectation of success in making the invention in light of the prior art," which is "not a guarantee." *Id*. at 1002 (citations omitted). Because the "known sterilization methods" in the prior art worked to create sterilized budesonide compositions, it was obvious to use them and claim a particular sterility level even though the particular result, itself, was unpredictable. *Id.*

Purified chemical compounds. And in the case of highly purified chemical compounds, the pattern again holds true. Using routine techniques to obtain an unpredictable particular level of purity does not make the resulting purity claims valid.

In *Cubist*, the patent owner appealed the invalidity of various compound claims which recited specific purity: "a daptomycin composition that is at least 97% pure relative to certain daptomycin-related impurities." *Cubist Pharms., Inc. v. Hospira, Inc.*, 805 F.3d 1112, 1127 (Fed. Cir. 2015). The district court found the compound claims obvious because methods to obtain the claimed purity were obvious, so the resulting particular level of purity was not inventive even if it was unpredictable. As this Court ruled, "[a]lthough the district court focused on the two limitations relating to the mechanics of the purification process, the court's focus on

those limitations does not undermine its obviousness analysis." *Id*. at 1128. That is because the prior art already disclosed that various purification techniques, including "micelle filtration and anion exchange chromatography" were the "keys to the purification process." *Id*.

B. Using Routine Published Prior Art Crystallization Techniques Results In Form A, Rendering The Claimed Invention Obvious.

Just as in *Pfizer*, *AstraZeneca*, and *Cubist*, even though particular claimed polymorph properties are unpredictable, those polymorphs that result from nothing more than routine published prior art procedures are obvious. While the district court required absolute predictability, and therefore found the resulting Form A polymorph non-obvious, that was too high a legal bar. Tapentadol hydrochloride was already disclosed in the prior art, and the Byrn article disclosed only 9 routine solvents for polymorph screens. (Appx57373.) Just like the 53 anions in *Pfizer*, the 9 solvents were routine and commonly used in pharmaceutical applications. In fact, ***any*** of the solvents disclosed in Byrn resulted in at least some of the claimed Form A.[2] *See infra* Section IV. And as in *Pfizer*, using the Form A polymorph imparted

[2] The claims of the '364 patent recite the use of various solvents and conditions all resulting in Form A and all disclosed in Byrn. (Appx57373.) For example, claim 12 recites a recrystallization using "a solvent selected from acetone, acetonitrile, and isopropanol" and then as little as just "allowing the solution to crystallize." (Appx406 at 19:54-20:3.) The claim itself therefore further confirms that all Grünenthal did is claim a routine polymorph screen.

no special therapeutic effect. *See infra* Section II.B.4. Similarly, like in *AstraZeneca*, the claimed polymorph is invalid as obvious because it is nothing more than the result of routine processes known in the published prior art. And for the same reasons as in *Cubist*, patentability should not be imparted based on the specific claimed result, where it was based on an obvious approach. Even though the particular crystal structure and resulting X-ray patterns that represent Form A were not predictable, the claims were the result of following routine published prior art procedures and the particular crystal form added nothing to the art. Because the polymorph screen was so well established by 2004,[3] and the established solvents all resulted in the claimed Form A polymorph, it is not patentable to claim Form A, an obvious and readily-available polymorph.

1. A person of ordinary skill had a reasonable expectation of success in conducting a routine polymorph screen published by Byrn.

The district court disregarded the proper Federal Circuit standard and instead required absolute predictability, thereby discounting the established polymorph screening in the Byrn article that would have resulted in Form A.

[3] The Byrn article was relied upon in a proceeding before the Board of Appeal for the European Patent Office. There, the Board found that in light of the prior art, including the Byrn article, that a skilled person "would be familiar with routine methods for screening for polymorphs by crystallisation from a range of different solvents under different conditions." (A63858, p.10) (citing to the Byrn article as "document [10]").

The district court found facts consistent with a conclusion of obviousness but misapplied the law when reaching its conclusion. According to the district court, "while each individual technique performed during a polymorph screen may be routine, polymorph screening consists of an unpredictable application of those routine techniques" and the results "would have been impossible to predict." (Appx143-144.) But that was not the correct legal analysis—so long as the technique to perform the polymorph screen was known and routine and employed with a reasonable expectation of success, the resulting polymorphs are obvious (barring any secondary considerations, of which there are none in this case). The Byrn paper expressly taught that "*[t]he first step* in the polymorphs decision tree is to crystallize the substance from a number of different solvents in order to attempt to answer the question: *Are polymorphs possible*." (Appx57373 (emphasis added).) The district court agreed, moreover, that the Byrn article "explains steps to detect polymorphism" and "specifically lists certain solvents to use in the recrystallization experiments." (Appx141.) Standard recrystallization techniques like cooling and evaporation are taught, specifically stating that "[n]ew crystal forms can often be obtained by cooling hot saturated solutions or partly evaporating clear saturated solutions." (Appx57373.) And Appellee's own expert Dr. Bernstein conceded that polymorphs in pharmaceutical products are common: the district court credited his testimony "that about 30 to 35% of all compounds are polymorphic." (Appx139.)

Indeed, in this case, the '737 patent clearly indicated that the tapentadol disclosed was "made in crystalline form." (Appx138.)

There is no dispute that a person of ordinary skill in the art would know how to do the crystallization. Both sides' experts explained that polymorph screening was known and routine. (Appx9717-9719 at 80:4-82:14); *see also* Appx11023 at 10:11-16.) The district court agreed that it was common knowledge to do a polymorph screen, and that "[b]y 2000, Grünenthal generally understood that pharmaceutical companies 'take consideration of polymorphism when they are developing pharmaceutical compounds.'" (Appx140.) Indeed, named inventor Dr. Gruss admitted that polymorph screening was known, testimony again credited by the district court: "polymorph investigation is to apply various parameters on the crystallization like temperature ranges, like various solvents to extend as broad as possible range of investigations in order to understand and characterize the compounds or the compound under consideration." (*Id.*) Even Cross-Appellant's crystallization expert, Dr. Joel Bernstein, has written that "[c]rystallization from solution is one of the first laboratory skills that chemists acquire, and applying variations to the conventional methods has been the traditional strategy in the search for polymorphs." (Appx11023 at 10:11-16, Appx59465.)

2. Following the Byrn article would have provided Form A to any person of ordinary skill in the art.

The district court summarized Appellant's polymorph screen argument as follows: "Defendants argue that 'a routine polymorph screen, like the one described in the Byrn article, would have revealed Form A of tapentadol hydrochloride' as one of the two polymorphs." (Appx143.) The district court, however, disagreed that the claims were obvious, based on the fact that the specific properties of Form A were not predictable based on the prior art. But it cannot be disputed that any person of ordinary skill in the art following known polymorph screening steps—and those expressly disclosed in the Byrn article—would have arrived at Form A.

As a preliminary issue, the district court erred—both legally and factually—when it held that a person of ordinary skill in the art would not have started with tapentadol hydrochloride to do a polymorph screen. It made the unsupported one-sentence finding that "[t]here is nothing in particular in the '737 patent that would have motivated a POSA studying crystal structure to select tapentadol hydrochloride from amongst the many compounds disclosed in the '737 patent." (Appx142.) As a legal matter, Alkem was not required to prove a "lead compound" analysis, which is what the district court implied, and which would mean starting with tapentadol hydrochloride in particular for otherwise obvious improvements over the prior art. Rather, the "lead compound" analysis should be limited to new chemical compounds. The "lead compound" analysis has not been applied to modifications

of known chemical compounds that do not change the chemical compound itself, such as salts of known compounds. *See, e.g.*, *Pfizer*, 480 F.3d at 1362.

And as a factual matter, the district court clearly erred in finding there was no reason to select tapentadol hydrochloride. There was ample evidence in the patent itself, which the district court did not even address in its opinion: (1) the '737 patent itself discloses only 28 example compounds, and reports that all of the compounds according to the invention which "were investigated exhibited a pronounced analgesic effect," (Appx386 at 23:10-12); (2) the district court used that very same disclosure to find that the '593 patent—which has the same specification as the '737 patent—had utility because "a POSA would have had a reasonable expectation that Example 25 (tapentadol hydrochloride) would have a dose-dependent antinociceptive effect due to its structural similarity to the family of compounds that demonstrated analgesic activity" (Appx119); and (3) for the same reason, the district court also found the '593 patent met the *Antares* test that it "clearly and unequivocally disclose[d] the newly claimed invention as a separate invention." *Antares Pharma, Inc. v. Medac Pharma Inc.*, 771 F.3d 1354, 1362 (Fed. Cir. 2014); (Appx91, Appx124). Moreover, the district court also ignored the undisputed fact that tapentadol hydrochloride was the one compound from the '737 patent disclosed in the prior art as a promising pain reliever in the 2002 World Health Organization listing. (Appx58128, Appx58101.) Tapentadol was thus already a drug known to

be in development. There simply is no doubt that a person of ordinary skill in the art would have known to start with tapentadol hydrochloride—even assuming such a showing is required—because tapentadol hydrochloride was specifically identified as an useful analgesic in the prior art.

As to the FDA requirement for a polymorph screen, the facts in this case compel finding that the routine prior art screen for tapentadol would have resulted in at least some Form A. (Appx11036 at 23:6-23, Appx11040 at 27:1-12, Appx11041-11043 at 28:10-30:14, Appx57789-57792.) SSCI, as any POSA would have done, followed the evaporation crystallization protocol disclosed in the Byrn article and used eight of the nine solvents listed in the Byrn article. (Appx57791-57792, Appx57373.) In ***just three weeks***, SSCI reported back to Grünenthal with its first results—those easiest to obtain—reflecting the standard conditions from the Byrn article. (Appx57774, Appx57789-57792, Appx59452.) And no matter what solvent or conditions SSCI used in its first screen, any time crystalline material was formed, some Form A was present. (Appx57791-57792, Appx49384, Appx49388, Appx49393-49395, Appx9718-9719 at 81:13-82:14, Appx11043 at 30:6-10.) A person of skill in the art would have gotten the same results as SSCI obtained, *i.e.*, for all the solvents, if any crystalline material formed, there was always Form A present. That is all the asserted claims require.

Polymorph Form A was the necessary by-product of following the routine Byrn screen as applied to the tapentadol hydrochloride disclosed in the '737 patent. Indeed, it is not disputed that following the very protocol in the '737 patent itself resulted in either Form A or Form B tapentadol hydrochloride. Both parties tested the procedure and confirmed that result at trial. (Appx130-131, Appx133 Moreover, Grünenthal ***even admitted at trial*** that the compounds "obtained by the procedure described in example 25 of U.S. Pat. No. 6,248,737" were in fact Form A tapentadol. (Appx49384, Appx49392; Appx63720 at 50:18-52:7; Appx63721 at 57:14-58:9, 58:19-59:3; 59:9-10; 59:12-18; Appx63395 at 102:5-10, Appx6339 at 107:12-16; Appx10906 at 29:6-8.) It was not surprising that Form A was so ubiquitous, because absent any extreme temperature conditions or impurities, Grünenthal's own data confirmed that Form A was the stable form at room temperature. (Appx147, Appx47379, Appx49619, Appx49397, Appx57774.) In fact, the only batches ever made according to the '737 patent that resulted in predominantly Form B had substantial impurities and were yellow in color—instead of the white disclosed in the '737 patent—and Cross-Appellants avoided anticipation only by arguing that the prior art Example 25 in the '737 patent "does not contain a purity limitation." (Appx135.) Given the nearly anticipatory prior art, and the inherent properties of Form A, any person of ordinary skill in the art would have identified and obtained Form A.

This case is therefore very much like *Santarus, Inc. v. Par Pharms., Inc.*, which addressed the issue of whether a particularly claimed unpredictable property could be patented when it was an inherent property of an otherwise obvious combination. 694 F.3d 1344 (Fed. Cir. 2012). In that case, the obviousness issue was "whether a solid dosage form of non-enteric coated PPI such as omeprazole would have been obvious." *Id*. at 1351. The claims required non-enteric coated PPI, and also referred to very precise blood levels that could not have been predicted *a priori*: "an initial serum concentration of the proton pump inhibitor greater than about 0.1 μg/ml is obtained at any time within about 30 minutes after administration." *Id*. at 1353. Nonetheless, because the formulation itself was obvious, this Court found that the patent owner was "incorrect that the claims reciting specific blood serum concentrations of PPI would have been nonobvious." *Id*. at 1354. That is because "an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations." *Id*. "To hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property." *Id*.

Similarly here, crystalline tapentadol is expressly disclosed in the prior art and SSCI simply tested it to find an inherent property—the crystal structure of Form A—which Grünenthal then patented. Grünenthal cannot avoid obviousness merely by

claiming the resulting inherent property of a routine screen, *i.e.*, combining the Byrn crystallization method in the prior art with tapentadol hydrochloride, also in the prior art. In other words, Grünenthal did not specially create or select Form A or ever set out to create a polymorph with its crystal structure. Rather, Form A's crystal structure was merely the by-product of the routine SSCI polymorph screen that Grünenthal hired it to do.

3. The district court erroneously discounted the Byrn article by relying on other district court cases that never addressed the Byrn article.

As shown above, the Byrn article was important to obviousness because it was never considered by the Patent Office, yet contained both express motivation (FDA guidance to evaluate polymorphs) and established routine procedures (listing nine solvents) for doing a polymorph screen. The district court discounted its teachings because other courts had not relied on that reference in other, unrelated litigation. This was error.

In other decisions, parties challenged polymorph patents by referring generally to the knowledge of a person of ordinary skill, without referencing Byrn, indeed any particular prior art that provided the details for a polymorph screen. In sharp contrast, here Alkem provided a specific reference that articulates both motivation and routine procedures. Thus, in those other district court cases (*In re Armodafinil*, *Merck*, and *Takeda*), the patents were found non-obvious because of the lacking particularized guidance. (Appx144); *In re Armodafinil Patent Litigation*,

939 F. Supp. 2d 456, 490 (D. Del. 2013); *Merck & Cie v. Watson Labs., Inc.*, 125 F. Supp. 3d 503 (D. Del. 2015) *rev'd on other grounds*, 833 F.3d 1347 (Fed. Cir. 2016); *Takeda Pharm. Co. v. Handa Pharm., LLC*, Case No. C-11-00840, 2013 U.S. Dist. LEXIS 187604, at *232-33 (N.D. Cal. Oct. 17, 2013).

The *In re Armodafinil* court concluded that there was "no suggestion of the structure *or method of making form I armodafinil* in the alleged prior art" and that "nothing taught or suggested the means of obtaining Form I." 939 F. Supp. 2d. at 500 (emphasis added). Similarly, in *Takeda*, the court found that none of the cited prior art references disclosed the method that was actually used to crystallize the claimed material. 2013 U.S. Dist. LEXIS 187604 at *112-113. And in *Merck*, "[b]oth sides' experts agree[d] that finding an unknown polymorph requires experimentation," but did not discuss or address known prior art techniques 125 F. Supp. 3d at 514.

Of course this case is starkly different and easily distinguishable from those earlier district court decisions. Here, unlike in prior cases, Byrn provided express guidance about how to screen polymorphs, at least to find those that are easy to find. The Byrn article taught the specific solvents and conditions used in a standard crystallization polymorph screen. And when SSCI used those very solvents in the crystallization technique already disclosed in Byrn, it made Form A every time. (Appx57791-57792, Appx49384, Appx49388, Appx49393-49395, Appx9718-9719

at 81:13-82:14, Appx11043 at 30:6-10.) And there was evidence that following that very procedure resulted in the claimed Form A polymorph.

Despite the obvious difference in this case—which relied upon the Byrn article's explicit guidance on routine methods for screening polymorphs—and prior cases—which did not—the district court discounted the Byrn article because "the Byrn article was published in 1995, long before many of the cases discussed above." (Appx145.) There was no indication that the Byrn article ***was even of record*** in any of the prior district court decisions, so this finding was irrelevant and expressed the district court's apparent confusion. Appellant used the Byrn article precisely to confirm expressly what was known in the art, which was not addressed in prior cases. The fact that the Byrn article was published before other district court opinions is meaningless where Byrn was not discussed in those opinions, and the district court erred in discounting the Byrn article on that basis. Having shown that obtaining Form A is obvious, claims 1-3 directed to that form are invalid, as is claim 25 directed to a dosage form using Form A tapentadol.

4. The absence of any asserted secondary considerations further confirms obviousness of the polymorph claims.

Cross-Appellants offered no evidence of any secondary considerations, a fact that the district court confirmed in its opinion. (Appx144.) The sheer lack of any secondary considerations whatsoever—no asserted commercial success, no unexpected results, no failure of others—confirms the obviousness of the asserted

polymorph claims. Cross-Appellants found no objective evidence that would indicate the claims were not obvious. There is no particular benefit to the claimed polymorph, as opposed to the disclosure of the compound itself. Indeed, when Appellants argued for invalidity based on lack of utility, all that Cross-Appellants could offer in response was that Form A is the only stable polymorph at room temperature. As the district court found, "Form A is the form that tends to persist (and [ ] Form B will tend to convert to Form A) at room temperature." (Appx147.) The lack of secondary considerations, coupled with the confirmation that Form A is the only readily-available polymorph that is known to exist for tapentadol hydrochloride, confirms obviousness.

C. Using Routine Published Prior Art Crystallization Techniques Results In Form A, Rendering The Claimed Invention At Least Obvious To Try.

In the alternative, it would have been at least obvious to try the limited set of crystallization solvents and conditions in the Byrn article as applied to tapentadol hydrochloride, resulting in the claimed Form A. The Supreme Court in *KSR* approved the "obvious to try" approach: "the fact that a combination was obvious to try might show that it was obvious under § 103." 550 U.S. at 421. Proving an invention was obvious to try means showing "a design need or market pressure to solve a problem" and "a finite number of identified, predictable solutions" to try. *Id.* "If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." *Id.*

Cross-Appellants concede that "obvious to try" is an appropriate analysis, but the district court did not separately address it. Cross-Appellants included it in their own post-trial conclusions of law, "[i]n *KSR*, the Supreme Court held that 'the fact that a combination was obvious to try might show that it was obvious,' but *only* if there is a design need or market pressure to solve a problem and there are a finite number of predictable solutions that leads to anticipation of success." Both of the *KSR* steps apply here, making the claimed Form A polymorph obvious to try: (1) there was an express motivation to solve a problem because the FDA directed pharmaceutical companies to do a polymorph screen for chemical compounds and (2) there was a finite number of choices that were already published in the prior art in order to do that polymorph screen.

First, there was motivation to conduct a polymorph screen of tapentadol hydrochloride. As discussed above, the FDA in 1987 had already issued guidelines requiring that "[a]ppropriate analytical procedures should be used to determine whether (or not) polymorphism occurs." (Appx57314; Appx139.) The regulatory requirement provided a design need and market pressure to do a polymorph screen, which was at that time already a well understood procedure. Named inventor Dr. Buschmann admitted that, in the industry, "it was considered important also to take consideration of the so-called solid phase of the compound." (Appx8647 at 77:20-22.)

Second, there were a finite number of predictable solutions for performing a polymorph screen, disclosed in the Byrn article, and in fact, the article specifically and expressly explained that it was teaching how to implement the FDA's general guidance. The article was created because "[i]nterest in the subject of pharmaceutical solids stems in part from the FDA's drug substance guidelines." (Appx57372.) A person of ordinary skill of course already knew how to do routine polymorph screens, but the Bryn article confirms that fact expressly. There were nine specific solvents disclosed in the Byrn article, along with the teaching to use standard evaporation or cooling to extract a crystal form. And using those limited number of solvents, all that resulted in crystals included the claimed Form A. (Appx57791-57792, Appx49384, Appx49388, Appx49393-49395, Appx9718-9719 at 81:13-82:14, Appx11043 at 30:6-10.) The screening experiments led to the reasonably anticipated success, namely discovering the readily-available and easy-to-find crystalline forms of tapentadol, here Form A, since that was the only polymorph stable at room temperature. Indeed, the fact that following the procedure and using the solvent disclosed in the '737 prior art patent itself led to only either Form A or Form B tapentadol, already led a person of ordinary skill far down the path of doing a routine screen and verifying that Form A is obtained. Therefore, the screening experiments from Byrn were "obvious to try."

This case is similar to *In re Kubin*, where this Court applied *KSR* to find claims directed to complex DNA molecules encoding a specific "p38" protein invalid as obvious. 561 F.3d at 1351. In that case, the Court recognized that the specific claimed polynucleotide sequence for the gene was not predictable, but confirmed that predictability was not the proper standard. *Kubin* made clear that *KSR* is not limited to only the "predictable arts." *Id*. Rather, the Court held that a person of ordinary skill "had every motivation to seek and every reasonable expectation of success in achieving the sequence of the claimed invention," because of known standard techniques. *Id*. at 1361.

The *Kubin* court found that the "obvious to try" elements had been met because the prior art taught "a protein of interest, a motivation to isolate the gene coding for that protein, and illustrative instructions to use a monoclonal antibody specific to the protein for cloning this gene." *Id.* at 1360. That was sufficient to meet the test set out previously in *O'Farrell* that "an obviousness finding was appropriate where the prior art 'contained *detailed enabling methodology* for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.'" *Id.* (quoting *In re O'Farrell*, 853 F.2d 894, 902 (Fed. Cir. 1988).

This Court thus found that where there was motivation to pursue a particular approach, and the approach was well known, the claimed invention falls within the

KSR proviso that "the claimed invention is 'the product not of innovation but of ordinary skill and common sense.'" *Id*. In fact, the very next sentence in *Kubin* couches the motivation-plus-known-approach test "in the familiar terms of this court's longstanding case law" that a POSA would have had a "resoundingly 'reasonable expectation of success' in deriving the claimed invention." *Id*. At bottom, claims directed to what anyone of ordinary skill in the art would do are unworthy of patent protection because they are obvious or obvious to try. Accordingly, just as in *Kubin*, the claimed Form A obtained is obvious to try as the claimed invention "is 'the product not of innovation but of ordinary skill and common sense.'" *Id*. And again, the absence of any asserted secondary considerations whatsoever further compels a conclusion that the claimed invention was at least obvious to try.

The record evidence at trial conclusively demonstrated that Forms A and B—which were already in the prior art by virtue of the '737 patent—have nearly indistinguishable properties. There is no dispute that both forms have the same bioavailability. (Appx10864 at 288:5-8, Appx11029 at 16:15-18.) Grünenthal's solubility studies showed that the solubilities of both polymorphs are also very similar. (Appx49617.) Grünenthal even found that the dissolution curves for capsules containing Form A or Form B were "identical." (Appx494618.) Appellee's

own expert Dr. Bernstein had to concede that the bioavailability and solubility of the two forms were similar. (Appx11029 at 16:15-18, Appx10864 at 288:9-13.)

CONCLUSION

For these reasons, the judgment of non-invalidity should be reversed and the asserted claims held invalid as obvious. At a minimum, the case should be remanded so that invalidity can be determined under the correct obviousness standard.

Dated: September 7, 2017

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CERTIFICATE OF SERVICE

I, Rose E. Olejniczak, being duly sworn according to law and being over the age of 18, upon my oath deposes and states that:

Counsel Press was retained by SCHIFF HARDIN LLP, Attorneys for Defendant-Appellant Alkem Laboratories Limited, to print this document. I am an employee of Counsel Press.

On September 7, 2017, SCHIFF HARDIN LLP authorized me to electronically file the foregoing Opening Brief of Defendant-Appellant Alkem Laboratories Limited with the Clerk of the Federal Circuit using the CM/ECF System, which will serve e-mail notice of such filing on the following attorneys:

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Upon acceptance by the Court of the e-filed document, I will cause six paper copies of the brief to be filed with the Court, via Federal Express, within the time provided in the Court's rules.

/s/ Rose E. Olejniczak
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CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitations of Fed. Cir. R. 32(a). This brief contains 9,784 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(f) and Fed. Cir. R. 32(b). This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6). This brief has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in fourteen (14) point Times New Roman font.

Dated: September 7, 2017

/s/ Imron T. Aly
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ADDENDUM

ADDENDUM TABLE OF CONTENTS

Order of Final Judgment and Injunction, etc. entered 04/11/2017, D.I. 582 in Case No. 2:13-4507 .....Appx23 – Appx29

Order re Patents U.S. Patent Nos. RE39,593, 7,994,364, and 8,536,130, entered 09/30/2016, D.I. 537 in Case No. 2:13-4507.....Appx30 – Appx32

Opinion re Patents 593, 364 and 130, entered 09/30/2016, D.I. 536 in Case No. 2:13-4507 .....Appx33 – Appx199

U.S. Patent No. 6,278,737.....Appx373 – Appx387

U.S. Patent No. 7,994,364.....Appx388 – Appx407

U.S. Patent No. 8,309,060.....Appx408 – Appx427

U.S. Patent No. 8,536,130.....Appx428 – Appx438

U.S. Patent No. RE39,593 .....Appx439 – Appx464

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

DEPOMED, INC. and GRÜNENTHAL GMBH, Plaintiffs/Counterclaim Defendants, v. ACTAVIS ELIZABETH LLC and ALKEM LABORATORIES LIMITED, Defendants/Counterclaim Plaintiffs.	Civil Action No. 2:13-cv-04507-CCC-MF
AND CONSOLIDATED CASES	Civil Action No. 2:13-cv-07803-CCC-MF Civil Action No. 2:13-cv-06929-CCC-MF Civil Action No. 2:14-cv-03941-CCC-MF Civil Action No. 2:14-cv-04617-CCC-MF Civil Action No. 2:15-cv-06797-CCC-MF

FINAL JUDGMENT AND INJUNCTION[1]

THIS MATTER, having come before the Court on the patent infringement claims of plaintiffs Depomed, Inc. ("Depomed") and Grünenthal GmbH ("Grünenthal") (collectively, "Plaintiffs"), and the counterclaims and defenses of defendants Actavis Elizabeth LLC, Actavis UT, Actavis LLC, Actavis, Inc. (collectively, "Actavis"), Roxane Laboratories, Inc. ("Roxane"), and Alkem Laboratories Ltd. ("Alkem") (all together, "Defendants"), a bench trial having been held by this Court, and the Court having issued its Opinion in this matter on September 30, 2016 (Dkt. 536, Case No. 13-04507),

[1] This serves as Final Judgment as to all claims and counterclaims asserted in each of the above-referenced actions with the following exception: pursuant to the Court's November 19, 2015 Order (Dkt. 287, Case No. 13-04507), all proceedings related to U.S. Patent No. 8,309,060 are stayed.

IT IS on this 11 day of April, 2017, hereby

ORDERED, ADJUDGED, and DECREED as follows:

1. This Court has jurisdiction over the subject matter of the above consolidated actions and has personal jurisdiction over the parties for purposes of the above consolidated actions.

I. U.S. Patent No. RE39,593

A. Infringement

2. Judgment is hereby entered in favor of Plaintiffs, and against Defendants, on Plaintiffs' claim of infringement of U.S. Patent No. RE39,593 (the "'593 Patent").

3. Judgment is hereby entered against Defendants on their respective counterclaims for a declaratory judgment of non-infringement of the '593 Patent.

4. Claims 8, 61, 117, and 147 of the '593 Patent are infringed under 35 U.S.C. § 271(e)(2)(A) by the following Abbreviated New Drug Applications ("ANDAs") (collectively, "Defendants' ANDAs"):

A. Actavis's ANDA Nos. 204971, 206657, and 204972;

B. Roxane's ANDA Nos. 205057 and 206418; and

C. Alkem's ANDA Nos. 205015 and 205016.

5. Submission of Defendants' ANDAs to the U.S. Food & Drug Administration ("FDA") constitutes acts of infringement of the '593 Patent under 35 U.S.C. § 271(e)(2)(A).

6. Each of Defendants, their affiliates and subsidiaries, and all of their officers, agents, servants, employees, and attorneys, and all persons and entities in active concert or participation or privity with any of them, and their successors and assigns, are hereby enjoined from engaging in the commercial manufacture, use, or sale within the United States of the products described in Defendants' ANDAs (the "ANDA Products") or the active pharmaceutical

ingredient (tapentadol hydrochloride) thereof, from offering to sell the ANDA Products or the active pharmaceutical ingredient (tapentadol hydrochloride) thereof within the United States, or from importing the ANDA Products or the active pharmaceutical ingredient (tapentadol hydrochloride) thereof into the United States before the expiration of the '593 Patent on August 5, 2022. This paragraph does not restrict Defendants' activities that fall within the scope of 35 U.S.C. § 271(e)(1), including, for example, the sale, manufacture, importation, or use of tapentadol hydrochloride solely for uses reasonably related to the development and/or submission of information to FDA.

7. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval by FDA of Defendants' ANDAs shall be a date which is not earlier than August 5, 2022 or, to the extent FDA determines that pediatric exclusivity is available, the date any such exclusivity ends. Depomed will provide written notice to Defendants of such grant of pediatric exclusivity within five (5) business days of receiving such an award of exclusivity from FDA.

B. Validity and/or Enforceability

8. Judgment is hereby entered against Defendants on their respective counterclaims for a declaratory judgment of invalidity and/or unenforceability of the '593 Patent.

9. The Court finds that claims 8, 61, 117, and 147 of the '593 Patent are not invalid under 35 U.S.C. § 1 *et seq*.

II. U.S. Patent No. 7,994,364

A. Infringement

10. Judgment is hereby entered in favor of Plaintiffs, and against Defendants, on Plaintiffs' claim of infringement of U.S. Patent No. 7,994,364 (the "'364 Patent").

11. Judgment is hereby entered against Defendants on their respective counterclaims for a declaratory judgment of non-infringement of the '364 Patent.

12. Claims 1, 2, 3, and 25 of the '364 Patent are infringed by Defendants' ANDAs

under 35 U.S.C. § 271(e)(2)(A).

13. Submission of Defendants' ANDAs to FDA constitutes acts of infringement of the '364 Patent under 35 U.S.C. § 271(e)(2)(A).

14. Each of Defendants, their affiliates and subsidiaries, and all of their officers, agents, servants, employees, and attorneys, and all persons and entities in active concert or participation or privity with any of them, and their successors and assigns, are hereby enjoined from engaging in the commercial manufacture, use, or sale within the United States of the ANDA Products or the active pharmaceutical ingredient (tapentadol hydrochloride Form A) thereof, from offering to sell the ANDA Products or the active pharmaceutical ingredient (tapentadol hydrochloride Form A) thereof within the United States, or from importing the ANDA Products or the active pharmaceutical ingredient (tapentadol hydrochloride Form A) thereof into the United States before the expiration of the '364 Patent on June 27, 2025. This paragraph does not restrict Defendants' activities that fall within the scope of 35 U.S.C. § 271(e)(1), including, for example, the sale, manufacture, importation, or use of tapentadol hydrochloride Form A solely for uses reasonably related to the development and/or submission of information to FDA.

15. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval by FDA of Defendants' ANDAs shall be a date which is not earlier than June 27, 2025 or, to the extent FDA determines that pediatric exclusivity is available, the date any such exclusivity ends. Depomed will provide written notice to Defendants of such grant of pediatric exclusivity within five (5) business days of receiving such an award of exclusivity from FDA.

B. Validity and/or Enforceability

16. Judgment is hereby entered against Defendants on their respective counterclaims for a declaratory judgment of invalidity and/or unenforceability of the '364 Patent.

17. The Court finds that claims 1, 2, 3, and 25 of the '364 Patent are not invalid under 35 U.S.C. § 1 *et seq*.

18. The Court finds that the '364 Patent is not unenforceable under the doctrine of unclean hands.

III. U.S. Patent No. 8,536,130

A. Infringement

1. *Alkem*

19. Judgment is hereby entered in favor of Plaintiffs and against Alkem on Plaintiffs' claim of infringement of U.S. Patent No. 8,536,130 (the "'130 Patent").

20. Judgment is hereby entered for Plaintiffs, and against Alkem, on Alkem's counterclaim for a declaratory judgment of non-infringement of the '130 Patent.

21. Claims 1, 2, 3, and 6 of the '130 Patent are infringed under 35 U.S.C. § 271(e)(2)(A) by Alkem's ANDA No. 205016.

22. Submission of Alkem's ANDA No. 205016 to FDA constitutes an act of infringement of the '130 Patent under 35 U.S.C. § 271(e)(2)(A).

23. Alkem, its affiliates and subsidiaries, and all of its officers, agents, servants, employees, and attorneys, and all persons and entities in active concert or participation or privity with any of them, and their successors and assigns, are hereby enjoined from engaging in the commercial manufacture, use, or sale within the United States of the products described in Alkem's ANDA No. 205016 (the "ANDA No. 205016 products") or the active pharmaceutical ingredient (tapentadol hydrochloride) thereof for use in treating polyneuropathic pain, from offering to sell the ANDA No. 205016 Products or the active pharmaceutical ingredient (tapentadol hydrochloride) thereof for use in treating polyneuropathic pain within the United States, or from importing the ANDA No. 205016 Products for use in treating polyneuropathic pain or the active pharmaceutical ingredient (tapentadol hydrochloride) with knowledge that it will be used for treating polyneuropathic pain into the United States before the expiration of the '130 Patent on September 22, 2028. This paragraph does not restrict Defendants' activities that fall

within the scope of 35 U.S.C. § 271(e)(1), including, for example, the sale, manufacture, importation, or use of tapentadol hydrochloride for treatment of polyneuropathic pain, solely in connection with uses reasonably related to the development and/or submission of information to FDA.

24. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval by FDA of Alkem's ANDA No. 205016 shall be a date which is not earlier than September 22, 2028 or, to the extent FDA determines that pediatric exclusivity is available, the date any such exclusivity ends. Depomed will provide written notice to Defendants of such grant of pediatric exclusivity within five (5) business days of receiving such an award of exclusivity from FDA.

2. Actavis and Roxane

25. Judgment is hereby entered against Plaintiffs on their claim of infringement of the '130 Patent.

26. Judgment is hereby entered for Actavis and Roxane, and against Plaintiffs, on their respective counterclaims for a declaratory judgment of non-infringement of the '130 Patent.

27. Claims 1 and 2 of the '130 Patent are not infringed under 35 U.S.C. § 271(e)(2)(A) by Actavis's ANDA No. 204972 or Roxane's ANDA No. 206418.

28. Submission of Actavis's ANDA No. 204972 and Roxane's ANDA No. 206418 to FDA does not constitute acts of infringement of the '130 Patent under 35 U.S.C. § 271(e)(2)(A).

B. Validity and/or Enforceability (as to All Defendants)

29. Judgment is hereby entered against Defendants on their respective counterclaims for a declaratory judgment of invalidity and/or unenforceability of the '130 Patent.

30. The Court finds that claims 1, 2, 3, and 6 of the '130 Patent are not invalid under 35 U.S.C. § 1 *et seq*.

* * * * *

31. Consistent with the Court's November 19, 2015 Order (Dkt. 287, Case No. 13-04507), all proceedings relating to U.S. Patent No. 8,309,060 (the "'060 patent") (Plaintiffs' Count V at Dkt. 12 and 146, Case No. 13-04507 and Actavis's Fifth and Sixth Counts at Dkt. 39, Case No. 13-04507 and Actavis's Fifth, Sixth and Seventh Counts at Dkt. 132, 133, and 150, Case No. 13-04507) are stayed pending resolution of the Federal Circuit appeal from *Endo Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC*, No. 12-cv-8115 et al. (S.D.N.Y.).

32. Pursuant to Federal Rule of Civil Procedure 54(b), the Court determines that there is no just reason for delay in entering final judgment as to all claims adjudged in this Final Judgment, because doing so would prejudice the parties. This Final Judgment, and any appeal therefrom, will have no impact on the pending and stayed '060 patent proceedings. Likewise, the '060 patent proceedings (including the Court's previous Order staying those proceedings) and the resolution of the appeal in *Endo* will have no impact on this Final Judgment (or any appeal therefrom).

33. Pursuant to Fed. R. Civ. P. 58(a), this is the FINAL JUDGMENT of the Court. *See supra* n. 1.

34. Pursuant to Fed. R. Civ. P. 54, Plaintiffs are the Prevailing Party entitled to costs. Plaintiffs shall serve and file their Bill of Costs and Disbursements in accordance with Local Rule 54.1.



Claire C. Cecchi
U.S. District Judge

NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE DEPOMED PATENT LITIGATION	Civil Action No.: 13-4507 (CCC-MF) Civil Action No.: 15-6797 (CCC-MF) **ORDER**

CECCHI, District Judge.

This matter comes before the Court on a consolidated[1] Hatch-Waxman patent infringement action brought by Plaintiffs Depomed, Inc. ("Depomed") and Grünenthal GmbH ("Grünenthal") (collectively, "Plaintiffs"). The Defendants in the consolidated action are Actavis Elizabeth LLC, Actavis UT, Actavis LLC, Actavis, Inc. (collectively, "Actavis"), Roxane Laboratories, Inc. ("Roxane"), and Alkem Laboratories Ltd. ("Alkem"). It appearing that:

1. Defendants have sought approval from the United States Food and Drug Administration ("FDA") to market generic versions of Plaintiffs' NUCYNTA® tapentadol hydrochloride products.
2. Plaintiffs have asserted claims in three patents against Defendants: U.S. Patent No. RE39,593 (the "'593 patent"), U.S. Patent No. 7,994,364 (the "'364 patent"), and U.S. Patent No. 8,536,130 (the "'130 patent").
3. This Court conducted a bench trial in this matter beginning March 9, 2016 through March 23, 2016. The parties submitted post-trial briefing and proposed findings of

[1] This case, docket number 13-4507, is the lead case in the consolidated action. The member cases are 13-7803, 13-6929, 14-3941, 14-4617, and 15-6797.

fact and conclusions of law on April 18, 2016. Closing arguments were held on April 27, 2016.

4. The parties stipulated to bifurcation of Actavis's third counterclaim to correct or delete the FDA use code for the '130 patent. [*See* ECF No. 407.] On May 9, 2016, this Court entered a Consent Order, adjourning that bifurcated hearing without date. [ECF No. 465.] The parties have represented to the Court that they have requested clarification from the FDA on the current status of the use code.

Accordingly, for the reasons set forth in this Court's accompanying Opinion,

IT IS on this 30th date of September, 2016

ORDERED that no finding of invalidity shall issue as to the '593 patent; and it is further

ORDERED that no finding of invalidity shall issue as to the '364 patent; and it is further

ORDERED that no finding of unenforceability shall issue as to the '364 patent; and it is further

ORDERED that no finding of invalidity shall issue as to the '130 patent; and it is further

ORDERED that, pursuant to the March 4, 2016 Stipulated Order of Infringement, all Defendants infringe the asserted claims of the '593 patent; and it is further

ORDERED that, pursuant to the March 4, 2016 Stipulated Order of Infringement, all Defendants infringe the asserted claims of the '364 patent; and it is further

ORDERED that only Defendant Alkem induces infringement of claims 1, 2, 3, and 6 of the '130 patent; and it is further

ORDERED that no finding of induced infringement shall issue against Defendants Actavis and Roxane as to the '130 patent; and it is further

ORDERED that no finding of contributory infringement shall issue against any of the Defendants as to the '130 patent; and it is further

ORDERED that, in order to maintain the status quo until the Court enters final judgment, and in light of the findings set forth above and in the accompanying Opinion, Defendants are hereby enjoined from launching their generic tapentadol hydrochloride products; and it is further

ORDERED that the parties are directed to submit a proposed form of judgment consistent with this Order and the accompanying Opinion; and it is further

ORDERED that Actavis's third counterclaim to correct or delete the FDA use code for the '130 patent is hereby **SEVERED** from this action and returned to Case No. 15-6797, which shall be reopened by the Clerk; and it is further

ORDERED that the accompanying Opinion will be unsealed on Friday October 21, 2016 unless an appropriate motion to seal same (pursuant to Local Civil Rule 5.3(c)) is filed by October 14, 2016.

SO ORDERED.

CLAIRE C. CECCHI, U.S.D.J.

[*FILED UNDER SEAL***]**

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE DEPOMED PATENT LITIGATION	Civil Action No.: 13-4507 (CCC-MF) **OPINION** **[***FILED UNDER SEAL***]**

CECCHI, District Judge.

I. INTRODUCTION

This is a consolidated[1] Hatch-Waxman patent infringement action brought by Plaintiffs Depomed, Inc. ("Depomed") and Grünenthal GmbH ("Grünenthal") (collectively, "Plaintiffs"). The Defendants in the consolidated action are Actavis Elizabeth LLC, Actavis UT, Actavis LLC, Actavis, Inc. (collectively, "Actavis"), Roxane Laboratories, Inc. ("Roxane"), and Alkem Laboratories Ltd. ("Alkem").

Plaintiffs have asserted three patents against Defendants: U.S. Patent No. RE39,593 (the "'593 patent"), U.S. Patent No. 7,994,364 (the "'364 patent"), and U.S. Patent No. 8,536,130 (the "'130 patent") (collectively, the "patents-in-suit"), which are directed to compositions and methods relating to Plaintiffs' NUCYNTA® tapentadol hydrochloride products, including NUCYNTA® IR, NUCYNTA® ER, and NUCYNTA® Oral Solution.[2] Defendants have sought approval from the United States Food and Drug Administration ("FDA") to market generic

[1] This case, docket number 13-4507, is the lead case in the consolidated action. The member cases are 13-7803, 13-6929, 14-3941, 14-4617, and 15-6797.

[2] Plaintiffs have also asserted U.S. Patent No. 8,309,060 against Actavis. All proceedings relating to that patent have been stayed by Order entered on November 19, 2015 [ECF No. 287].

versions of tapentadol hydrochloride. Plaintiffs allege that Defendants will infringe the patents-in-suit by marketing their generic products.

The Court conducted a bench trial in this matter beginning March 9, 2016 through March 23, 2016. The parties submitted post-trial briefing and proposed findings of fact and conclusions of law on April 18, 2016. Closing arguments were held on April 27, 2016.[3]

This Opinion constitutes the Court's findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a). The findings of fact are based on the Court's observations and credibility determinations of the witnesses who testified and a thorough review of all the evidence admitted at trial. For the reasons stated herein, the Court finds as follows:

As to the '593 patent, Defendants have not met their burden of proving by clear and convincing evidence that the '593 patent is invalid. As Defendants stipulated to infringement of the '593 patent, judgment of infringement will be entered in favor of Plaintiffs on the '593 patent.

As to the '364 patent, Defendants have not met their burden of proving by clear and convincing evidence that the '364 patent is invalid. As Defendants stipulated to infringement of the '364 patent, judgment of infringement will be entered in favor of Plaintiffs on the '364 patent.

As to the '130 patent, Plaintiffs have met their burden of proving induced infringement of the '130 patent by a preponderance of the evidence as to Alkem. Plaintiffs have not met their burden of proving induced infringement of the '130 patent by a preponderance of the evidence as

[3] The parties stipulated to bifurcation of Actavis's third counterclaim to correct or delete the FDA use code for the '130 patent. [*See* ECF No. 407.] On May 9, 2016, this Court entered a Consent Order, adjourning that bifurcated hearing without date. [ECF No. 465.] On May 10, 2016, Plaintiffs filed a renewed motion to dismiss this counterclaim on the basis of mootness in light of actions taken by the FDA. [*See* ECF No. 466.] The parties have represented to the Court that they have requested clarification from the FDA on the current status of the use code. At this point, the Court will sever Actavis's counterclaim from the instant action and return it to its original docket, Case No. 15-6797.

to Actavis or Roxane. Plaintiffs have not met their burden of proving contributory infringement by a preponderance of the evidence against any of the Defendants. Defendants have not met their burden of proving by clear and convincing evidence that the '130 patent is invalid. Accordingly, judgment of infringement will be entered in favor of Plaintiffs against Alkem on the '130 patent. Judgment of noninfringement will be entered in favor of Actavis and Roxane on the '130 patent.

II. BACKGROUND

A. THE PARTIES

i. Plaintiff Grünenthal

Plaintiff Grünenthal is a corporation organized and existing under the laws of Germany. [Plaintiffs' Proposed Findings of Fact ("PFOF") ¶ 1; Pre-Trial Order ("PTO") ¶ 17.] Grünenthal owns all right, title, and interest in the patents-in-suit. [PFOF ¶ 2; PTO ¶¶ 18.]

ii. Plaintiff Depomed

Plaintiff Depomed is a California corporation. [PFOF ¶ 4; PTO ¶ 10.] Depomed is an exclusive licensee of the patents-in-suit, which it acquired from former plaintiff Janssen Pharmaceuticals, Inc. ("Janssen"). [PFOF ¶ 5; PTX-1563 at DM_0000020.] Depomed holds FDA-approved New Drug Applications ("NDA") for three formulations of NUCYNTA®—an immediate release formulation, an extended release formulation, and an oral solution—and it manufactures and markets NUCYNTA® branded products in the United States. [PFOF ¶ 8; PTO ¶¶ 11-16.]

iii. Defendant Actavis

Defendant Actavis submitted Abbreviated New Drug Application ("ANDA") Nos. 204791, 204972, and 206657 to the FDA, seeking approval to engage in the commercial manufacture, use, importation, offer for sale, and sale of generic tapentadol hydrochloride immediate release tablets, tapentadol hydrochloride extended release tablets, and 20 mg/mL

tapentadol hydrochloride oral solution, respectively. [PFOF ¶ 10; PTO ¶¶ 55, 60.] All three of Actavis's ANDAs have received tentative approval from the FDA, subject to this Court's resolution of the patent issues related to the patents-in-suit. [*See* PFOF ¶¶ 13-14.]

iv. Defendant Roxane

Defendant Roxane submitted ANDA Nos. 205057 and 206418 to the FDA, seeking approval to engage in the commercial manufacture, use, importation, offer for sale, and sale of generic tapentadol hydrochloride immediate release tablets and tapentadol hydrochloride extended release tablets, respectively. [PFOF ¶ 20; PTO ¶¶ 91, 96.] Roxane's ANDA No. 205057 for the immediate release formulation of tapentadol hydrochloride has received tentative approval from the FDA, subject to this Court's resolution of the patent issues related to the patents-in-suit. [PFOF ¶ 22.]

v. Defendant Alkem

Defendant Alkem submitted ANDA Nos. 205015 and 205016 to the FDA, seeking approval to engage in the commercial manufacture, use, importation, offer for sale, and sale of generic tapentadol hydrochloride immediate release tablets and tapentadol hydrochloride extended release tablets, respectively. [PFOF ¶ 16; PTO ¶¶ 75, 80, 81.] Alkem's ANDA No. 205015 has received tentative approval from the FDA, subject to this Court's resolution of the patent issues related to the patents-in-suit. [PFOF ¶ 18.]

B. THE PATENTS-IN-SUIT

i. The '593 patent

The '593 patent, entitled "1-PHENYL-3-DIMETHYLAMINOPROPANE COMPOUNDS WITH A PHARMACOLOGICAL EFFECTS", was issued by the United States Patent and Trademark Office ("USPTO") on April 24, 2007. [PFOF ¶ 25; PTO ¶ 23.] The '593 patent relates generally to a class of compounds and methods of using those compounds. [PTX-312.]

The '593 patent is a reissue of U.S. Patent No. 6,248,737 (the "'737 patent"), which was filed on June 6, 1995 and issued on June 19, 2001. [PFOF ¶ 28; PTO ¶ 26.] The '737 patent claims priority to German Patent Application No. 44 26 245.0, which was filed on July 23, 1994. [PFOF ¶ 29; PTO ¶ 27.]

The inventors listed on the '593 patent are Helmut Buschmann, Wolfgang Strassburger, and Elmar Friedrichs. [PTX-312.] The '593 patent was assigned to Grünenthal on July 17, 1995 and the assignment was recorded with the USPTO on August 1, 1995. [PFOF ¶ 27; PTO ¶ 25.]

ii. The '364 patent

The '364 patent, entitled "CRYSTALLINE FORMS OF (-)-(1R,2R)-3-(3-DIMETHYLAMINO-1-ETHYL-2-METHYLPROPYL)-PHENOL HCL," was issued by the USPTO on August 9, 2011. [PFOF ¶ 31; PTO ¶ 34.] The '364 patent relates generally to a crystalline form of tapentadol hydrochloride. [PTX-1458.]

The '364 patent issued from U.S. Patent App. No. 12/634,777, which was filed on December 10, 2009. [PFOF ¶ 33; PTO ¶ 37.] The '364 patent claims priority to European App. No. 04015091, which was filed on June 28, 2004. [PFOF ¶ 34; PTO ¶ 38.]

The inventors listed on the '364 patent are Andreas Fischer, Helmut Buschmann, Michael Gruss, and Dagmar Lischke. [PTX-1458.] The '364 patent was assigned to Grünenthal by the various inventors on April 13, 16, and 26, 2007 and the assignment was recorded with the USPTO on May 23, 2007. [PFOF ¶ 32; PTO ¶ 36.]

iii. The '130 patent

The '130 patent, entitled "USE OF 1 PHENYL-3-DIMETHYLAMINO-PROPANE COMPOUNDS FOR TREATING NEUROPATHIC PAIN," was issued by the USPTO on September 17, 2013. [PFOF ¶ 36; PTO ¶ 44.] The '130 patent relates generally to methods of using tapentadol hydrochloride to treat polyneuropathic pain. [PTX-485.]

The '130 patent issued from U.S. Patent App. No. 12/850,208, which was filed on August 4, 2010. [PFOF ¶ 38 PTO ¶ 47.] The '130 patent claims priority to German Patent App. No. 10 2007 012 165.4, which was filed on March 12, 2007. [PFOF ¶ 39; PTO ¶ 48.]

The inventors listed on the '130 patent are Thomas Christoph, Elmar Friedrichs, Babette-Yvonne Koegel, and Murielle Meen. [PTX-485.] The '130 patent was assigned to Grünenthal by the various inventors on September 16, 19, and 27, 2009 and the assignment was recorded with the USPTO on October 1, 2009. [PFOF ¶ 37; PTO ¶ 46.]

C. ISSUES TO BE DECIDED

Plaintiffs have asserted the following claims against Defendants:

'593 patent: Claims 8, 61, 117, and 147 [PFOF ¶ 30]

'364 patent: Claims 1, 2, 3, and 25 [PFOF ¶ 35]

'130 patent: Claims 1 and 2 (against all Defendants)

Claims 3 and 6 (against Alkem only) [PFOF ¶ 40]

Defendants have stipulated to infringement of the '593 and '364 patents. [ECF No. 400.] Defendants contend that the '593 patent is invalid, that the '364 patent is invalid and unenforceable, and that the '130 patent is not infringed and invalid.

The following issues must be decided by the Court.

i. '593 Patent – Invalidity

1. Obviousness: Defendants allege the asserted claims of the '593 patent would have been obvious to a Person of Ordinary Skill in the Art ("POSA") under 35 U.S.C. § 103.

2. Utility: Defendants allege that the asserted claims of the '593 patent lack utility under 35 U.S.C. § 101.

3. Written Description: Defendants allege that asserted claims 61, 117, and 147 of the '593 patent do not meet the written description requirement of 35 U.S.C. § 112.

4. Original Patent: Defendants allege that asserted claims 61, 117, and 147 of the '593 patent do not satisfy the original patent rule of 35 U.S.C. § 251.

5. Enablement: Defendants allege that asserted claim 8 of the '593 patent does not meet the enablement requirement of 35 U.S.C. § 112.

ii. '364 Patent – Invalidity

1. Inherent Anticipation: Defendants allege that the asserted claims of the '364 patent are inherently anticipated under 35 U.S.C. § 102.

2. Obviousness: Defendants allege that the asserted claims of the '364 patent would have been obvious to a POSA under 35 U.S.C. § 103.

3. Utility: Defendants allege that the asserted claims of the '364 patent lack utility under 35 U.S.C. § 101.

iii. '364 Patent – Unenforceability

1. Unclean Hands: Defendants allege that the '364 patent is unenforceable because the patentee acted with unclean hands during prosecution of the patent before the USPTO.

iv. '130 Patent – Infringement

1. Induced Infringement: Plaintiffs allege that Defendants will induce infringement of the asserted claims of the '130 patent under 35 U.S.C. § 271(b).

2. Contributory Infringement: Plaintiffs allege that Defendants will contribute to infringement of the asserted claims of the '130 patent under 35 U.S.C. § 271(c).

v. '130 Patent – Invalidity

1. Anticipation: Defendants allege that the asserted claims of the '130 patent are invalid as anticipated under 35 U.S.C. § 102.

2. Obviousness-type Double Patenting: Defendants allege that the asserted claims of the '130 patent are invalid under the doctrine of obviousness-type double patenting.

D. TRIAL WITNESSES

The following witnesses appeared and provided live testimony during the bench trial.

i. Plaintiffs' Fact Witnesses

1. Jack Anders

The Court heard testimony from Mr. Jack Anders, who is the Vice President of finance at Depomed. [3/9 Tr. (Anders) at 180.] Mr. Anders provided background testimony about Depomed as a company. He also testified about Depomed's purchase of the NUCYNTA® drug franchise from former Plaintiff Janssen Pharmaceuticals. Mr. Anders' testimony is relevant to the issue of irreparable harm.

2. Helmut Buschmann

The Court heard testimony from Helmut Buschmann, Ph.D. Dr. Buschmann is an inventor of the '593 patent and the '364 patent. [PTO at 293.] He is a former employee of Grünenthal, where he worked from 1992 through 2002. [3/10 Tr. (Buschmann) at 8:4-5.] While at Grünenthal, he ran a laboratory in the Synthetic Chemistry department and was later promoted to head of the department. [3/10 Tr. (Buschmann) at 8:6-9:8.] Dr. Buschmann's testimony is relevant to the issues of the validity of the '593 patent and the '364 patent.

3. Michael Gruss

The Court heard testimony from Michael Gruss, Ph.D. Dr. Gruss is an inventor of the '364 patent. [PTO at 293.] He is a former employee of Grünenthal, where he worked from 2000 through 2015. [3/10/2015 Tr. (Gruss) at 227:9-15.] While at Grünenthal, he was the head of a laboratory in the Process Development department. [3/10/2015 Tr. (Gruss) at 227:21-22.] Dr. Gruss's testimony is relevant to the issue of the validity of the '364 patent.

4. Thomas Christoph

The Court heard testimony from Thomas Christoph, Ph.D. Dr. Christoph is an inventor of the '130 patent. [PTO at 293.] He is an employee of Grünenthal, where has worked since 1996.

[3/14 a.m.[4] Tr. (Christoph) at 11:10-15.] Dr. Christoph began as the head of a laboratory in the Department of Pharmacology at Grünenthal, and was later promoted to head of the department. [3/14 a.m. Tr. (Christoph) at 11:10-20.] Dr. Christoph's testimony is relevant to the issue of the validity of the '130 patent.

5. Juergen Haeussler

The Court heard testimony from Juergen Haeussler, Ph.D. Dr. Haeussler is a scientist at Janssen. [PTO at 293.] Dr. Haeussler provided testimony regarding the FDA approval process for the NUCYNTA® products. His testimony is relevant mostly on the issue of induced and contributory infringement of the '130 patent.

ii. Plaintiffs' Expert Witnesses

1. William Roush

The Court heard expert testimony from William Roush, Ph.D. Dr. Roush's testimony is relevant to the issues of the validity and enforceability of the patents-in-suit.

2. Michael Ossipov

The Court heard expert testimony from Michael Ossipov, Ph.D. Dr. Ossipov's testimony is relevant to the issues of the validity of the '593 patent and the '130 patent.

3. Joel Bernstein

The Court heard expert testimony from Joel Bernstein, Ph.D. Dr. Bernstein's testimony is relevant to the issues of the validity and enforceability of the '364 patent.

4. Michelle Brown

The Court heard expert testimony from Michelle Brown, M.D. Dr. Brown's testimony is relevant to the issues of the infringement and validity of the '130 patent.

[4] "a.m." refers to the transcript from the morning session.

iii. Defendants' Expert Witnesses

1. Stephen Martin

The Court heard expert testimony from Stephen Martin, Ph.D. Dr. Martin's testimony is relevant to the issue of the invalidity of the '593 patent, specifically obviousness.

2. Christian Wolf

The Court heard expert testimony from Christian Wolf, Ph.D. Dr. Wolf's testimony is relevant to the issue of the invalidity of the '593 patent, specifically enablement and written description.

3. Jeffry Mogil

The Court heard expert testimony from Jeffry Mogil, Ph.D. Dr. Mogil's testimony is relevant to the issue of the invalidity of the '593 patent, specifically utility and enablement.

4. Jonathan W. Steed

The Court heard expert testimony from Jonathan W. Steed, Ph.D. Dr. Steed's testimony is relevant to the issue of the invalidity of the '364 patent, specifically inherent anticipation and obviousness.

5. Adam J. Matzger

The Court heard expert testimony from Adam J. Matzger, Ph.D. Dr. Matzger's testimony is relevant to the issue of the invalidity and unenforceability of the '364 patent, specifically utility and unclean hands.

6. Asokumar Buvanendran

The Court heard expert testimony from Asokumar Buvanendran, M.D. Dr. Buvanendran's testimony is relevant to the issues of noninfringement and invalidity of the '130 patent.

7. Michael Weinberger

The Court heard expert testimony from Michael Weinberger, M.D. Dr. Weinberger's testimony is relevant to the issues of noninfringement and invalidity of the '130 patent.

E. SCIENTIFIC PRINCIPLES

The three patents at issue involve principles of organic chemistry (specifically, stereochemistry), crystal forms of compounds (*i.e.*, polymorphism), and the treatment of different categories of pain. The following is an introduction to some of the scientific principles at issue in this litigation.

i. Stereochemistry

Stereochemistry is the branch of chemistry concerned with the three-dimensional arrangement of compounds and the effect it has on chemical reactions. "Molecules that have the same chemical substituents, but different spatial arrangements, are referred to as stereoisomers." *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1372 (Fed. Cir. 2006). Importantly, stereoisomers of a drug substance can have different biological effects. [*See* Claim Construction Opinion, ECF No. 332 at 3.]

Stereoisomers may have different physical properties, such as solubility, melting point, chromatographic mobility, and rotation of plain polarized light. [*Id.*] By convention, stereoisomers that rotate polarized light to the right are referred to as (+) or "d"; stereoisomers that rotate polarized light to the left are referred to as (–) or "l." *Sanofi-Synthelabo*, 470 F.3d at 1372 & n.1.; *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713, 720-21 (N.D. W. Va. 2004);

There are two types of stereoisomers: (1) enantiomers and (2) diastereomers. "Enantiomers are a pair of stereoisomers that are non-superimposable mirror images of each other . . . ." *Pfizer, Inc. v. Ranbaxy Labs. Ltd.*, 457 F.3d 1284, 1286 (Fed. Cir. 2006). This characteristic is "often

likened to the relative structures of a person's right and left hands." *Ortho-McNeil*, 348 F. Supp. 2d at 720. A molecule may have a maximum of one enantiomer—there is only one other molecule that can be its mirror image. Enantiomers have the same melting points as each other and they rotate plain polarized light in equal but opposite directions.

"Diastereomers," in contrast, are stereoisomers that are not mirror images of each other. [*See* Claim Construction Opinion, ECF No. 332 at 3.] Diastereomers have different physical properties such as solubility, melting point temperature, chromatographic mobility, etc. [*See id.*]

The number of diastereomers (and, by extension, the number of stereoisomers) that a molecule has is determined by the number of chiral centers in the molecule. A chiral center is a carbon atom that is bonded to four different substituent groups.

As part of stereochemistry nomenclature conventions, chemists use "R" and "S" as descriptors to convey information about the spatial arrangement of the compound. [DFOF ¶ 562; 3/17 Tr. (Wolf) at 138:8-139:17.] *See Ortho-McNeil*, 348 F. Supp. 2d at 720-21 ("Chemists also distinguish between enantiomers by designating an enantiomer as either 'R' or 'S' based upon the arrangement of certain atoms at the enantiomer's 'chiral center.' Where one enantiomer is an 'R,' the other will be an 'S.'").

ii. Polymorphs

Polymorphism is the ability of a chemical compound to crystallize in more than one crystal structure. [PFOF ¶ 142; 3/10 Tr. (Gruss) at 228:12-14.] Polymorphism occurs when there is more than one way of packing the molecules of a particular compound in a three-dimensional space. [PFOF ¶ 142; 3/15 Tr. (Steed) at 188:18-189:6.] Each crystal structure of a compound is referred to as a "polymorph."

A study of the polymorphs of a compound is referred to as a "polymorph investigation" or a "polymorph screen." A polymorph investigation involves applying various parameters to the

crystallization of a compound (*e.g.*, temperature ranges, solvents) in order to understand and characterize the solid state landscape of the compound under investigation. [PFOF ¶ 143; 3/10 Tr. (Gruss) at 228:15-21; 3/21 Tr. (Bernstein) at 214:11-215:13.] A polymorph investigation may involve the analytical techniques of X-ray Powder Diffraction ("XRPD"), X-ray Single Crystal Diffraction, Differential Scanning Calorimetry ("DSC"), thermogravimetric analysis ("TGA"), variable temperature XRPD, stage microscopy, and spectroscopic methods. [PFOF ¶ 144; 3/10 Tr. (Gruss) at 228:22-229:6; 3/15 Tr. (Steed) at 189:7-18.] While there are many techniques that may be used as part of a polymorph investigation, XRPD is considered the "gold standard" to identify the crystal form of a particular sample. [PFOF ¶ 147; 3/10 Tr. (Gruss) at 229:7-20.]

XRPD is a technique used to obtain an identification of the crystal structure of a given compound by measuring the diffraction of X-rays applied to that sample. [PFOF ¶ 145; 3/10 Tr. (Gruss) at 229:7-12; 3/21 Tr. (Bernstein) at 223:6-15.] The output from the XRPD technique is known as a "diffraction pattern." [PFOF ¶¶ 145-146; 3/10 Tr. (Gruss) at 229:7-12; 3/21 Tr. (Bernstein) at 223:6-15; 3/15 Tr. (Steed) at 190:4-11.] A diffraction pattern is characteristic of the particular crystal packing arrangement of a solid. [PFOF ¶ 146; 3/15 Tr. (Steed) at 190:4-11.] Each crystal structure (*i.e.*, each polymorph of a particular compound) has its own unique diffraction pattern. [PFOF ¶ 146; 3/15 Tr. (Steed) at 190:4-11.]

DSC is a technique in which heat is applied to a sample and a reference, and the difference in the amount of heat the samples take up is measured. [PFOF ¶ 149; 3/10 Tr. (Gruss) at 230:7-12, 241:2-17; 3/15 Tr. (Steed) at 189:14-18.] This technique can be used to detect solid phase transitions, such as melting or the transition from one polymorphic form to another. [PFOF ¶ 149; 3/10 Tr. (Gruss) at 230:7-12, 241:2-17; 3/15 Tr. (Steed) at 189:14-18.]

iii. Pain

1. Definition of "pain" and categories of pain

The word "pain" refers to a symptom, rather than an actual cause of symptoms. [PFOF ¶ 77; DTX-1667_0001; 3/14 p.m. Tr. (Brown) at 38:10-12.] The word "pain" can be defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." [PFOF ¶ 77; DTX-1667_0001; DTX-2012_0006; 3/14 p.m. Tr. (Brown) at 38:5-15.]

Pain can be characterized in a number of different ways. One way to characterize pain is by the length of time the pain lasts. "Acute pain" is pain that generally lasts between approximately three to six months, and is expected to self-limit, meaning that it will heal over time. [PFOF ¶ 78; 3/14 p.m. Tr. (Brown) at 40:1-3.] "Chronic pain" is pain that generally lasts longer than six months, and is not expected to heal. [PFOF ¶ 79; 3/14 p.m. Tr. (Brown) at 40:4-7.]

Another way to characterize pain is by the intensity of the pain. Pain can be measured in terms of grades such as mild, moderate, or severe. [PFOF ¶ 80; 3/14 p.m. Tr. (Brown) at 41:15-18.] Severe pain is the most intense type of pain. [PFOF ¶ 80; 3/14 p.m. Tr. (Brown) at 41:15-18.]

A third way to characterize pain is by the type of tissue damage causing the pain. For purposes of this litigation, the crucial distinction is between "nociceptive pain" and "neuropathic pain."

Nociceptive pain is pain that arises from actual or threatened damage to non-nerve tissue and is due to the activation of nociceptors from, for instance, a noxious stimulus. [PFOF ¶ 81; DTX-1667_0005; 3/11 Tr. (Weinberger) at 167:9-168:16; 3/14 p.m. Tr. (Brown) at 38:23-39:1.] Nociceptive pain is due to excessive stimulation of nociceptors localized in the skin, viscera, and other organs. [DTX-2012_0006.] Patients typically describe nociceptive pain as a throbbing or

aching pain. [PFOF ¶ 82; 3/14 p.m. Tr. (Brown) at 39:1-3.] Some examples of nociceptive pain include hitting a thumb with a hammer, a broken bone, or incisions made during surgery. [PFOF ¶ 82; 3/14 p.m. Tr. (Brown) at 39:1-3; 3/11 Tr. (Weinberger) at 168:6-16; 3/21 Tr. (Buvanendran) at 35:4-9.] Nociceptive pain can be either acute or chronic [PFOF ¶ 83; 3/14 p.m. Tr. (Brown) at 40:15-17] and it can be severe [PFOF ¶ 84; 3/14 p.m. Tr. (Brown) at 41:19-21].

Neuropathic pain is pain that is caused by a lesion or disease of the somatosensory nervous system, and therefore involves actual nerve tissue damage. [PFOF ¶ 85; DTX-1667_0004; 3/11 Tr. (Weinberger) at 168:17-21; 3/14 p.m. Tr. (Brown) at 39:6-9.] This is in contrast to nociceptive pain, which occurs with a normally functioning somatosensory nervous system. [DTX-1667_0005.] Neuropathic pain occurs due to a dysfunction of a nerve or group of nerves. [DTX-2012_0006.] Neuropathic pain is separate and distinct from nociceptive pain and patients describe the two differently. [PFOF ¶ 86; 3/14 p.m. Tr. (Brown) at 39:9-10; 3/11 Tr. (Weinberger) at 169:2-8.] Patients generally describe neuropathic pain as a burning, electrical, shocking, or pins and needles sensation. [PFOF ¶ 87; 3/14 p.m. Tr. (Brown) at 39:10-12; 3/11 Tr. (Weinberger) at 166:19-24.] Neuropathic pain can be severe. [PFOF ¶ 91; 3/14 p.m. Tr. (Brown) at 41:19-23; 3/21 Tr. (Buvanendran) at 41:9-11; 3/11 Tr. (Weinberger) at 186:21-23, 226:23-25.] Neuropathic pain can be, and often is, chronic because nerves and nerve tissue that are damaged do not regenerate readily. [PFOF ¶ 90; 3/14 p.m. Tr. (Brown) at 40:18-41:13; 3/21 Tr. (Buvanendran) at 41:9-11; 3/11 Tr. (Weinberger) at 226:23-227:8.] Because of this, neuropathic pain is more difficult to treat and harder to control than nociceptive pain. [PFOF ¶ 90; 3/14 p.m. Tr. (Brown) at 41:9-13.]

Within the category of neuropathic pain, mononeuropathic pain is pain that involves damage to a single nerve. [PFOF ¶ 89; 3/21 Tr. (Buvanendran) at 34:2-5.] Polyneuropathic pain is pain that involves multiple nerves. [PFOF ¶ 88 3/21 Tr. (Buvanendran) at 34:6-7.]

2. Treatment of Pain

The term "analgesia" refers to "absence of pain in response to stimulation which would normally be painful." [DTX-1667_0002.] In some contexts, the term "analgesia" has been used interchangeably with the term "antinociception" to refer to "a reduction in 'spontaneous' pain, or the pain elicited by a noxious stimulus." [DTX-2012_0006; 3/14 p.m. Tr. (Christoph) at 21:20-22:11.]

When dealing with pain, there are receptors in the body that are involved in signaling pain from the site of injury to the brain. [3/22 a.m. Tr. (Roush) at 77:13-16.] The human body has native ligands that interact with these receptors to ameliorate pain. [3/22 a.m. Tr. (Roush) at 77:18-21.]

There are many different compounds known to exhibit analgesic activity. These compounds can be categorized into classes by referring to their mechanism of analgesic action. One broad characterization is the distinction between agonists and antagonists. An agonist is a molecule that out-competes the native ligand by binding more tightly to the receptor. [3/22 a.m. Tr. (Roush) at 77:22-24.] An agonist drug "kicks the receptor into high gear, turns it on, and you get a much amplified effect, much amplified signal." [3/22 a.m. Tr. (Roush) at 77:24-78:1.] An antagonist drug, on the other hand is "the light switch to shut it off. So, an antagonist can bind, usually at the same site that it binds differently such that it shuts the whole thing off. It prevents, the antagonist prevents both the agonist and/or the native ligand from binding." [3/22 a.m. Tr. (Roush) at 78:2-7.]

One well-known group of agonists is known as the opioid agonists, which exhibit a mechanism of action generally referred to as "opioid activity" by binding to the body's opioid receptors. [*See* 3/22 a.m. Tr. (Roush) at 76:16-18.] Within the broad class of opioid agonists, there are three types—*mu*-opioid agonists, *kappa*-opioid agonists, and *delta*-opioid agonists. [3/22 a.m. Tr. (Roush) at 76:18-23, 81:3-6, 84:2-5.]

It is well-known that the opioid receptors are not the only biological target for achieving analgesia. [3/22 a.m. Tr. (Roush) at 84:12-14.] Other drugs achieve analgesia by way of reuptake antagonism. [*See* 3/22 a.m. Tr. (Roush) at 86:13-16.] One example is norepinephrine reuptake inhibitors, which antagonize norepinephrine receptors. [*See* 3/22 a.m. Tr. (Roush) at 86:13-22.] Another example is serotonin reuptake inhibitors, which antagonize serotonin receptors. [*See* 3/22 a.m. Tr. (Roush) at 97:7-10].

There are analgesics that interact with multiple receptors in the body. [*See* 3/22 a.m. Tr. (Roush) at 87:16-88:2.] These analgesic drugs are generally said to exhibit "polypharmacology." The "notion of polypharmacology really reflects the fact that we have a drug that's hitting at least two different targets that both, if you will, independently or cooperatively contribute to the analgesic property that arises from use of those compounds." [3/22 a.m. Tr. (Roush) at 87:23-88:2.] One example of a drug that exhibits polypharmacology is tramadol, which was known to possess both opioid activity (specifically, *mu*-opioid agonism) and non-opioid activity (specifically, norepinephrine reuptake inhibition and serotonin reuptake inhibition). [PFOF ¶ 93; DFOF ¶¶ 11, 15-20; DTX-866; DTX-1027; 3/16 Tr. (Martin) at 190:23-192:19, 194:25-195:13; 3/10 Tr. (Buschmann) at 89:14-18; 3/22 a.m. Tr. (Roush) 93:8-94:23, 99:2-101:11; PTX-57.]

F. BACKGROUND OF THE INVENTIONS

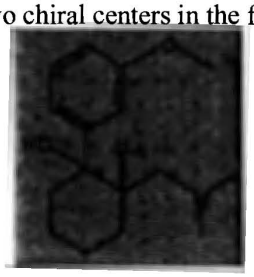
i. Invention of Tapentadol Hydrochloride

Dr. Helmut Buschmann first synthesized tapentadol hydrochloride in his lab at Grünenthal on January 26, 1994. [PFOF ¶ 118; 3/10 Tr. (Buschmann) at 26:11-27:2; PTX-345 at GRT-NUC00018944.] Dr. Buschmann's synthesis of tapentadol hydrochloride was done in the context of his work on a project at Grünenthal called the "Tramadol Successor" project. [PFOF ¶ 118; *See* 3/10 Tr. (Buschmann) at 10:7-12:7, 21:13-27:2; DTX-1027.] Therefore, the story of the invention of tapentadol hydrochloride begins with tramadol.

1. Tramadol

Grünenthal discovered tramadol in the early 1960s. [PFOF ¶ 92; 3/10 Tr. (Buschmann) at 10:4-6.] Tramadol was the first compound that Grünenthal developed successfully to market. [PFOF ¶ 92; Kogel Depo. at 111:20-22.]

As initially synthesized, tramadol was a mixture of the four possible stereoisomers resulting from variation of the two chiral centers in the following molecule:



The four stereoisomers consist of the two *threo* (or *trans*) enantiomers and the two *erythro* (or *cis*) enantiomers. [PFOF ¶ 92; DTX-2052_0002.] The *threo* enantiomers are the (*R*,*R*) and (*S*,*S*) stereoisomers and the *erythro* enantiomers are the (*R*,*S*) and (*S*,*R*) stereoisomers. [PFOF ¶ 92; DTX-2052_0002.]

As a marketed drug, tramadol is administered as a racemic mixture comprised of the two *threo* enantiomers: the (+) or (*R*,*R*) enantiomer and the (–) or (*S*,*S*) enantiomer. [PFOF ¶ 93; PTX-57 at ACT-TAP0016893.] The metabolite of each of these enantiomers, referred to as *O*-desmethyltramadol[5] ("ODMT"), also shows activity *in vitro*. [PFOF ¶ 93; DTX-691_0002.] Thus, the activity of tramadol in the body, can be viewed as the result of a mixture of four compounds—the two tramadol enantiomers and the two ODMT metabolites.

Tramadol is a complex drug that possesses both opioid and non-opioid mechanisms of action. [PFOF ¶ 92; DFOF ¶¶ 11, 15-20; DTX-866; DTX-1027.] Tramadol has three biological targets that contribute to its analgesic activity: (1) *mu*-opioid activity; (2) serotonin reuptake inhibition activity; and (3) norepinephrine reuptake inhibition activity. [PFOF ¶ 93; 3/22 a.m. Tr. (Roush) at 93:8-94:23, 99:2-101:11; 3/17 Tr. (Martin) at 65:9-24, 3/10 Tr. (Buschmann) at 9:18-10:6; PTX-57; DTX-1027.] Each of the four compounds in the tramadol mixture affects these biological targets to different degrees. [PFOF ¶ 93; DFOF ¶¶ 11, 15-20; DTX-866; DTX-1027; 3/22 a.m. Tr. (Roush) 93:8-94:23, 99:2-101:11; PTX-57.] Moreover, the enantiomers of tramadol are known to exhibit a synergistic effect *in vivo* on the patient, and both enantiomers are required for tramadol to provide its desired analgesic effect. [PFOF ¶ 93; DFOF ¶¶ 11, 15-20; DTX-866; DTX-1027; 3/22 a.m. Tr. (Roush) 93:8-94:23, 99:2-101:11; PTX-57.]

Tramadol is a relatively weak opioid, as it exhibits two to five time less potency than strong opioids. [PFOF ¶ 94; PTX-630 at GRT-NUC00183866; 3/23 Tr. (Brown at 20:19-21:2.] Tramadol also produces side effects that limit its use. [PFOF ¶ 94; DTX-1027_0006.]

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[5] The term "desmethyl" refers to a compound that has "lost the methyl group." Tramadol is a compound that has a methoxy group (also referred to as an "O-CH_3" or "O-methyl" group) on its aromatic ring. When tramadol is administered to a human, it gets metabolized by enzymes in the liver to ODMT by the removal of the methyl group from the aromatic oxygen. [*See* 3/16 Tr. (Martin) at 199:11-200:6.]

2. Tramadol Successor project at Grünenthal

Beginning in 1988, Grünenthal began focusing on discovering an analgesic by modifying the structure common to the enantiomers of tramadol. [PFOF ¶ 95; DTX-1027; 3/10 Tr. (Buschmann) at 10:7-27:2; DTX-1144_T.] In 1991, Grünenthal created a development memorandum for the "Tramadol Successor" project (the "Tramadol Successor Memorandum") that summarized the project's starting point, objectives, scientific rationale, methods, and strategies. [PFOF ¶ 96; DTX-1027.] The Tramadol Successor Memorandum contained a list of desirable characteristics for a successor drug, including: (1) being a single molecule (*i.e.*, unlike tramadol, which is a mixture of stereoisomers); (2) having good oral bioavailability; and (3) having no active metabolites (*i.e.*, unlike tramadol). [PFOF ¶ 97; DTX-1027_0008; 3/10 Tr. (Buschmann) at 12:8-13.] This list of desirable characteristics did not provide information about what the structural components of the molecule should be. [PFOF ¶ 97; 3/10 Tr. (Buschmann) at 12:8-13; 18:24-19:3.]

The Tramadol Successor Memorandum summarized the features that Grünenthal viewed as vital in a successor compound:

As shown in Fig. 3 using the example of the Tramadol molecule, opioid analgesics are characterized by 3 structural elements:

a) - an aromatic ring

b) - a tertiary nitrogen atom

c) -a partial structure holding the two first two components together in the correct configuration and at the correct distance.

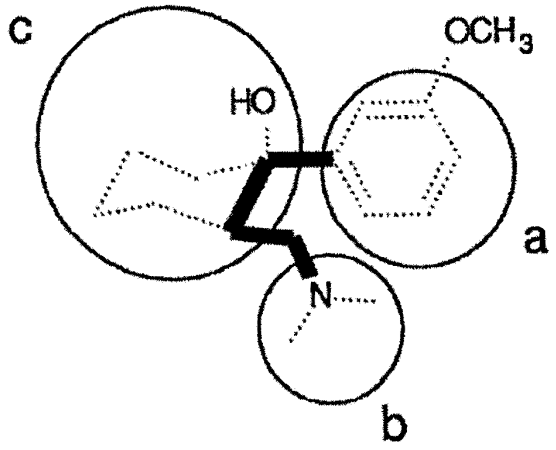


Figure 3: The basic elements for an effect on the opioid receptor on the example of the Tramadol molecule

[PFOF ¶ 99; DTX-1027_0013; 3/10 Tr. (Buschmann) at 14:21-15:4.] Grünenthal's strategy, as summarized in the Tramadol Successor Memorandum, was to "systematically vary the control structure of Tramadol," which involved many potential sources of variation, including those noted in circles a, b, and c in the figure shown above. [PFOF ¶ 100; DTX-1027_0013.]

By October 1991, Grünenthal had synthesized and tested approximately 550 new compounds as part of its Tramadol Successor project. [PFOF ¶ 101; 3/10 Tr. (Buschmann) at 11:22-12:1; DTX-1027_0013.] The following is a summary of Grünenthal's understanding of the components of tramadol:

a) With respect to circle "a" in the figure, Grünenthal viewed the aromatic ring system as important, but it contemplated that the ring system could have different substituents or could include more than one ring. [PFOF ¶ 102; DTX-1027_0013; 3/10 Tr. (Buschmann) at 15:5-18.]

b) With respect to circle "b" in the figure, Grünenthal viewed the tertiary nitrogen atom (*i.e.*, nitrogen atom fully substituted with three substituents) as important, but contemplated different substituents than those found in tramadol. [PFOF ¶ 103; DTX-1027_0013; 3/10 Tr. (Buschmann) at 15:19-16:8.]

c) With respect to circle "c" in the figure, Grünenthal considered it important to have a structure holding the first two components (the aromatic ring and the nitrogen) "together in the correct configuration and at the correct distance." [DTX-1027_0013.] It was known that a ring system restricts the conformation of the molecule to achieve this objective and allow the molecule to have optimal interaction with the targeted receptors. [PFOF ¶ 104; DTX-1027_0013; 3/10 Tr. (Buschmann) at 16:9-17:20.] Thus, the existence of a ring structure was considered important, although different size rings and substituted rings were contemplated. [PFOF ¶ 104; DTX-1027_0013; 3/10 Tr. (Buschmann) at 16:9-17:20.] Also with respect to circle "c," Grünenthal considered the hydroxyl (OH) group to be a crucial element for receptor interaction. [PFOF ¶ 105; 3/10 Tr. (Buschmann) at 17:21-18:1; DTX-1027_0013.]

Grünenthal segmented the active substances that had been synthesized as part of the Tramadol Successor project into four categories: (1) substances without opioid component; (2) substances with non-opioid effect, in addition to a weak opioid effect; (3) substances with a

balanced ratio of opioid and non-opioid component; and (4) substances with a predominant to exclusive opioid effect. [PFOF ¶ 106; 3/10 Tr. (Buschmann) at 18:2-19:3; DTX-1027_0016, DTX-1027_0028.] Grünenthal believed that "in order to minimize the opioid side effects, attention should be paid to a balanced ratio of opioid to non-opioid active components." [PFOF ¶ 106; DTX-1027_0007.] But Grünenthal scientists were unable to predict what pharmacological activity the test compounds would have (and therefore to which classification each would belong) based on the structure of the synthesized substances. [PFOF ¶ 108; 3/10 Tr. (Buschmann) at 18:2-19:3.]

As of the October 1991 Tramadol Successor Memorandum, scientists at Grünenthal did not know if it would be possible to create a new analgesic with the desired opioid and non-opioid activity, and they were pessimistic about the chances of achieving the desired characteristics in a single molecule. [PFOF ¶ 109; 3/10 Tr. (Buschmann) at 13:13-16, 19:16-22; DTX-1027_0009.] The Tramadol Successor Memorandum stated:

> The work carried out so far indicates, however, that not all the desired properties can be combined in one molecule. The search for the ideal substance must be continued, with the realistically very low prospect of success.

[DTX-1027_0031.]

3. Dr. Buschmann's work

In May 1992, Grünenthal hired Dr. Buschmann to run one of its laboratories. [PFOF ¶ 111; 3/10 Tr. (Buschmann) at 8:4-9:8.] Dr. Buschmann was provided a copy of the Tramadol Successor Memorandum and was assigned to synthesize compounds with potential analgesic activity as part of the project. [PFOF ¶ 112; 3/10 Tr. (Buschmann) at 10:7-11:5.] Dr. Buschmann's work consisted of the iterative process of synthesizing compounds, testing synthesized compounds for pharmacological activity, and using the test results to inform decisions about varying the structure

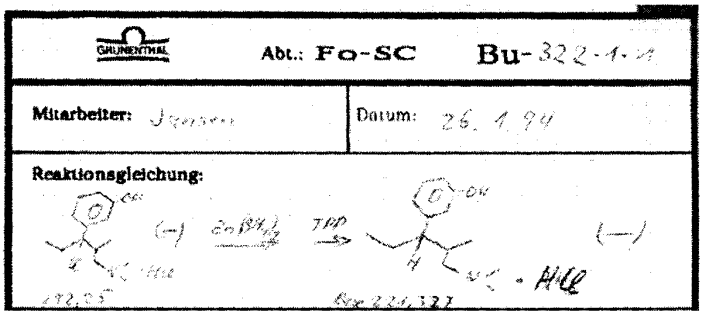
of subsequent synthesized compounds. [PFOF ¶ 113; 3/10 Tr. (Buschmann) at 23:19-24:20, 28:20-29:5.]

Consistent with the Tramadol Successor Memorandum's guidance, many of the compounds that Dr. Buschmann synthesized retained a cyclic structure. [PFOF ¶ 114; 3/10 Tr. (Buschmann) 21:13-15.] However, Dr. Buschmann also received permission to experiment with compounds that had a linear carbon chain structure. [PFOF ¶ 115; 3/10 Tr. (Buschmann) at 21:8-22:11.] Despite his receiving permission to synthesize linear compounds, many of Dr. Buschmann's colleagues, including his superiors, viewed his decision with disfavor, believing that the linear compounds would not be viable candidates for an analgesic drug because of their flexibility. [PFOF ¶ 115; 3/10 Tr. (Buschmann) at 22:1-7.] Consistent with the concerns about linear compounds, the first linear compound that Dr. Buschmann synthesized had low activity in a screening assay. [PFOF ¶ 116; 3/10 Tr. (Buschmann) at 22:17-23:18, 24:24-26:3; PTX-330 at GRT-NUC00014312.] Thus, to appease his superiors, Dr. Buschmann continued to synthesize cyclic compounds as well. [PFOF ¶ 115; 3/10 Tr. (Buschmann) at 22:8-16.]

By 1994, Grünenthal had begun to doubt whether any possible candidates for development of an analgesic drug would emerge from the Tramadol Successor project and considered stopping the project entirely. [PFOF ¶ 117; 3/10 Tr. (Buschmann) at 19:23-20:15.] At that time, Dr. Wolfgang Strassburger, the head of computational and chemical modeling at Grünenthal and an inventor on the '593 patent, opined in an internal memorandum dated January 19, 1994 that there was "no real prospect of success" for developing a tramadol successor with the desired profile. [PFOF ¶ 117; PTX-534_T; 3/10 Tr. (Buschmann) at 20:16-21:5, 80:11-24.] One week later, on January 26, 1994, Dr. Buschmann synthesized tapentadol hydrochloride. [PFOF ¶ 118; PTX-345 at GRT-NUC00018944; 3/10 Tr. (Buschmann) at 27:1-2.]

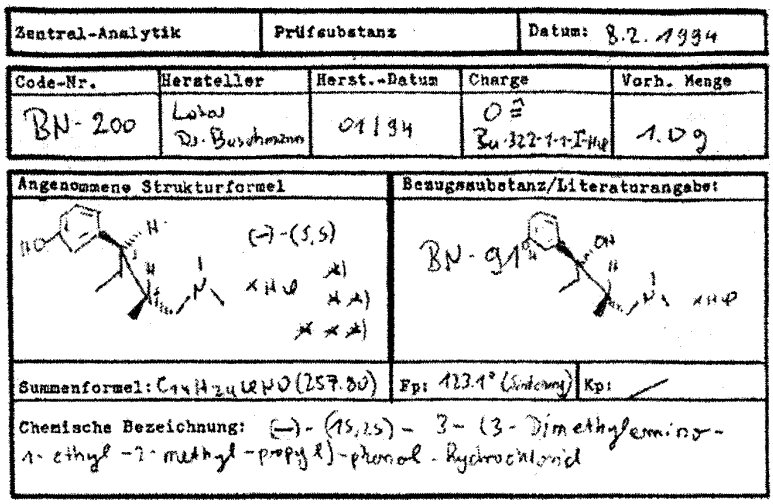
4. Dr. Buschmann's syntheses of tapentadol hydrochloride

Tapentadol hydrochloride was identified by Grünenthal as "Bu-322" because it was the 322nd compound synthesized in Dr. Buschmann's lab. [PFOF ¶ 118; 3/10 Tr. (Buschmann) at 27:6-12; PTX-345 at GRT-NUC00018944.] The first batch synthesized by Dr. Buschmann, which has been referred to as "Batch #0," was termed "Bu-322-1-1." [PFOF ¶ 118; 3/10 Tr. (Buschmann) at 27:13-19.] Dr. Buschmann's laboratory notebook from January 26, 1994 contains a description of the final step of the synthesis of Batch #0, which includes the two-dimensional structural formula (*i.e.*, without stereochemistry representations) for tapentadol hydrochloride:



[PTX-345 at GRT-NUC00018944.]

Tapentadol hydrochloride was also identified by Grünenthal as "BN-200" because it was the 200th compound sent from Dr. Buschmann's lab for pharmacological testing. [PFOF ¶ 118 3/10 Tr. (Buschmann) at 28:2-8; PTX-326 at GRT-NUC00013281.] Dr. Buschmann's laboratory notebook from February 8, 1994 depicts the three-dimensional structural formula for tapentadol hydrochloride:



Zentral-Analytik	Prüfsubstanz	Datum: 8.2.1994

Code-Nr.	Hersteller	Herst.-Datum	Charge	Vorh. Menge
BN-200	Labor Dr. Buschmann	01/94	02 Bu-322-1-1-THP	1.0 g

Angenommene Strukturformel	Bezugssubstanz/Literaturangabe:
(−)-(1S,2S)	BN-91

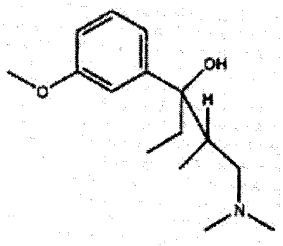
Summenformel: $C_{14}H_{24}NO$ (257.80)	Fp: 123.1° (Sintern)	Kp:

Chemische Bezeichnung: (−)-(1S,2S)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phenol-Hydrochlorid

[PTX-326 at GRT-NUC00013281.]

Dr. Buschmann's first synthesis of tapentadol hydrochloride followed a synthetic methodology using a starting material that was generated by treating a ketone with an aromatic Grignard reagent to generate a mixture of stereoisomers of a compound called Bu-41.[6] Dr. Buschmann testified that there were four steps involved in the synthesis of Batch #0:

[6] Based on the testimony regarding the naming conventions employed by Grünenthal, the Court understands that Bu-41 was the 41st compound that had been synthesized in Dr. Buschmann's laboratory. Dr. Buschmann testified that Bu-41 has the following chemical structure:



[*See* 3/10 Tr. (Buschmann) at 29:6-30:2; Buschmann Demonstrative at 3; *see also* 3/10 Tr. (Buschmann) at 27:9-16.]

1. The first step of the Batch #0 synthesis involved separating the stereoisomers of Bu-41 into (+) Bu-41 and (–) Bu-41. [PFOF ¶ 121; 3/10 Tr. (Buschmann) at 30:2-3; 3/22 p.m. Tr. (Roush) at 10:12-24.]
2. The second step of the Batch #0 synthesis involved using the (–) Bu-41 stereoisomer and cleaving the phenolic methyl ether to yield the free phenol. [PFOF ¶ 121; 3/10 Tr. (Buschmann) at 30:3-5; 3/22 p.m. Tr. (Roush) at 11:8-12, 24:10-19.]
3. The third step of the Batch #0 synthesis involved replacing the aliphatic hydroxyl (OH) group with chlorine. [PFOF ¶ 121; 3/10 Tr. (Buschmann) at 30:6-7; 3/22 p.m. Tr. (Roush) at 10:25-11:4, 24:10-19.]
4. The fourth step of the Batch #0 synthesis involved replacing the chlorine atom with a hydrogen atom. [PFOF ¶ 121; 3/10 Tr. (Buschmann) at 30:7-9; 3/22 p.m. Tr. (Roush) at 11:5-7, 24:10-19.]

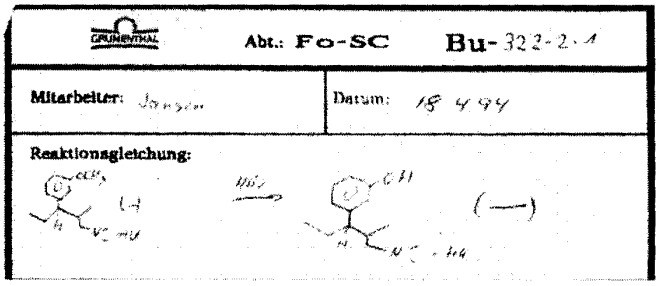
Dr. Buschmann's Batch #0 synthesis was specifically designed to retain the stereochemistry of his starting compound, (–) Bu-41 through the final product—*i.e.*, the functional groups attached to the two chiral carbons in the molecule stayed in the same relative positions from (–) Bu-41, through each intermediate step, to Bu-322. [PFOF ¶ 122; 3/10 Tr. (Buschmann) at 30:10-31:8; Buschmann Demonstrative[7] at Pages 5-7; 3/22 p.m. Tr. (Roush) at 14:8-16:10; Roush Demonstrative at Pages 46-48, 50.]

[7] Some of the citations in this Opinion include the demonstratives presented by the witnesses at trial. The demonstratives do not constitute evidence. Any demonstrative included in the citations is for convenience and informational purposes only and is to be understood in the context of the testimony given in conjunction with the demonstrative.

Dr. Buschmann sent samples of Batch #0 to Grünenthal's analytic department, which performed an independent analysis of the compound's purity, structure, and stability through a number of tests. [PFOF ¶ 123; 3/10 Tr. (Buschmann) at 31:9-37:10, 42:4-15; PTX-326 at GRT-NUC00013281-94.] After characterization, the samples were transferred to Grünenthal's pharmacological department, where they were tested *in vivo* through the mouse writhing test under the supervision of Dr. Elmar Friedrichs, who is one of the inventors of the '593 patent. [PFOF ¶ 124; 3/10 Tr. (Buschmann) at 43:3-49:11; PTX-1602 at GRT-NUC00008123-8135.]

After the initial testing of tapentadol hydrochloride showed that it had promising characteristics and it was recommended for further pharmacological testing, Dr. Buschmann resynthesized the compound in April 1994 in order to make larger amounts for additional testing.[8] [PFOF ¶ 125; 3/10 Tr. (Buschmann) at 37:11-22.] This resynthesis of the compound yielded a batch of tapentadol hydrochloride termed "Bu-322-2-1," and is commonly referred to as "Batch #1." [PFOF ¶ 125; 3/10 Tr. (Buschmann) at 37:23-38:25; PTX-345 at GRT-NUC00018952-53.] Dr. Buschmann's laboratory notebook from April 18, 1994 contains a description of the final step of the synthesis of Batch #1, which includes the two-dimensional structural formula (*i.e.*, without stereochemistry representations) for tapentadol hydrochloride:

[8] The original search for drug compounds at Grünenthal begins (as did Dr. Buschmann's original synthesis of tapentadol hydrochloride) in the Medicinal/Synthetic Chemistry department, which generally involves small amounts of material (up to around 1 gram). [PFOF ¶ 162; 3/10 Tr. (Gruss) at 255:11-20; 3/10 Tr. (Buschmann) at 76:7-77:2.] Later, scale up to amounts from 10 grams to kilograms occurs in the Chemical Development and Process Development departments. [*Id.*] When a process for producing a compound is scaled up, the original synthetic route from the Synthetic Chemistry department is often changed in order to increase chemical yields and achieve the correct quantity of material. [PFOF ¶ 163; 3/10 Tr. (Buschmann) at 77:3-13.] This was the case for tapentadol. [PFOF ¶ 163; 3/10 Tr. (Buschmann) at 77:14-16.]



[PTX-345 at GRT-NUC00018952.]

Dr. Buschmann testified that there were four steps involved in the synthesis of Batch #1:

1. The first step of the Batch #1 synthesis was identical to the first step of the Batch #0 synthesis and involved separating the stereoisomers of Bu-41 into (+) Bu-41 and (–) Bu-41. [PFOF ¶ 126; 3/10 Tr. (Buschmann) at 39:2-11, 30:2-3; 3/22 p.m. Tr. (Roush) at 10:12-24, 26:12-18.]
2. The second step of the Batch #1 synthesis involved using the (–) Bu-41 stereoisomer and replacing the aliphatic hydroxyl (OH) group with chlorine. [PFOF ¶ 126; 3/10 Tr. (Buschmann) at 39:2-11, 30:6-7; 3/22 p.m. Tr. (Roush) at 10:25-11:4, 26:12-18.]
3. The third step of the Batch #1 synthesis involved replacing the chlorine atom with a hydrogen atom. [PFOF ¶ 126; 3/10 Tr. (Buschmann) at 39:2-11, 30:7-9; 3/22 p.m. Tr. (Roush) at 11:5-7, 26:12-18.]
4. The fourth step of the Batch #1 synthesis involved cleaving the phenolic methyl ether to yield the free phenol. [PFOF ¶ 126; 3/10 Tr. (Buschmann) at 39:2-11, 30:3-5; 3/22 p.m. Tr. (Roush) at 11:8-12, 26:12-18.]

The Batch #1 synthesis contains the same steps as the Batch #0 synthesis but the order of transformations was changed. [PFOF ¶ 127; 3/10 Tr. (Buschmann) at 39:2-11; 3/22 p.m. Tr. (Roush) at 24:10-19.] The chemistries (including the retention of stereochemistry) were identical.

[PFOF ¶ 127; 3/10 Tr. (Buschmann) at 39:2-11; 3/22 p.m. Tr. (Roush) at 24:10-19.] Dr. Buschmann testified that reason for changing the order of steps was to make it easier to synthesize multigram quantities of the final product. [PFOF ¶ 127; 3/10 Tr. (Buschmann) at 39:5-41:3.]

After Dr. Buschmann synthesized Batch #1, he sent a sample to the analytical department for analysis of its purity to ensure that it would be appropriate to use it in further experiments in animals. [PFOF ¶ 129; 3/10 Tr. (Buschmann) at 41:19-43:2; DTX-1183.] Samples of Batch #1 were subsequently used for further pharmacological testing. [PFOF ¶ 129; 3/10 Tr. (Buschmann) at 43:3-45:2.]

ii. Prosecution of the '593 Patent

Beginning in late February 1994 and continuing up to and after the July 23, 1994 filing date of the original German patent application that led to the '593 patent, Grünenthal obtained isolated animal test data from the mouse writhing test[9] for tapentadol hydrochloride as well as other compounds falling within the claims of the '593 patent. [PFOF ¶ 131; 3/10 Tr. (Buschmann) at 45:8-49:11; PTX-1602 at GRT-NUC0008123-35.] Dr. Buschmann's synthesis of linear 1-phenyl-3-dimethylaminopropane compounds, as well as the work of Dr. Wolfgang Strassburger and Dr. Elmar Friedrichs to analyze and test the compounds, led to the filing of German Patent Application 44 26 245.0 and issuance of the '737 patent, which was later reissued as the '593 patent. [PFOF ¶ 132; 3/10 Tr. (Buschmann) at 62:21-63:9; Friedrichs Depo. at 131:17-20; PTX-668, PTX-303, PTX-306, PTX-312.]

[9] In the mouse writhing test, mice are injected with pheylquinone, causing them to experience nociceptive pain and writhe in an easily observable and stereotypic manner. [PFOF ¶ 338; 3/23 Tr. (Ossipov) at 118:24-121:4.] The analogous condition in humans is peritonitis, which is very painful. [PFOF ¶ 338; 3/23 Tr. (Ossipov) at 199:6-22.]

The synthesis of tapentadol hydrochloride is disclosed in Example 25 of the '593 patent. [PFOF ¶ 133; 3/22 p.m. Tr. (Roush) at 8:17-22, 10:7-11:12.] The synthesis in Example 25 (which incorporates the synthesis steps disclosed in Example 2 and Example 24) contains the same steps as Dr. Buschmann's Batch #1 synthesis. [PFOF ¶ 133; 3/22 p.m. Tr. (Roush) at 10:7-11:12, 26:12-18 3/10 Tr. (Buschmann) at 56:15-25, PTX-345 at GRT-NUC00018953; PTX-312 at 19:12-30.] The chemical structure disclosed in Example 25 of the original German application, the U.S. application, the '737 patent, and the '593 patent is the same structure drawn in Dr. Buschmann's laboratory notebook for tapentadol hydrochloride. [PFOF ¶ 134; 3/10 Tr. (Buschmann) at 57:9-12, 63:10-22, 67:2-7; 3/22 p.m. Tr. (Roush) at 9:2-10:6; PTX-303 at GRT-NUC00008515, PTX-306 at GRT-NUC00009333, PTX-345 at GRT-NUC00018953, PTX-668 at JN_NUCYNTA_0058138, PTX-312 at GRT-NUC00009605.] While Example 25 states that tapentadol hydrochloride "crystallised out" at the end of the synthesis ['593 patent at 19:19:9], the patent does not discuss the solid state crystal form of tapentadol hydrochloride.

The specifications of the German application, the '737 patent, and the '593 patent discuss mouse writhing test pharmacological investigations that Grünenthal undertook with respect to 1-phenyl-3-dimethylaminopropane compounds disclosed and claimed by the '593 patent. [PFOF ¶ 135; 3/22 p.m. Tr. (Roush) at 23:9-18; 3/23 Tr. (Ossipov) at 115:19-25; PTX-303; PTX-306; PTX-312; PTX-668.] A table is provided in the specification recording data resulting from these tests. The numerical ED_{50} values[10] or % inhibition values for certain compositions were recorded in the table. [PFOF ¶ 135; 3/22 p.m. Tr. (Roush) at 23:9-18; 3/23 Tr. (Ossipov) at 115:19-25.]

[10] An ED_{50} value refers to the effective dose at which the number of mouse writhes is inhibited by 50%. This value is derived from a statistical analysis of the dose-response curve, and at least three dosing levels are required to generate an ED_{50} value. [PFOF ¶¶ 345-346; '593 patent at 22:3-40; 3/23 Tr. (Ossipov) at 125:11-18, 128:14-17; Friedrichs Depo. at 207:1-10.]

iii. Further Development of Tapentadol Hydrochloride

After filing a patent application, Grünenthal continued to test tapentadol hydrochloride and other candidates developed through the Tramadol Successor project. [PFOF ¶ 137.] In February 1995, tapentadol hydrochloride was one of eight compounds (including both linear and cyclic compounds) that Grünenthal accepted for further development and Phase I clinical testing in humans. [PFOF ¶ 137; 3/10 Tr. (Buschmann) at 73:19-74:16; PTX-537_T at GRT-NUC00067193_T-94_T.] In March 1995, tapentadol hydrochloride was one of four (of the eight) compounds that Grünenthal selected for further development. [PFOF ¶ 138; Friedrichs Depo at 114:10-115:7, 116:9-18.] In August 1997, Grünenthal reported positive clinical results for tapentadol hydrochloride, which led to its selection as a candidate for the large-scale clinical trials that ultimately supported the marketing approval for tapentadol hydrochloride. [PFOF ¶¶ 139-140; 3/10 Tr. (Buschmann) at 74:17-76:6, 79:11-24; PTX-597_T at GRT-NUC00150198_T.]

Among other areas of development, two areas in which Grünenthal focused were (1) investigation of the crystalline forms of tapentadol hydrochloride (*i.e.*, the work that led to the '364 patent) and (2) investigation of tapentadol hydrochloride's ability to treat neuropathic pain (*i.e.*, the work that led to the '130 patent).

1. Crystalline forms of tapentadol hydrochloride

a. Establishment of solid state facilities at Grünenthal

Up until the late 1990's, Grünenthal had focused its work entirely on the synthesis of organic compounds and had hired only organic chemists to work on synthesizing organic compounds. [PFOF ¶¶ 150, 153; 3/10 Tr. (Gruss) at 230:13-231:6, 236:14-22; 3/10 Tr. (Buschmann) at 78:14-79:10.] The work leading to the '593 patent had not included any investigation of solid state crystalline forms of the compounds. [*Id.*] In the late 1990's, Dr. Buschmann began discussions with Grünenthal management about solid state and crystalline

polymorph investigations, which had never been done at Grünenthal. [PFOF ¶¶ 150-151; 3/10 Tr. (Buschmann) at 78:5-79:10; 3/10 Tr. (Gruss) at 230:13-231:6, 236:14-22, 266:11-19.]

At that time, Dr. Buschmann requested that a technician in the Analytical Chemistry department named Dagmar Lischke (an inventor of the '364 patent), perform some preliminary studies of the crystal structure of several compounds, including tapentadol hydrochloride. [PFOF ¶ 154; 3/10 Tr. (Gruss) at 231:7-15, 233:4-8.] Also at that time, Dr. Andreas Fischer (an inventor of the '364 patent) performed XRPD and single crystal diffraction analyses on a sample of tapentadol hydrochloride for Grünenthal.[11] [PFOF ¶ 156; Fischer Depo. at 63:10-12; 3/10 Tr. (Gruss) at 266:20-24.]

In May 2000, Dr. Buschmann hired Dr. Michael Gruss, the first inorganic chemist ever employed at Grünenthal, to establish solid state facilities at Grünenthal. [PFOF ¶¶ 152, 153; 3/10 Tr. (Buschmann) at 78:14-79:10; 3/10 Tr. (Gruss) at 227:11-228:10, 266:11-19.] Dr. Gruss was the first person to perform systematic solid state investigations at Grünenthal (unlike Ms. Lischke's work, which had been individual tests done by request). [PFOF ¶ 157; 3/10 Tr. (Gruss) at 230:22-231:21.] Dr. Gruss began his work at Grünenthal by investigating a handful, but not all, of the compounds under development. [PFOF ¶¶ 157-158; 3/10 Tr. (Gruss) at 231:19-232:1.] Shortly after joining Grünenthal, Dr. Gruss became involved with solid state investigations of tapentadol hydrochloride. [PFOF ¶ 159; 3/10 Tr. (Gruss) at 232:2-10.]

b. Solid state investigation of tapentadol hydrochloride

The core group of people that worked on the solid state investigation of tapentadol hydrochloride were Dr. Gruss, Dr. Buschmann, Dr. Fischer, and Ms. Lischke (the four inventors

[11] Dr. Fischer was at the time working at an external research organization called F & E Analytics, but he later joined Grünenthal in 2001. [PFOF ¶ 156; Fischer Depo. at 63:6-7; 3/10 Tr. (Gruss) at 232:17-25.]

of the '364 patent). [PFOF ¶ 160; 3/10 Tr. (Gruss) at 232:11-16.] Prior to Dr. Gruss's arrival at Grünenthal, Ms. Lischke had performed DSC and TGA studies on tapentadol hydrochloride and she suspected that five or six crystal forms of tapentadol hydrochloride existed. [PFOF ¶¶ 154-155; 3/10 Tr. (Gruss) at 231:7-15, 233:4-8, 233:24-234:3; 239:21-24.] As discussed above, before this time (*e.g.*, during the work that lead to the '593 patent) Grünenthal did not have knowledge of the crystalline polymorphic forms of tapentadol hydrochloride. [*See* PFOF ¶¶ 150, 153; 3/10 Tr. (Gruss) at 230:13-231:6, 236:14-22; 3/10 Tr. (Buschmann) at 78:14-79:10.]

After Dr. Gruss joined Grünenthal, he and Ms. Lischke collected samples of tapentadol hydrochloride from various departments at Grünenthal (which had samples produced by different synthetic methods) to study further. [PFOF ¶ 161; 3/10 Tr. (Gruss) at 234:9-12, 254:18-256:15.] Dr. Gruss and Ms. Lischke also collected new samples of tapentadol hydrochloride and obtained new solid state analytical data on the samples. [PFOF ¶ 164; 3/10 Tr. (Gruss) at 234:4-8.] In 2001, Dr. Gruss reviewed the XRPD and DSC data on the tapentadol hydrochloride samples and discovered that there were two crystal forms of tapentadol hydrochloride, Form A and Form B. [PFOF ¶¶ 165, 168; 3/10 Tr. (Gruss) at 234:13-18.]

Among the samples Dr. Gruss analyzed in 2001 was Dr. Buschmann's Batch #0, which had been synthesized in 1994. [PFOF ¶ 175; 3/10 Tr. (Gruss) at 244:9-10.] Dr. Gruss testified that the diffraction pattern for Batch #0 showed only Form B. [PFOF ¶ 175; 3/10 Tr. (Gruss) at 244:11-20.]

Grünenthal subsequently commissioned one of its employees, a technician named Marita Müeller, to attempt to resynthesize tapentadol hydrochloride following the method of Example 25 of the '737 patent. [PFOF ¶ 175; 3/10 Tr. (Gruss) at 257:10-24.] Ms. Müeller successfully synthesized tapentadol hydrochloride twice. [PFOF ¶ 394; 3/16 Tr. (Steed) at 44:19-22; 3/16 Tr.

(Matzger) at 112:11-14; 3/22 p.m. Tr. (Roush) at 29:7-23.] The diffraction patterns for both compounds produced by Ms. Müeller's syntheses showed only Form B. [PFOF ¶ 175; 3/10 Tr. (Gruss) at 259:16-260:3, 261:11-19; PTX-491.] Thus, Grünenthal concluded that the synthesis of Example 25 produces Form B of tapentadol hydrochloride. [*See id.*]

Of the other samples that Dr. Gruss had collected from different departments at Grünenthal, some of the patterns did not appear at first to match the pattern for Form A or the pattern for Form B, and Dr. Gruss considered whether there might be additional polymorphic forms. [PFOF ¶ 167; 3/10 Tr. (Gruss) at 246:3-247:5.] However, after analyzing the patterns, he determined that every sample was either Form A, Form B, or a mixture of the two forms, thus confirming that Grünenthal had only discovered the existence of two polymorphic forms. [PFOF ¶ 167; 3/10 Tr. (Gruss) at 246:3-247:5.]

From its internal investigations, Grünenthal was aware of the existence of Form A of tapentadol hydrochloride, which it concluded was the newly discovered form that had not been produced by the method of Example 25. [PFOF ¶ 173; 3/10 Tr. (Gruss) at 237:23-238:3; Fischer Depo. at 63:10-12; PTX-511_T.] Grünenthal had done some additional work investigating the forms, including determining the lattice parameters of Form B and performing single crystal structure analysis on Form A. [PFOF ¶ 173; 3/10 Tr. (Gruss) at 237:23-238:3; Fischer Depo. at 63:10-12; PTX-511_T.]

In addition to the internal solid state investigations, Dr. Gruss and Dr. Buschmann also hired an external company called SSCI to conduct systematic polymorphism investigations on tapentadol hydrochloride. [PFOF ¶ 171; 3/10 Tr. (Gruss) at 236:14-237:22.] In 2003, Grünenthal hired another external company called Crystallics to conduct further investigations on the crystallization of tapentadol hydrochloride. [PFOF ¶ 174; 3/10 Tr. (Gruss) at 238:4-14.] There

was continuous work on the investigation of the crystal forms of tapentadol hydrochloride at least until Dr. Gruss left the company in 2010. [PFOF ¶ 174; 3/10 Tr. (Gruss) at 234:4-8, 235:13-23.]

2. Treatment of neuropathic pain with tapentadol

In 1996, Grünenthal hired Dr. Thomas Christoph (an inventor of the '130 patent) to start a neuropathic pain department and perform neuropathic pain studies on tapentadol hydrochloride. [PFOF ¶ 176; 3/14 a.m. Tr. (Christoph) at 11:10-12:5.] Prior to hiring Dr. Christoph, Grünenthal lacked the capabilities to perform *in vivo* neuropathic pain modeling. [PFOF ¶ 176; 3/14 a.m. Tr. (Christoph) at 12:10-15.] Neuropathic pain studies generally involve damaging a nerve to induce hypersensitivity. [PFOF ¶ 176; 3/14 a.m. Tr. (Christoph) at 16:17-17:3.] At the time, there were a number of models available for studying neuropathic pain.

a. Mononeuropathic pain studies

Beginning in 1998, Dr. Christoph first studied tapentadol hydrochloride using the Bennett model and the Chung model, both of which are mononeuropathic pain models. [PFOF ¶¶ 177-178; 3/14 a.m. Tr. (Christoph) at 17:4-23:24; PTX-452; PTX-453.] The results of each study showed that tapentadol hydrochloride demonstrated a dose-dependent inhibition of mononeuropathic pain. [PFOF ¶¶ 177-178; 3/14 a.m. Tr. (Christoph) at 20:15-18, 23:1-10; PTX-452 at GRT-NUC44427; PTX-453 at GRT-NUC44513.]

In 2000, Dr. Christoph supervised tolerance and cross tolerance tests on tapentadol hydrochloride using the Bennett model to investigate the extent to which subjects become resistant to tapentadol hydrochloride when it is used continuously to treat mononeuropathic pain. [PFOF ¶ 179; 3/14 a.m. Tr. (Christoph) at 23:25-24:5; PTX-477).] These tests indicated that tapentadol hydrochloride inhibits neuropathic pain through a mechanism of action in addition to opiate receptor antagonism. [PFOF ¶ 179; PTX-477 at GRT-NUC00054638; 3/14 a.m. Tr. (Christoph) at 23:18-29:9.] Later experiments demonstrated that tapentadol hydrochloride possessed both a

mu-opioid and a noradrenergic (*i.e.*, norepinephrine reuptake inhibition) mechanism of action. [PFOF ¶ 180; PTX-737 at JN_NUCYNTA_0321242; 3/14 a.m. Tr. (Christoph) at 55:9-56:7.] Dr. Christoph also demonstrated that tapentadol hydrochloride lacks a serotonergic (*i.e.*, serotonin reuptake inhibition) mechanism of action. [PFOF ¶ 180; PTX-744 at JN_NUCYNTA_715982 ("Thus, the current study demonstrates contribution of μ-opioidergic and noradrenergic but not serotonergic activity of [tapentadol hydrochloride] in the spinal nerve ligation model of neuropathic pain."); 3/14 a.m. Tr. (Christoph) at 57:13-16.]

b. Polyneuropathic pain studies

After conducting mononeuropathic studies, Dr. Christoph wanted to perform polyneuropathic pain trials but his laboratory at Grünenthal lacked the capabilities. [PFOF ¶ 181; 3/14 a.m. Tr. (Christoph) at 29:20-22.] Grünenthal hired Dr. Murielle Meen (an inventor of the '130 patent) to assist Dr. Christoph in developing and implementing polyneuropathic pain models. [PFOF ¶ 181; 3/14 a.m. Tr. (Christoph) at 29:23-30:4.]

The first polyneuropathic pain model used in Dr. Christoph's lab was the streptozotocin ("STZ") model. [PFOF ¶ 182; 3/14 a.m. Tr. (Christoph) at 29:13-19; PTX-454.] Streptozotocin induces diabetes in rats, leading to diabetic polyneuropathic pain. [PFOF ¶ 182; 3/14 a.m. Tr. (Christoph) at 29:13-19, 30:15-31:25.] The evidence from the STZ experiments demonstrated that tapentadol hydrochloride was effective in treating polyneuropathic pain. [PFOF ¶ 183; 3/14 a.m. Tr. (Christoph) at 32:21-33:14; PTX-454 at GRT-NUC44807.] Because pain wiring in rats is similar to that of humans, based on the *in vivo* evidence from the STZ model in rats, Dr. Christoph expected that tapentadol hydrochloride would be effective for treating polyneuropathic pain in humans. [PFOF ¶ 184; PTX-454 at GRT-NUC00044810; 3/14 a.m. Tr. (Christoph) at 33:15-34:4, 17:9-23.] Subsequent to the STZ model, Dr. Christoph obtained additional evidence supporting

the ability of tapentadol hydrochloride to treat polyneuropathic pain by using the vincristine model. [PFOF ¶ 185; PTX-455 at GRT-NUC44840; 3/14 a.m. Tr. (Christoph) at 34:8-35:1, 35:18-24.]

G. THE PRODUCTS AT ISSUE

i. Plaintiffs' NUCYNTA® products

1. NUCYNTA® IR

On January 22, 2008, Janssen submitted NDA No. 22304 to the FDA for approval of NUCYNTA® IR (50, 75, 100 mg) immediate release tablets. [PFOF ¶ 41; PTX-829 at JN_NUCYNTA_1634456.] At the time, Janssen also submitted a clinical overview to health authorities, including the FDA, in support of its efforts to gain approval for NUCYNTA® IR. [PFOF ¶ 42; PTX-1555; 3/11 Tr. (Haeussler) at 109:14-110:2.] Janssen's submission demonstrated the efficacy of tapentadol hydrochloride through pain studies of bunionectomies and end-stage degenerative joint disease. [PFOF ¶ 43; PTX-1555 at JN_NUCYNTA_0319295-97.] Preclinical and clinical testing demonstrated that tapentadol hydrochloride, due to its dual mechanisms of action, provided the benefit of delivering pain relief similar to opioids but with an improved tolerability profile and reduced side effects. [PFOF ¶ 44; 3/11 Tr. (Haeussler) at 110:3-113:5; PTX-1555 at JN_NUCYNTA_0319284-85.] On November 20, 2008, the FDA approved NDA No. 22304 for NUCYNTA® IR (50, 75, 100 mg). [PFOF ¶ 45; PTX-829 at JN_NUCYNTA_1634456.] NUCYNTA® IR is indicated for "the management of moderate to severe acute pain in adults." [PFOF ¶ 47; PTX-829 at JN_NUCYNTA_1634456.]

2. NUCYNTA® Oral Solution

On December 15, 2011, Janssen submitted NDA No. 203794 to the FDA for approval of NUCYNTA® oral solution (20 mg/mL). [PFOF ¶ 48; PTX-829 at JN_NUCYNTA_1634456.] On October 15, 2012, the FDA approved NDA No. 203794. [PFOF ¶ 49; PTX-829 at JN_NUCYNTA_1634456.] The NUCYNTA® oral solution (20 mg/mL) is indicated for "the

management of moderate to severe acute pain in adults." [PFOF ¶ 50; PTX-829 at JN_NUCYNTA_1634456.]

3. NUCYNTA® ER

a. Original NUCYNTA® ER label with one indication

On November 30, 2009, Janssen submitted NDA No. 200533 to the FDA for approval of NUCYNTA® ER (50, 100, 150, 200, 250 mg) extended release tablets. [PFOF ¶ 51; PTX-829 at JN_NUCYNTA_1634457.] At the time, Janssen also submitted a clinical overview to health authorities, including the FDA, in support of its efforts to gain approval for NUCYNTA® ER. [PFOF ¶ 52; PTX-1551; 3/11 Tr. (Haeussler) at 113:6-22.]

Prior to submitting its NDA for NUCYNTA® ER, Janssen met with the FDA to discuss the specific data requirements that the FDA would need to make a decision on approval. [PFOF ¶ 53; 3/11 Tr. (Haeussler) at 113:23-114:9.] Dr. Haeussler testified that Janssen expressed interest at that time in obtaining approval for two indications—one indication for the management of chronic moderate to severe pain ("Indication 1") and a second indication for diabetic peripheral neuropathic pain ("Indication 2"). [PFOF ¶ 53; 3/11 Tr. (Haeussler) at 114:10-15.] The FDA explained that, in order for Janssen to obtain approval for Indication 1, Janssen would need to provide evidence of two positive, clinically relevant studies of different pain conditions. [PFOF ¶ 54; 3/11 Tr. (Haeussler) at 116:12-117:19.] The FDA stated that one of the two studies could be a study on pain associated with diabetic peripheral neuropathy ("DPN"). [PFOF ¶ 54; 3/11 Tr. (Haeussler) at 116:22-117:1.]

Janssen then inquired what the FDA would require in order to approve Indication 2. [3/11 Tr. (Haeussler) at 117:2-7.] The FDA responded "that like for any specific indication, they required replicative evidence which means that two positive studies are required in the same condition specifically to get that specific indication label." [3/11 Tr. (Haeussler) at 117:2-7.]

Janssen's November 2009 submission to FDA sought approval for only Indication 1 (*i.e.*, treatment of moderate to severe chronic pain). [*See* PTX-829 at JN_NUCYNTA_1634457.] Janssen supported its claims of efficacy for Indication 1 with studies of three pain conditions—(1) chronic lower back pain ("CLBP"), (2) chronic painful osteoarthritis ("OA"), and (3) DPN.[12] [PFOF ¶ 55; 3/11 Tr. (Haeussler) at 117:8-19; PTX-1551 at JN_NUCYNTA_0074680.] Dr. Haeussler testified that Janssen selected these three chronic pain conditions based on FDA guidance and because they are three of the most common chronic pain conditions that present with pain severe enough to warrant opioid therapy. [PFOF ¶ 56; DFOF ¶ 2536; 3/11 Tr. (Haeussler) at 118:14-24; PTX-1551 at JN_NUCYNTA_0074683.]

On August 25, 2011, the FDA approved NDA No. 200533 for NUCYNTA® ER (50, 100, 150, 200, 250 mg). [PFOF ¶ 60; PTX-829 at JN_NUCYNTA_1634457.] From this FDA approval, Janssen obtained permission to market its NUCYNTA® ER product for Indication 1. [PFOF ¶ 61; PTX-1499 at JN_NUCYNTA_0273432.] Specifically, the approved label stated:

> NUCYNTA® ER is an opioid analgesic indicated for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

[DFOF ¶ 2514; PTX-1499 at JN_NUCYNTA_0273432.]

In approving the label, the FDA found only the CLBP and DPN studies (but not the OA study) to be positive and sufficient for inclusion in the NUCYNTA® ER label. [PFOF ¶¶ 61-62; PTX-1499 at JN_NUCYNTA_0273457-59; 3/11 Tr. (Haeussler) at 121:17-122:16.] Accordingly, the label contained summaries of these two clinical studies demonstrating the efficacy of

[12] The DPN study in Janssen's submission to show the efficacy of NUCYNTA® ER for Indication 1 was identified as PAI-3015/KF36. [PFOF ¶ 59; 3/11 Tr. (Hauessler) at 118:25-119:25; PTX-727; PTX-1551 at JN_NUCYNTA_0074680.]

NUCYNTA® ER for the treatment of moderate to severe chronic pain. [DFOF ¶ 2515; PTX-1499 at JN_NUCYNTA_0273457-59.]

b. Current NUCYNTA® ER label with two indications

On October 28, 2011, Janssen submitted a supplemental NDA to the FDA seeking approval of an additional indication for NUCYNTA® ER. [PFOF ¶ 65; PTX-829 at JN_NUCYNTA_1634457.] Specifically, Janssen sought approval of Indication 2 for the treatment of neuropathic pain associated with DPN. [PFOF ¶ 65; PTX-829 at JN_NUCYNTA_1634457.] To obtain approval for Indication 2, Janssen successfully conducted a second DPN study[13] that was virtually the same as the first DPN study Janssen had submitted in support of Indication 1. [PFOF ¶ 67; 3/11 Tr. (Haeussler) at 127:24-128:18.] On August 28, 2012, the FDA approved Janssen's supplemental NDA, giving Janssen permission to market NUCYNTA® ER for Indication 2. [PFOF ¶ 68; PTX-829 at JN_NUCYNTA_1634457.] Specifically, the new approved label stated:

> NUCYNTA® ER is an opioid agonist indicated for the management of:
>
> - moderate to severe chronic pain in adults
> - neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults
>
> when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

[13] This second DPN study was identified as PAI-3027/KF56. [PTX-732.]

[PFOF ¶ 69; PTX-695; 3/11 Tr. (Haeussler) at 128:19-129:17.] The new approved label identified and described the CLBP and DPN studies from the original label as well as the second DPN study.[14] [PFOF ¶ 70; PTX-695 at JN_NUCYNTA_0064256-58.]

The wording of the two indications was later updated in 2014 as part of the FDA's efforts to harmonize opioid-related labels. [PFOF ¶ 71 3/11 Tr. (Haeussler) at 129:18-130:1.] Accordingly, the current approved label for NUCYNTA® ER states:

> NUCYNTA® ER is an opioid agonist indicated for the management of:
>
> - pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
>
> - neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

[PFOF ¶ 75; PTX-1383; PTX-829 at JN_NUCYNTA_1634457.]

ii. Defendants' tapentadol hydrochloride products

1. Actavis

a. Actavis's tapentadol hydrochloride immediate release tablets

Actavis submitted ANDA No. 204971 to the FDA under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), seeking FDA approval to engage in the commercial manufacture, use, importation, offer for sale, and sale of generic 50 mg, 75 mg and 100 mg tapentadol hydrochloride tablets. [PTO ¶ 55.] ANDA No. 204971 contains certifications pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV),[15] alleging that the claims of the '593 and '364

[14] In the label, the two DPN studies were referred to as "DPN-1" and "DPN-2." [PTX-695 at JN_NUCYNTA_0064257-58.]

[15] This certification is referred to as a "Paragraph IV certification."

patents are "invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, importation, offer for sale, or sale" of the proposed drug products that are the subject of Actavis' ANDA" No. 204971. [PTO ¶ 56.] On or about August 1, 2013, Janssen and Grünenthal received a letter dated July 30, 2013 constituting the notice of ANDA No. 204971, including the Paragraph IV certification(s), required by 21 U.S.C. § 355(j)(2)(B)(i)-(ii). [PTO ¶ 57.] Actavis was aware of the '593 and '364 patents at the time it submitted ANDA No. 204971 to the FDA. [PTO ¶ 58.] On August 14, 2013, under the provisions of the Hatch-Waxman Act, Janssen and Grünenthal timely amended their Complaint for infringement of the '593 and '364 patents to include ANDA No. 204971. [*See* Case No. 13-4507, ECF No. 12.]

Actavis's proposed generic NUCYNTA® IR product that is the subject of ANDA No. 204971 contains tapentadol hydrochloride. [PTO ¶ 103.] That product contains crystalline Form A of tapentadol hydrochloride. [PTO ¶ 104.]

b. Actavis's tapentadol hydrochloride oral solution

Watson Laboratories ("Watson") submitted ANDA No. 206657 to the FDA under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), seeking FDA approval to engage in the commercial manufacture, use, importation, offer for sale, and sale of a generic tapentadol oral solution of 20 mg/mL. [PTO ¶ 69.] On March 9, 2015, Watson notified the Court that Watson had changed its name to Actavis Laboratories UT, Inc. [PTO ¶ 70; Case No. 2:14-cv-04617-CCC-MF, ECF No. 64.] Actavis's ANDA No. 206657 contains a Paragraph IV certification alleging that the '593 and '364 patents "are invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, importation, offer for sale or sale of the" ANDA No. 206657 Product. [PTO ¶ 71.] From on or about June 12, 2014 to on or about June 24, Janssen and Grünenthal received letters constituting notice of ANDA No. 206657, including the Paragraph IV certification, required by 21 U.S.C. § 355(j)(2)(B)(i)-(ii). [PTO ¶ 72.] Actavis was aware of

the '593 and '364 patents when ANDA 206657 was submitted to the FDA. [PTO ¶ 73.] Under the provisions of the Hatch-Waxman Act, Janssen and Grünenthal timely commenced litigation against Watson, now Actavis UT, on July 23, 2014. [PTO ¶ 74; Case No. 14-4617, ECF No. 1.]

The proposed generic NUCYNTA® oral solution product that is the subject of ANDA No. 206657 contains tapentadol hydrochloride. [PTO ¶ 105.] Actavis uses and has used crystalline Form A of tapentadol hydrochloride to manufacture its proposed generic NUCYNTA® oral solution product that is the subject of ANDA No. 206657. [PTO ¶ 106.]

c. Actavis's tapentadol hydrochloride extended release tablets

Actavis submitted ANDA No. 204972 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), seeking FDA approval to engage in the commercial manufacture, use, importation, offer for sale, and sale of generic 50 mg, 100 mg, 150 mg, 200 mg and 250 mg tapentadol hydrochloride extended release tablets. [PTO ¶ 60.] Actavis's ANDA No. 204972 contains Paragraph IV certifications alleging that the '593 and '364 patents are "invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, importation, offer for sale, or sale of the proposed drug products that are the subject of Actavis' ANDA" No. 204972. [PTO ¶ 61.] On or about June 13, 2013, Janssen and Grünenthal received a letter dated June 12, 2013 constituting the notice of ANDA No. 204972, including the Paragraph IV certifications to the '593 and '364 patents, required by 21 U.S.C. § 355(j)(2)(B)(i)-(ii). [PTO ¶ 62.] Actavis was aware of the '593 and '364 patents at the time it submitted ANDA No. 204972 to the FDA. [PTO ¶ 63.] Under the provisions of the Hatch-Waxman Act, Janssen and Grünenthal timely commenced litigation against Actavis on July 25, 2013. [PTO ¶ 64; Case No. 13-4507, ECF No. 1.]

Actavis has been aware of the existence of the '130 patent since at least September 17, 2013. [PTO ¶ 63.] Actavis's ANDA No. 204972 does not contain a Paragraph IV

certification as to the '130 patent. [PTO ¶ 64.] Rather, it contains a statement pursuant to 21 U.S.C. § 355(j)(2)(A)(viii)[16] stating that "its proposed labelling for Tapentadol Extended-Release Tablets, 50 mg, 100 mg, 150 mg, 200 mg and 250 mg does not contain any indications covered by" the '130 patent. [PTO ¶ 64.] Actavis filed the Section viii statement on or about March 15, 2015. [PTO ¶ 65.] Actavis's Section viii statement and proposed label submitted therewith, "carved out" Indication 2 from its proposed ANDA No. 204972 products. [PTO ¶ 66.] Indication 1 remains in Actavis's proposed label for its proposed ANDA No. 204972 products. [PTO ¶ 66.] Depomed and Grünenthal commenced litigation against Actavis concerning the '130 patent on September 11, 2015. [PTO ¶ 67; Case No. 15-6797, ECF No. 1.] Although Actavis moved to dismiss the Complaint, the Court allowed Plaintiffs' claim for declaratory judgment of induced infringement and contributory infringement to proceed to trial. [Case No. 15-6797, ECF No. 55.]

Actavis's proposed generic NUCYNTA® ER product that is the subject of ANDA No. 204972 contains tapentadol hydrochloride. [PTO ¶ 103.] That product contains crystalline Form A of tapentadol hydrochloride. [PTO ¶ 104.]

Actavis's proposed label has only one indication. The label states:

> Tapendadol extended-release is an opioid agonist indicated for the management of:
>
> - Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

[DFOF ¶ 2558; DTX-1653_0124; 3/11 Tr. (Weinberger) at 183:11-16.] In addition to carving out Indication 2 from its proposed label, Actavis has carved out all other references to neuropathic

[16] This statement is referred to as a "Section viii statement."

pain or neuropathy that are contained in the NUCYNTA® ER label. [DFOF ¶ 2559; DTX-1653.] Thus, Actavis's proposed label does not contain the words "neuropathic pain," "neuropathy," "polyneuropathic pain," or "polyneuropathy." [DFOF ¶ 2560; 3/11 Tr. (Weinberger) at 186:4-14; 3/14 p.m. Tr. (Brown) at 112:12-21.] Actavis's proposed label does not contain information about either the DPN-1 or the DPN-2 clinical trials. [DFOF ¶ 2561; DTX-1653.] The only clinical trial summary in Actavis's proposed label is that of the CLBP study. [*Id.*]

2. Roxane

a. Roxane's tapentadol hydrochloride immediate release tablets

Roxane submitted ANDA No. 205057 to the FDA under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), seeking FDA approval to engage in the commercial manufacture, use, importation, offer for sale, and sale of generic 50 mg, 75 mg, and 100 mg tapentadol hydrochloride tablets. [PTO ¶ 91.] Roxane's ANDA No. 205057 contains a Paragraph IV certification alleging that the '593 and '364 patents are "invalid, not infringed, and/or unenforceable." [PTO ¶ 92.] From on or about October 8, 2013 to on or about October 21, 2013, Janssen and Grünenthal each received a letter dated October 3, 2013 constituting notice of ANDA No. 205057, including the Paragraph IV certification, required by 21 U.S.C. § 355(j)(2)(B)(i)-(ii). [PTO ¶ 93.] Roxane was aware of the '593 and '364 patents at the time it submitted ANDA No. 205057 to the FDA. [PTO ¶ 94.] Under the provisions of the Hatch-Waxman Act, Janssen and Grünenthal timely commenced litigation against Roxane on November 14, 2013. [PTO ¶ 91; Case No. 13-6929, ECF No. 1.]

Roxane's proposed generic NUCYNTA® IR product that is the subject of ANDA No. 205057 contains tapentadol hydrochloride. [PTO ¶ 107.] That product contains crystalline Form A of tapentadol hydrochloride. [PTO ¶ 108.]

b. Roxane's tapentadol hydrochloride extended release tablets

Roxane submitted ANDA No. 206418 to the FDA under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), seeking FDA approval to engage in the commercial manufacture, use, importation, offer for sale, and sale of generic 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg tapentadol hydrochloride extended release tablets. [PTO ¶ 96.] Roxane's ANDA No. 206418 contained a Paragraph IV certification alleging that the '593, '364, and '130 patents "are invalid, are not infringed, and/or are unenforceable." [PTO ¶ 97.] From on or about May 9, 2014 to on or about May 14, 2014, Janssen and Grünenthal each received a letter dated May 8, 2014 constituting notice of ANDA No. 206418, including the Paragraph IV certification, required by 21 U.S.C. § 355(j)(2)(B)(i)-(ii). [PTO ¶ 98.] Roxane was aware of the '593, '364, and '130 patents at the time it submitted ANDA No. 206418 to the FDA. [PTO ¶ 99.] Under the provisions of the Hatch-Waxman Act, Janssen and Grünenthal timely commenced litigation against Roxane on June 19, 2014 [PTO ¶ 100; Case No. 14-3941, ECF No. 1.]

Roxane's proposed generic NUCYNTA® ER product that is the subject of ANDA No. 206418 contains tapentadol hydrochloride. [PTO ¶ 107.] That product contains crystalline Form A of tapentadol hydrochloride. [PTO ¶ 108.]

Roxane's original proposed label for its ANDA product included the same two indications for which NUCYNTA® ER is currently approved, although with the outdated wording prior to the FDA regulations harmonizing opioid labels. [DFOF ¶ 2548; 3/21 Tr. (Buvanendran) at 37:25-38:8.] As filed, Roxane's proposed label stated:

> Tapentadol Extended-Release Tablets are an opioid agonist indicated for the management of:
>
> - moderate to severe chronic pain in adults
> - neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults

> when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

[DFOF ¶ 2547; DTX-1589.]

On April 17, 2015, Roxane amended its ANDA No. 206418 by converting its Paragraph IV certification as to the '130 patent into a Section viii statement, stating that "the labeling for the drug product for which [Roxane] is seeking approval does not include the indication that is covered by" the '130 patent. [PTO ¶ 101; DFOF ¶¶ 2549-2551; PTX-922.] Roxane's Section viii statement, and proposed label submitted therewith, "carved out" Indication 2 as well as all other references to neuropathic pain from its proposed label. [PTO ¶ 102; DFOF ¶ 2549; DTX-2020; DTX-1566; DTX-1568.] Indication 1 remains in Roxane's proposed label. [PTO ¶ 102; DFOF ¶ 2550; DTX-1566.]

Roxane's proposed label does not contain information about either the DPN-1 or the DPN-2 clinical trials. [DFOF ¶ 2553; DTX-1566.] The only clinical trial summary in Roxane's proposed label is that of the CLBP study. [*Id.*] Furthermore, Roxane's proposed label does not contain the words "neuoropathic pain" or "neuropathy," other than the following language:

> *Information describing the use of Tapentadol Extended Release Tablets in patients with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy is approved for Janssen Pharmaceuticals, Inc. However, due to Janssen Pharmaceuticals, Inc.'s marketing exclusivity rights, this drug is not labeled with that information.*

[DFOF ¶¶ 2552, 2554; DTX-1566.]

3. Alkem

a. Alkem's tapentadol hydrochloride immediate release tablets

Alkem submitted ANDA No. 205015 to the FDA under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), seeking FDA approval to engage in the commercial manufacture, use, importation, offer for sale, and sale of generic 50 mg, 75 mg and 100 mg

tapentadol hydrochloride tablets. [PTO ¶ 75.] ANDA No. 205015 contains Paragraph IV certification(s) alleging that the claims of the '593 and '364 patents are "invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of the drug product described by Alkem's ANDA" No. 205015. [PTO ¶ 76.] On or about June 20, 2013, Janssen and Grünenthal received a letter dated June 19, 2013 constituting the notice of ANDA No. 205015, including the Paragraph IV certification(s), required by 21 U.S.C. § 355(j)(2)(B)(i)-(ii). [PTO ¶ 77.] Alkem was aware of the '593 and '364 patents at the time it submitted ANDA No. 205015 to the FDA. [PTO ¶ 78.] Under the provisions of the Hatch-Waxman Act, Janssen and Grünenthal timely commenced litigation against Alkem on July 25, 2013. [PTO ¶ 79; ECF No. 1.]

Alkem's proposed generic NUCYNTA® IR product that is the subject of ANDA No. 205015 contains tapentadol hydrochloride. [PTO ¶ 109.] That product contains crystalline Form A of tapentadol hydrochloride. [PTO ¶ 110.]

b. Alkem's tapentadol hydrochloride extended release tablets

Alkem submitted ANDA No. 205016 to the FDA under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), seeking FDA approval to engage in the commercial manufacture, use, importation, offer for sale, or sale of at least generic 100 mg, 200 mg and 250 mg tapentadol hydrochloride extended release tablets. [PTO ¶ 80.] Alkem's ANDA No. 205016 was amended to further seek FDA approval to engage in the commercial manufacture, use, importation, offer for sale, or sale of generic 50 mg and 150 mg tapentadol hydrochloride extended release tablets. [PTO ¶ 81.] ANDA No. 205016 contains Paragraph IV certification(s) that the patents-in-suit are "invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of the drug product described by Alkem's ANDA" No. 205016. [PTO ¶ 82.] On or about July 1, 2013, Janssen and Grünenthal received a letter dated June 28, 2013 constituting the notice of ANDA No. 205016, including the Paragraph IV certifications to the '593

and '364 patents, required by 21 U.S.C. § 355(j)(2)(B)(i)-(ii). [PTO ¶ 83.] Under the provisions of the Hatch-Waxman Act, Janssen and Grünenthal timely commenced litigation against Alkem on the '593 and '364 patents on July 25, 2013. [PTO ¶ 84; Case No. 13-4507, ECF No. 1.] On or about November 14, 2013, Janssen and Grünenthal received a letter dated November 13, 2013 constituting the notice of Alkem's amendment of ANDA No. 205016, including the Paragraph IV certification to the '130 patent, required by 21 U.S.C. § 355(j)(2)(B)(i)-(ii). [PTO ¶ 85.] Under the provisions of the Hatch-Waxman Act, Janssen and Grünenthal timely commenced litigation against Alkem on the '130 patent on December 23, 2013. [PTO ¶ 86; Case No. 13-7803, ECF No. 1.] On or about July 8, 2014 and July 9, 2014 Janssen and Grünenthal each received a letter dated July 7, 2014, constituting the notice of Alkem's amendment of ANDA No. 205016, including the Paragraph IV certifications, required by 21 U.S.C. § 355(j)(2)(B)(i)-(ii). [PTO ¶ 87.] Under the provisions of the Hatch-Waxman Act, Janssen and Grünenthal timely amended their complaints against Alkem on August 20, 2014. [PTO ¶¶ 88-89; Case No. 13-7803, ECF No. 57; Case No. 13-4507, ECF No. 146.] Alkem was aware of the '593 and '364 patents at the time it submitted ANDA No. 205016 to the FDA. Alkem was aware of the '130 patent at the time it submitted its amendment to ANDA No. 205016 identified in its November 13, 2013 notice letter to the FDA. [PTO ¶ 90.]

Alkem's proposed generic NUCYNTA® ER product that is the subject of ANDA No. 205016 contains tapentadol hydrochloride. [PTO ¶ 109.] That product contains crystalline Form A of tapentadol hydrochloride. [PTO ¶ 110.] Alkem's proposed label for its ANDA product contains the same two indications as NUCYNTA® ER:

> Tapentadol extended release tablets are opioid agonist indicated for the management of:

- pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

- neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

[PTX-225.] Alkem's label also contains information about the same clinical studies as the NUCYNTA® ER label. [*Id.*]

III. LEGAL STANDARDS

A. INFRINGEMENT

Under the Patent Act:

> [W]hoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent.

35 U.S.C. § 271(a). The statute also prohibits a person from indirectly infringing a patent. *See* 35 U.S.C. § 271(b)-(c). The two types of indirect infringement are induced infringement, *see* 35 U.S.C. § 271(b), and contributory infringement, *see* 35 U.S.C. § 271(c). "The patentee bears the burden of proving infringement by a preponderance of the evidence." *SRI Int'l v. Matsushita Elec. Corp.*, 775 F.2d 1107, 1123 (Fed. Cir. 1985)

i. Induced Infringement

Under 35 U.S.C. § 271(b), "[w]hoever actively induces infringement of a patent shall be liable as an infringer." A threshold question in the inducement analysis is whether there is evidence of direct infringement by another. *Limelight Networks, Inc. v. Akamai Techs., Inc.*, 134 S. Ct. 2111, 2117 (2014) ("[W]here there has been no direct infringement, there can be no inducement of infringement under § 271(b)."); *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1056 (Fed. Cir. 2010). Once it is determined that there is evidence of direct infringement by

another, the Court must determine whether the defendant has the requisite specific intent to encourage that direct infringement. *AstraZeneca*, 633 F.3d at 1056.

To establish induced infringement, a patent holder must demonstrate that the infringer "'knowingly induced infringement and possessed specific intent to encourage another's [direct] infringement.'" *Id.* (quoting *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006)). The Federal Circuit has stated that circumstantial evidence can be sufficient to support a finding of specific intent. *Id.* at 1060.

In 2015, the Federal Circuit provided the following summary of the law of inducement:

> Infringement only exists where there is evidence that goes beyond a product's characteristics or the knowledge that it may be put to infringing uses. Inducement can be found where there is [e]vidence of active steps taken to encourage direct infringement, which can in turn be found in advertising an infringing use or instructing how to engage in an infringing use. But such instructions need to evidence intent to *encourage* infringement. The question is not just whether instructions describ[e] the infringing mode, but whether the instructions teach an infringing use of the device *such that* we are willing to infer from those instructions an affirmative intent to infringe the patent. Merely describ[ing] an infringing mode is not the same as recommend[ing], encourag[ing], or promot[ing] an infringing use, or suggesting that an infringing use should be performed.

Takeda Pharm. U.S.A., Inc. v. West-Ward Pharm. Corp., 785 F.3d 625, 630-31 (Fed. Cir. 2015) (citations, footnote, and internal quotation marks omitted). The *Takeda* court went on to discuss the applicability of these principles "in the Hatch-Waxman context where, as here, it is alleged that the drug label induces infringement by physicians." *Id.* at 631. The *Takeda* court stated:

> The label must encourage, recommend, or promote infringement. The mere existence of direct infringement by physicians, while necessary to find liability for induced infringement, is not sufficient for inducement. As we stated in [a prior case] in the ANDA context, it is well-established that mere knowledge of possible infringement by others does not amount to inducement; specific intent and action to induce must be proven.

Id. (internal citations and quotation marks omitted).

ii. Contributory Infringement

Under 35 U.S.C. § 271(c),

> Whoever offers to sell or sells within the United States or imports into the United States a component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use, shall be liable as a contributory infringer.

Contributory infringement is found where: (1) there is direct infringement; (2) the accused infringer had knowledge of the patent at issue; (3) the product has no substantial non-infringing uses; and (4) the product is a material part of the invention. *Fujitsu Ltd. v. Netyear Inc.*, 620 F.3d 1321, 1326 (Fed. Cir. 2010).

Once a patentee has made out a *prima facie* showing that a product is not "suitable for substantial non-infringing use," the burden then shifts to the accused infringer to demonstrate otherwise. *Golden Blount, Inc. v. Robert H. Peterson Co.*, 438 F.3d 1354, 1363 (Fed. Cir. 2006). A non-infringing use is "substantial" if it is "not unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental." *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1327 (Fed. Cir. 2009). The inquiry is "essentially a quantitative one"—"substantial non-infringing use can be shown when 'a significant number of [uses] would be non-infringing.'" *Pickholtz v. Rainbow Techs., Inc.*, 260 F. Supp. 2d 980, 989 (N.D. Cal. 2003) (quoting *Sony Corp. of Am. V. Universal Studios*, 464 US 417, 443 (1984)).

B. INVALIDITY

Issued patents are presumed valid. *See* 35 U.S.C. § 282. To rebut this presumption, Defendants bear the burden of proving invalidity by clear and convincing evidence. *Titan Tire*

Corp. v. Case New Holland, Inc., 566 F.3d 1372, 1376 (Fed. Cir. 2009) ("Because of this presumption, an alleged infringer who raises invalidity as an affirmative defense has the ultimate burden of persuasion to prove invalidity by clear and convincing evidence, as well as the initial burden of going forward with evidence to support its invalidity allegation.").

i. Utility – 35 U.S.C. § 101

The utility requirement is established in 35 U.S.C. § 101 ("Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter . . . ." (emphasis added)). A "patent may not be granted to an invention unless substantial or practical utility for the invention has been discovered and disclosed." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1563 (Fed. Cir. 1996). It is the claims that "define the invention to be tested for utility." *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 956 (Fed. Cir. 1983).

"The threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip, Inc. v. Orange Bang, Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). An application need only "show that an invention is useful" and "disclose a use which is not so vague as to be meaningless." *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005). To lack utility, "the claimed device must be totally incapable of achieving a useful result." *Juicy Whip*, 185 F.3d at 1366 (internal citation omitted).

With respect to pharmaceutical patents, the Federal Circuit "has long held that practical utility may be shown by adequate evidence of any pharmacological activity." *Fujikawa*, 93 F.3d at 1564. The Federal Circuit further noted:

> It may be difficult to predict, however, whether a novel compound will exhibit pharmacological activity, even when the behavior of analogous compounds is known to those skilled in the art. Consequently, testing is often required to establish practical utility. But the test results need not absolutely prove that the compound is pharmacologically active. All that is required is that the tests be *reasonably* indicative of the desired pharmacological response. In

> other words, there must be a sufficient correlation between the tests and an asserted pharmacological activity so as to convince those skilled in the art, to a reasonable probability, that the novel compound will exhibit the asserted pharmacological behavior.

Id. (internal quotations and citations omitted).

ii. Anticipation – 35 U.S.C. § 102

1. Anticipation

A reference is anticipatory under 35 U.S.C. § 102(b) if "the prior art reference . . . disclose[s] each and every feature of the claimed invention, either explicitly or inherently." *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1375 (Fed. Cir. 2006) (citation omitted). Whether a prior art reference anticipates a patent claim is a question of fact and must be proven by clear and convincing evidence. *See Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000).

2. Inherent Anticipation

Under 35 U.S.C. § 102, "a [claim] limitation or the entire invention is inherent and in the public domain if it is the 'natural result flowing from' the explicit disclosure of the prior art." *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003) (quoting *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001)). "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation . . . ." *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002). "Inherency, however, *may* not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Cont'l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991) (internal quotation marks and citations omitted). To prove inherent anticipation, a party must show that, though a feature of the invention is not explicitly disclosed in the prior art, it "necessarily and inevitably" flows from

practice of the prior art. *See Schering Corp.*, 339 F.3d at 1379. "Inherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art." *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295 (Fed. Cir. 2002). Therefore, if the teachings of the prior art can be practiced in a way that yields a product lacking the allegedly inherent property, the prior art in question does not inherently anticipate. *See Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047-48 (Fed. Cir. 1995) (finding no inherent anticipation where testing evidence demonstrated that the prior art example could yield crystals of either the claimed polymorph or a different polymorph).

iii. Obviousness – 35 U.S.C. § 103

To prove that an asserted claim of a patent is invalid as obvious under 35 U.S.C. § 103, Defendants bear the burden of establishing by clear and convincing evidence that the "differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law that is predicated on several factual inquiries. *See Richardson-Vicks v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). Specifically, there are four considerations: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness, such as long-felt but unsolved need, failure of others, praise by others in the industry, and unexpected results. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

A party challenging the validity of a patent based on obviousness must demonstrate by clear and convincing evidence that the invention described in the patent would have been obvious to a POSA at the time the invention was made. In determining what would have been obvious to a POSA, the use of hindsight is not permitted. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398,

421 (2007) (cautioning against "the distortion caused by hindsight bias" and "arguments reliant upon *ex post* reasoning"). In *KSR*, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.* at 418-19.

"Obviousness does not require absolute predictability of success," but rather, requires "a reasonable expectation of success." *See Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988)). Obviousness "cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). While the Federal Circuit has noted that pharmaceuticals can be an "unpredictable art" to the extent that results may be unexpected, it also recognizes that evidence of a "finite number of identified, predictable solutions" or alternatives "might support an inference of obviousness." *See Eisai Co. Ltd. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008).

iv. Enablement – 35 U.S.C. § 112

A patent specification must contain a written description "of the manner and process of making and using [the invention], in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same . . . ." 35 U.S.C. § 112. To be enabled, the specification must teach a POSA "how to make and use the full scope of the claimed invention without undue experimentation." *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1378 (Fed. Cir. 2009) (citation omitted). A patentee need not "include in the specification that which is already known and available to [a POSA]" and "not every last detail is to be described, else patent specifications would turn into production specifications, which they

were never intended to be." *Koito Mfg. Co. v. Turn-Key-Tech, LLC*, 381 F.3d 1142, 1156 (Fed. Cir. 2004) (citation omitted).

"Enablement is not precluded by the necessity for some experimentation such as routine screening." *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988). Furthermore, the test for undue experimentation "is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.* at 737 (citation omitted). The *Wands* factors that may be considered in determining whether a disclosure would require undue experimentation include: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *Id.*

v. **Written Description – 35 U.S.C. § 112**

A patent's specification must "contain a written description of the invention." 35 U.S.C. § 112. The specification must "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm. Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). The test for written description "requires an objective inquiry into the four corners of the specification from the perspective of a [POSA]." *Id.*

"[W]hether a patent complies with the written description requirement will necessarily vary depending on the context. Specifically, the level of detail required . . . varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Id* (citation omitted). Regarding new compounds, an adequate written description "requires a precise definition, such as by structure, formula, chemical name, physical properties, or other properties . . ." *Id.* at 1350.

vi. **Original Patent – 35 U.S.C. § 251**

A patentee is precluded from obtaining a reissue patent to cover any invention other than "the invention disclosed in the original patent." 35 U.S.C. § 251. A reissue application must find support in the original patent's description such that the original description "clearly allow[s] persons of ordinary skill in the art to recognize that the inventor invented what is claimed." *Antares Pharma, Inc. v. Medac Pharma Inc.*, 771 F.3d 1354, 1362 (Fed. Cir. 2014) (citation omitted). The original patent rule requires that new claims must be to matter "explicitly disclosed and taught" rather than merely "suggested or indicated in the specification." *Id.* at 1361.

vii. **Obviousness-Type Double Patenting**

The judicially created doctrine of obviousness-type double patenting exists to prevent a patentee from securing a second patent on the same or obvious variation of an earlier-expiring patent claim, and thus improperly extending the right to exclude others from practicing the invention. *Abbvie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Trust*, 764 F.3d 1366, 1373-74 (Fed. Cir. 2014). Obviousness-type double patenting is analyzed by first construing the two claims and then determining whether the differences between the earlier and later claim render the later-expiring claim patentably distinct from the earlier-expiring claim. *Id.* at 1374. The question of whether the claims are patentably distinct is based on a POSA's understanding as of the filing date of the later-expiring claim. *Amgen Inc. v. Hoffman-LaRoche Ltd.*, 580 F.3d 1340, 1355 (Fed. Cir. 2009).

C. UNENFORCEABILITY

i. **Unclean Hands**

The doctrine of unclean hands is based on "the equitable maxim that 'he who comes into equity must come with clean hands.'" *Precision Instrument Mfg. Co. v. Auto. Maint. Mach. Co.*, 324 U.S. 806, 814 (1945). This doctrine operates to prevent litigants who have themselves

engaged in misconduct from prevailing on claims in equity. "As an equitable doctrine, application of unclean hands rests within the sound discretion of the trial court." *In re New Valley Corp.*, 181 F.3d 517, 525 (3d Cir. 1999); *see also Precision Instrument*, 324 U.S. at 815 ("This maxim necessarily gives wide range to the equity court's use of discretion in refusing to aid the unclean litigant. It is 'not bound by formula or restrained by any limitation that tends to trammel the free and just exercise of discretion.'" (quoting *Keystone Driller Co. v. Gen. Excavator Co.*, 290 U.S. 240, 245 (1933)).

Courts of equity "apply the maxim requiring clean hands only where some unconscionable act of one coming for relief has immediate and necessary relation to the equity that he seeks in respect of the matter in litigation." *See Keystone Driller*, 290 U.S. at 245. "Any willful act concerning the cause of action which rightfully can be said to transgress equitable standards of conduct is sufficient cause for the invocation of the maxim . . . ." *Precision Instrument*, 324 U.S. at 815.

In the patent context, the doctrine of unclean hands may render a patent unenforceable by a patentee who has engaged in misconduct in practicing before the United States Patent and Trademark Office ("USPTO"). *See generally Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1306-07 (Fed. Cir. 2011). In this context, an unclean hands defense must be evaluated with an eye toward the nature of patent prosecution, which is an ex parte non-adversarial proceeding in which the USPTO relies heavily on the applicant's duty to disclose information material to patentability. *See* 37 C.F.R. § 1.56 ("Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the [USPTO], which includes a duty to disclose to the [USPTO] all information known to that individual to be material to patentability . . . ."). The Supreme Court has noted:

> By reason of the nature of an application for patent, the relationship of attorneys to the [USPTO] requires the highest degree of candor and good faith. In its relation to applicants, the [USPTO] . . . must rely upon their integrity and deal with them in a spirit of trust and confidence.

Kingsland v. Dorsey, 338 U.S. 318, 319-20 (1949); *see also U.S. Indus. v. Norton Co.*, Case No. 80-359, 1980 U.S. Dist. LEXIS 16801, at *37-38 (N.D.N.Y Oct. 22, 1980) ("Given . . . the recognition that patent prosecutions are *ex parte*, non-adversarial proceedings, a relationship of trust exists between the applicant and the [USPTO]. The trust relationship is essential to a workable patent system because the [USPTO] is compelled to rely on the applicants for disclosure of many of the facts upon which its decisions are based. Consequently, the highest standards of honesty, good faith and candor by the applicants is required." (internal citations omitted)).

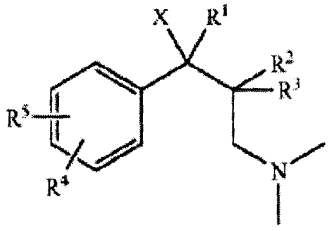
The doctrine of unclean hands generally requires a showing of intent. *See Therasense*, 649 F.3d at 1290. "Because direct evidence of deceptive intent is rare, a district court may infer intent from indirect and circumstantial evidence." *Id.*; *see also Bankers Trust Co. of W. N.Y. v. Crawford*, 781 F.2d 39, 44 (3d Cir. 1986) ("Bad faith may be established by circumstantial evidence and each case must depend on its peculiar facts."). "But deceptive intent must be 'the single most reasonable inference drawn from the evidence.'" *Ohio Willow Wood Co. v. Alps S., LLC*, 813 F.3d 1350, 1358 (Fed. Cir. 2016) (quoting *Therasense*).

IV. DISCUSSION

A. '593 PATENT – INVALIDITY

Plaintiffs have asserted claims 8, 61, 117, and 147 of the '593 patent. Defendants contend that each of these claims is invalid. As discussed above, to rebut the presumption that the '593 patent is valid, Defendants bear the burden of proving invalidity by clear and convincing evidence. *Titan Tire*, 566 F.3d at 1376.

Claim 8 is a method claim directed to "a method of treating a mammal suffering from pain" comprising administering a compound that is a member of a genus of 1-phenyl-3-dimethylaminopropane chemical compounds:

> **8**. A method of treating a mammal suffering from pain, said method comprising administering to said mammal an effective analgesic amount of a 1-phenyl-3-dimethyl-aminopropane compound corresponding to formula I
>
> I
>
> 
>
> wherein
>
> X represents OH, F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group;
>
> R^1 is a C_{1-4}-alkyl group;
>
> R^2 represents H or a C_{1-4}-alkyl group and R^3 represents H or a straight chain C_{1-4}-alkyl group, or R^2 and R^3 together form a C_{4-7} cycloalkyl radical, and
>
> R^5 represents H, and R^4 represents meta-O—Z, where Z is H, C_{1-3}-alkyl, $PO(OC_{1-4}alkyl)_2$, $CO(OC_{1-5}$-alkyl), $CONH—C_6H_4—(C_{1-3}$-alkyl) or $CO—C_6H_4—R^7$, in which R^7 is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^8)_2$, where R^8 is C_{1-4}-alkyl or 4-morpholino,
>
> or R^4 represents meta-S—C_{1-3}-alkyl, meta-Cl, meta-F, meta-$CR^9R^{10}R^{11}$, ortho-OH, ortho-O—C_{2-3}-alkyl, para-F or para-$CR^9R^{10}R^{11}$, where R^9, R^{10} and R^{11} independently represent H or F, or
>
> R^5 represents para-Cl, para-F, para-OH or para-O—C_{1-3}-alkyl, and R^4 represents meta-Cl, meta-F, meta-OH or meta-O—C_{1-3}-alkyl, or
>
> R^4 and R^5 together represent 3,4-OCH=CH— or 3,4-OCH=CHO—, or a salt thereof with a physiologically acceptable acid.

['593 patent at 24:64-25:34.] It is undisputed that tapentadol hydrochloride is one of the chemical compounds that is within the scope of the genus in claim 8. [*See* '593 patent at 19:12-22.] Specifically, tapentadol hydrochloride is a chemical compound of claim 8, wherein:

X represents H (hydrogen);
R^1 is a C_2 alkyl group (ethyl group);
R^2 represents H (hydrogen);
R^3 represents a C_1 alkyl group (methyl group);
R^4 represents a meta-OH group (hydroxyl group);
R^5 represents H (hydrogen); and
the "salt thereof" is hydrochloride.

[*Compare* '593 patent at 25:1-34, *with* '593 patent at 19:12-22.]

Claim 61 is a species claim directed to the chemical compound tapentadol hydrochloride:

> *61. (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride (−21).*

['593 patent at 32:19-20.]

Claim 117 is a dependent claim, depending from method claim 8, wherein the specific compound to be administered is tapentadol hydrochloride:

> *117. A method according to claim 8, wherein the compound is (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride (−21).*

['593 patent at 38:8-10.]

Claim 147 is directed to a pharmaceutically acceptable salt of tapentadol:

> *147. A pharmaceutically acceptable salt of (−)-(1R,2R)-3R-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol.*

['593 patent at 40:31-32.] The hydrochloride salt of tapentadol (*i.e.* tapentadol hydrochloride) is one such pharmaceutically acceptable salt.

i. '593 Patent Obviousness

Defendants contend that asserted claims 8, 61, 117, and 147 of the '593 patent are invalid for obviousness under 35 U.S.C. § 103. [PTO ¶¶ 1463, 989-1119.] Defendants bear the burden of proving by clear and convincing evidence that the invention described in the asserted claims of the '593 patent—tapentadol hydrochloride and its use to treat pain—would have been obvious to a POSA in 1994 at the time the invention was made. *See KSR*, 550 U.S. at 413.

Defendants' obviousness contentions are based on the "lead compound" analysis that the Federal Circuit has established for determining obviousness of chemical compounds. [PTO ¶¶ 991-1081; Defendants' Post-Trial Brief ("Defs. Br.") at 2.] On this issue, Defendants presented the expert testimony of Dr. Steven Martin, who opined that the prior art would have motivated a POSA to select tramadol as a lead compound and then modify it to arrive at the claimed invention, tapentadol hydrochloride. [*See generally* 3/16 Tr. (Martin) at 161:17-286:9; 3/17 Tr. (Martin) at 4:17-131:1.]

Plaintiffs contend that Defendants' obviousness analysis is improperly driven by hindsight. [PTO ¶¶ 367-517; Plaintiffs' Post-Trial Brief ("Pls. Br.") at 16.] On this issue, Plaintiffs presented the expert testimony of Dr. William Roush, who testified credibly that the prior art would not have motivated the selection of tramadol (either as a racemic mixture, its individual enantiomers, or its metabolites) as a lead compound. Dr. Roush further testified that, even had a POSA begun with tramadol as a lead compound, the prior art did not motivate the modifications necessary to arrive at tapentadol hydrochloride. [*See generally* 3/22 a.m. Tr. (Roush) at 49:18-136:5; 3/22 p.m. Tr. (Roush) at 4:3-161:20.]

1. The law of chemical obviousness

In describing its "lead compound" analysis, the Federal Circuit has stated:

> Proof of obviousness based on structural similarity requires clear and convincing evidence that a medicinal chemist of ordinary skill would have been motivated to select and then to modify a prior art compound (*e.g.*, a lead compound) to arrive at a claimed compound with a reasonable expectation of success that the new compound would have similar or improved properties compared with the old.

Daiichi Sankyo Co. v. Matrix Labs., Ltd., 619 F.3d 1346, 1352 (Fed. Cir. 2010) (citations omitted). Thus, the two step analysis requires a showing by clear and convincing evidence that (1) "a chemis [17] of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts," and (2) "the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291-92 (Fed. Cir. 2012) (citations omitted).

2. Analysis of the chemical obviousness of tapentadol hydrochloride

For the reasons that follow, the Court finds that Defendants have not met their burden of proving either element of the lead compound analysis by clear and convincing evidence. First, Defendants have not clearly and convincingly shown that a POSA would have selected tramadol or its metabolites as lead compounds. Second, Defendants have not clearly and convincingly shown that the prior art motivates the modifications necessary to convert the lead compound (tramadol) to the claimed invention (tapentadol hydrochloride).

a. Selection of tramadol as a lead compound

The problem that the inventors addressed and solved by the inventions claimed in the '593 patent was the discovery of new analgesics. The patent's specification describes this

[17] The parties are in substantial agreement as to the definition of a POSA with respect to the '593 patent, which would include education and experience in organic chemistry, medicinal chemistry, and synthesizing organic compounds. [*See* PFOF ¶ 252; DFOF ¶ 7.]

purpose, noting that "the treatment of chronic and non-chronic pain conditions is of great importance in medicine." [PFOF ¶ 253; PTX-312 at 1:19-57.]

In developing a new analgesic, a POSA in 1994 would have been interested in optimizing analgesic potency of a drug in order to administer lower doses of the drug and thereby minimize side effects resulting from off-target properties. [PFOF ¶ 256; 3/22 a.m. Tr. (Roush) at 73:19-22, 75:16-25.] A POSA would have also been interested in reducing side effects, but would have recognized that no drug is completely safe, in part because no drug binds cleanly to only one biological target. [PFOF ¶ 257; 3/17 Tr. (Martin) at 85:1-25.] A POSA would have therefore recognized that, in choosing a starting point for developing a new analgesic, every potential drug would have had problems that a POSA would have sought to overcome through investigation of the structure-activity relationship ("SAR") of the drug. [PFOF ¶ 259; 3/22 a.m. Tr. (Roush) at 76:1-10.]

i. Selection of tramadol from among the large universe of potential starting points

In selecting a lead compound for further development of an improved analgesic, a POSA would become familiar with the universe of compounds that have analgesic activity. [DFOF ¶ 9; 3/16 Tr. (Martin) at 187:21-188:11.] A POSA would investigate the analgesic properties of those compounds, including the mechanisms of analgesic activity and the known side effects. [*Id.*]

A POSA in 1994 had a large universe of potential compounds from which to choose a starting point. The '593 patent lists a number of classes of compounds known to treat chronic and non-chronic pain conditions, including opioids and other compounds such as tramadol, as examples previously known in the art. [PFOF ¶ 253; PTX-312 at 1:19-57.] The prior art includes publications disclosing several classes of compounds of which a POSA would have known and from which a POSA could have chosen a lead compound for developing a new analgesic. [PFOF

¶ 254; 3/22 a.m. Tr. (Roush) at 68:13-69:11.] Each class of compounds can be defined in terms of its mechanisms of action or in terms of its biological targets for achieving analgesia. [PFOF ¶ 254; 3/22 a.m. Tr. (Roush) at 69:3-6.]

One class of compounds from which a POSA could have chosen a starting point for developing a new analgesic was morphine derivatives. [PFOF ¶ 255; 3/22 a.m. Tr. (Roush) at 71:17-72:11.] It was well known that morphine analogues could be developed into new analgesics. [PFOF ¶ 255; 3/22 a.m. Tr. (Roush) at 71:17-72:11; *see generally* PTX-188; PTX-1055).] In developing morphine analogues, medicinal chemists had tried to simplify the morphine core structure by removing functional groups from it. [PFOF ¶ 255; 3/22 a.m. Tr. (Roush) at 72:12-23; 3/16 Tr. (Martin) at 204:5-18, 262:22-25, 267:4-7.] Medicinal chemists had also tried to add complexity to the morphine core structure by adding functional groups to it. [PFOF ¶ 255; 3/22 a.m. Tr. (Roush) at 72:23-73:17; 3/17 Tr. (Martin) at 99:5-10.] Many analogues of morphine were known to be more potent than morphine. [PFOF ¶ 258; 3/22 a.m. Tr. (Roush) at 73:23-74:25; PTX-1055.] While morphine and its derivatives were known to have side effects, such side effects would not have dissuaded a POSA from choosing morphine or its derivatives as a starting point. [PFOF ¶ 259; 3/22 a.m. Tr. (Roush) at 75:8-25.]

Additional classes of compounds that a POSA would have been motivated to investigate when choosing a starting point for developing a new analgesic were opioid agonists, including *mu*-opioid agonists, *kappa*-opioid agonists, and *delta*-opioid agonists. [PFOF ¶¶ 260-65; 3/22 a.m. Tr. (Roush) at 76:15-84:9, DFOF ¶ 10; 3/16 Tr. (Martin) at 189:7-12; PTX-139; PTX-188; PTX-1055.] One prior art *mu*-opioid agonist (4-aryl-4-dimethylaminocyclohexane) was known to be 10,000 times more potent than morphine. [PFOF ¶ 262; 3/22 a.m. Tr. (Roush) at 78:11-79:3; PTX-1055 at 391.] *Kappa*-opioid and *delta*-opioid agonists were known to have advantages over

mu-opioid agonists, such as reduction or elimination of side effects including respiratory depression, cardiac toxicity, dependency, addiction, and constipation. [PFOF ¶¶ 263-64; 3/22 a.m. Tr. (Roush) at 81:7-83:22; PTX-188 at ALK_TAP_0000424; PTX-139 at ACT-TAP0186379.]

A POSA would also have been motivated to investigate additional classes of compounds, such as cannabinoids (which a POSA would have expected to have different activities and side effects from opioids) [PFOF ¶ 266; 3/22 a.m. Tr. (Roush) at 84:10-85:9], non-steroidal anti-inflammatory drugs ("NSAIDs"), specific COX-2 inhibitors [PFOF ¶ 267; 3/22 a.m. Tr. (Roush) at 85:10-86:9], α_2-adrenoceptor (*i.e.*, norepinephrine) reuptake antagonists, tricyclic antidepressants, and GABA receptor agonists [PFOF ¶ 268; 3/22 a.m. Tr. (Roush) at 86:10-87:12].

Finally, a POSA could have investigated the family of compounds known to exhibit polypharmacology. [PFOF ¶ 269; 3/22 a.m. Tr. (Roush) at 87:13-88:10.] These compounds exhibit multiple mechanisms of analgesic action by interacting with more than one analgesic receptor target, cooperatively contributing to the compounds' analgesic activity. [PFOF ¶ 269; 3/22 a.m. Tr. (Roush) at 87:13-88:10; *see also* PTX-139.] Of the class of compounds exhibiting pharmacology, compounds exhibiting both opioid and non-opioid activity, such as tramadol, are just one subset. [*See* PFOF ¶ 269; *Cf.* 3/22 p.m. Tr. (Roush) at 50:17-20.]

From this large number of potential starting compounds, Defendants focus their arguments on tramadol and its metabolites. [Defs. Br. at 3.] Tramadol is a compound known to exhibit polypharmacology. [PFOF ¶ 269; DFOF ¶ 11; 3/16 Tr. (Martin) at 190:23-192:19; 3/22 a.m. Tr. (Roush) at 93:22-94:3; 3/10 Tr. (Buschmann) at 89:14-90:3.] Specifically, tramadol is known to possess both opioid and non-opioid activities. [PFOF ¶ 269; DFOF ¶ 11; 3/16 Tr. (Martin) at 190:23-192:19; 3/22 a.m. Tr. (Roush) at 93:22-94:3; 3/10 Tr. (Buschmann) at 89:14-90:3. DTX-1027_0004; DTX-866.] As of 1994, tramadol was the only such compound that was known

to be safe and effective based on clinical trials in humans and approved for sale in Europe. [DFOF ¶ 12; 3/22 p.m. Tr. (Roush) at 66:5-71:15; DTX-2059; DTX-2060.] Defendants argue, based on the testimony of Dr. Martin, that because tramadol was "atypical" in its possession of both opioid and non-opioid activities, a POSA would have been motivated to investigate it as a lead compound. [Defs. Br. at 4; DFOF ¶ 20; 3/16 Tr. (Martin) at 190:23-192:23, 194:25-195:13; *see also* DFOF ¶¶ 9-43.]

Defendants' argument assumes that a POSA would have been specifically motivated to investigate compounds with polypharmacology and more specifically compounds possessing both opioid and non-opioid activities. [*See* 3/16 Tr. (Martin) at 223:5-6 ("I think initially our goal was to find something with the dual mode of action.").] Defendants' expert, however, did not provide a sufficient explanation for this assumption. Plaintiffs' expert, Dr. Roush, opined that Dr. Martin's focus on this opioid/non-opioid combination as the driving factor for lead compound selection was driven by hindsight—*i.e.*, he worked backwards from his knowledge that the patented invention, tapentadol hydrochloride, possesses both opioid and non-opioid activity. [3/22 a.m. Tr. (Roush) at 70:11-71:8; 92:15-93:5.] Further, Plaintiffs presented evidence that a POSA would have been dissuaded from starting with compounds exhibiting polypharmacology because the unpredictable effects of structural changes on a compound's biological function are often multiplied when multiple mechanisms of action are involved. [PFOF ¶ 270; 3/22 p.m. Tr. (Roush) at 158:21-159:14.]

The evidence showed it was publicly known that many pharmaceutical firms were actively seeking to develop new analgesics as of July 1994. [PFOF ¶ 287; 3/10 Tr. (Buschmann) at 52:24-54:25; 3/22 a.m. Tr. (Roush) at 89:2-90:9, 91:19-22; 3/22 p.m. Tr. (Roush) at 4:3-7:15; DTX-1144_0018-25.] At least 52 different analgesic drug development efforts were ongoing at

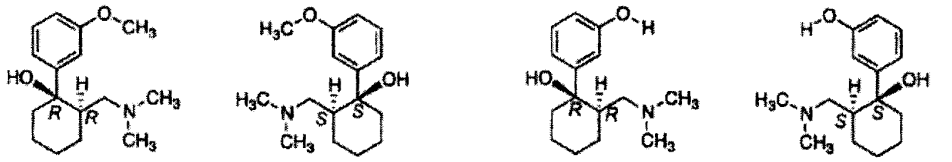
that time, with researchers investigating a variety of biological pathways. [*Id.*] Only Grünenthal began with tramadol as a starting point. [PFOF ¶ 288; 3/10 Tr. (Buschmann) at 52:24-54:25; 3/22 a.m. Tr. (Roush) at 91:19-22; 3/22 p.m. Tr. (Roush) at 6:22-7:6. In fact, Dr. Buschmann testified that Grünenthal's internal choice to pursue a compound with multiple mechanisms of action was regarded as risky because most pharmaceutical companies screen potential drug candidates to focus on the development of single-molecule drugs with activity optimized for a single target. [PFOF ¶ 107; 3/10 Tr. (Buschmann) at 13:17-14:20.]

In light of the evidence presented, Defendants have not proven by clear and convincing evidence that a POSA would have been motivated to select tramadol as a lead compound from among the vast number of potential starting points.

ii. Selection of (-)-ODMT from among the four compounds of tramadol and ODMT

As explained above, tramadol can be viewed as a mixture of four compounds—the two enantiomers of tramadol and the metabolite of each. [DFOF ¶ 21; 3/16 Tr. (Martin) at 197:8-200:6.] The tramadol mixture of enantiomers, the ODMT mixture of enantiomers, and each of the four individual compounds were studied in the prior art for their analgesic activity. [DFOF ¶ 22; 3/16 Tr. (Martin) at 200:12-24.] The following is a summary of the evidence Dr. Martin presented about the prior art teachings:

Date	Prior Art	Summary
1978	Flick	Racemic tramadol and O-desmethyltramadol
1978	Frankus	Tramadol, two enantiomers of tramadol, cis- form of tramadol
1988	Hennies	Racemic tramadol and O-desmethyltramadol
1992	Driessen I	Racemic tramadol, two enantiomers of tramadol, racemic O-desmethyltramadol
1993	Driessen II	Racemic tramadol, two enantiomers of tramadol, racemic O-desmethyltramadol
1992	Raffa I	Racemic tramadol
1993	Raffa II	Racemic tramadol, two enantiomers of tramadol
1993	Sevcik	Enantiomers of tramadol and O-desmethyltramadol



(+)-tramadol (–)-tramadol (+)-O-desmethyltramadol (–)-O-desmethyltramadol

[*See* 3/16 Tr. (Martin) at 200:25-202:6; Martin Demonstrative at 17.] From the evidence presented, Defendants contend that a POSA would have determined that the (–) enantiomer of ODMT (also known as "S,S-ODMT") would be the most promising individual compound to select as a lead compound. [DFOF ¶ 39; 3/16 Tr. (Martin) at 222:22-224:2; Martin Demonstrative at 20.] Defendants' contention is based on Dr. Martin's analysis of the prior art teachings that S,S-ODMT had a dual mechanism of action, that no metabolism of S,S-ODMT is necessary because it already lacks the aryl methyl group, that it is more active than R,R-Tramadol, and that it has low serotonin activity. [*See* DFOF ¶¶ 22-39; 3/16 Tr. (Martin) at 200:25-222:21; Martin Demonstrative at 20; DTX-691; DTX-758; DTX-694; DTX-733; DTX-736.] Defendants assert that Dr. Martin's analysis was based exclusively on references which qualify as prior art to the '593 patent and he

did not use hindsight driven analysis in reaching his opinions. [DFOF ¶¶ 40-43; 3/16 Tr. (Martin) at 224:3-225:11.]

Plaintiffs presented evidence that a POSA would not have been motivated to separate the enantiomers of tramadol. [*See generally* PFOF ¶¶ 276-281; 3/22 a.m. Tr. (Roush) at 94:4-23.] Specifically, because it was known that the different enantiomers and metabolite enantiomers exhibited different mechanisms of action, it was necessary to administer both enantiomers of tramadol. [PFOF ¶¶ 276-77; 3/22 a.m. Tr. (Roush) at 94:4-23; Roush Demonstrative at 18; PTX-57; DTX-691; DTX-694; DTX-736; DTX-758; DTX-866.] In fact, the prior art taught that the antinociceptive action of tramadol resulted from a complimentary and synergistic interaction of the enantiomers and metabolites. [PFOF ¶¶ 277-78; 3/22 a.m. Tr. (Roush) at 94:19-23; PTX-57; 3/17 Tr. (Martin) at 65:9-66:17.] The evidence showed that prior to July 1994, all known clinical use of tramadol involved administration of both enantiomers, with no evidence of the individual enantiomers of tramadol ever being clinically administered separately. [PFOF ¶ 281; 3/17 Tr. (Martin) at 61:19-24.]

Plaintiffs also presented evidence that a POSA would not have had an expectation of successfully obtaining all three of tramadol's mechanisms of action by administering only one of the enantiomers or metabolites. [*See generally* PFOF ¶¶ 282-289; 3/22 a.m. Tr. (Roush) at 94:22-98:23; Roush Demonstrative at 18-19.] As explained above, tramadol exhibits three mechanisms of action—(1) *mu*-opioid activity, (2) norepinephrine reuptake inhibition, and (3) serotonin reuptake inhibition. [PFOF ¶¶ 92-93; 3/22 a.m. Tr. (Roush) at 93:8-94:23, 99:2-101:11; PTX-57; DTX-1027.] The tramadol enantiomers affect these three targets to different degrees. [PFOF ¶¶ 92-93; 3/22 a.m. Tr. (Roush) at 93:8-94:23, 99:2-101:11; PTX-57; DTX-1027.] Plaintiffs' expert opined that a POSA would not have been motivated to select one of the

enantiomers (or metabolites) and modify it so as to produce the results that could simply be achieved by administering the racemic mixture. [PFOF ¶¶ 282-283; 3/22 a.m. Tr. (Roush) at 94:22-96:20, 119:3-120:14.]

Ultimately, Plaintiffs' evidence demonstrated that the clinical profile of tramadol was known to result from the fortuitous interaction of the tramadol enantiomers on analgesia but not on side effects. [PFOF ¶ 280; 3/22 a.m. Tr. (Roush) at 100:13-21; 3/17 Tr. (Martin) at 67:25-68:11; PTX-57.] Defendants have not proven by clear and convincing evidence that a POSA investigating tramadol would have been motivated to specifically choose as a starting point the (-)-ODMT compound over the other three compounds in the tramadol mixture.

b. Modification of tramadol to achieve tapentadol

By 1978, the SAR of tramadol had been studied extensively, as documented in a paper by researchers named K. Flick, E. Frankus, and E. Friedrichs. [DFOF ¶¶ 44-46; DTX-715 (German); DTX-834 (English)[18]; 3/16 Tr. (Martin) at 227:25-230:3.] Defendants contend that, based on the findings of *Flick* and others about the SAR of tramadol, a POSA would have identified the "pharmacophore"—the structural components of tramadol that were essential for biological activity and therefore should not be altered. [DFOF ¶¶ 44-47; *Flick* at DTX-834_0012-15; 3/16 Tr. (Martin) at 229:25-230:3.]

Defendants' expert, Dr. Martin, opined that the prior art would have informed a POSA that the tramadol pharmacophore consists of three elements. [*See generally* DFOF ¶¶ 47-62; 3/16 Tr. (Martin) at 230:4-261:16].

1. Dr. Martin opined that the first element of the tramadol pharmacophore is the dimethylamino group, which was known to significantly interact with the opioid

[18] This Opinion will refer to DTX-834, which is the English version of the paper, as "*Flick*."

receptor. [*See* DFOF ¶¶ 48-50; 3/16 Tr. (Martin) at 230:4-240:8; *Flick* at Table 3, DTX-834_0012 ("The analgesic activity is associated with the dimethylamino group. The replacement of one or both methyl groups with hydrogen eliminates the activity. Substitution with higher alkyl groups or with substituents in which the nitrogen was integrated into a ring system also leads to loss of effect.").]

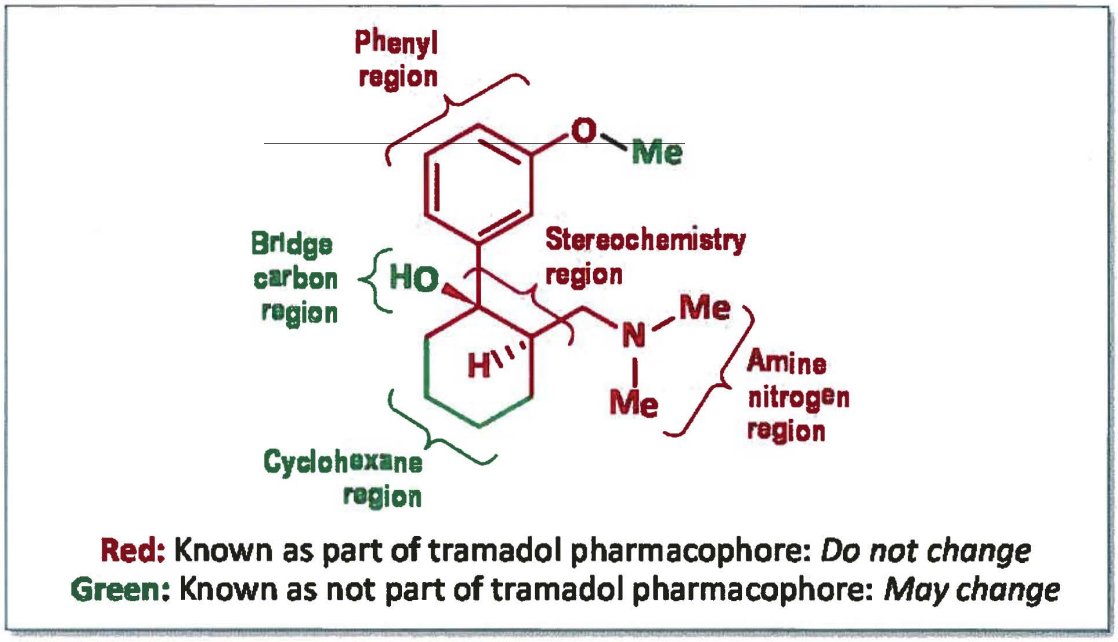
2. Dr. Martin opined that the second element of the pharmacophore is the aromatic oxygen substituent, which *Flick* teaches should either be meta-hydroxy or meta-methoxy. [*See* DFOF ¶¶ 51-54; 3/16 Tr. (Martin) at 247:2-252:13; *Flick* at Table 5.]
3. Dr. Martin opined that the third element of the tramadol pharmacophore is the relative stereochemistry. [*See* DFOF ¶¶ 57-59; 3/16 Tr. (Martin) at 254:13-258:3; DTX-717 (German); DTX-2052 (English).[19]]

After identifying the tramadol pharmacophore, Dr. Martin posited that a POSA would have been motivated to investigate changing the other elements of tramadol—*i.e.*, those elements that were not part of the pharmacophore.

1. One change Dr. Martin discussed was the substitution on the aromatic oxygen. [*See* DFOF ¶¶ 52-54; 3/16 Tr. (Martin) at 247:2-252:13, 261:3-5; *Flick* at Table 5.]
2. A second change Dr. Martin proposed investigating was the substitution on the bridge carbon. [*See* DFOF ¶¶ 55-56; 3/16 Tr. (Martin) at 241:16-245:10, 261:6-7; 262:9-263:17; *Flick* at Table 4.]
3. A third portion of the molecule Dr. Martin proposed changing was the cyclohexane region. [*See* DFOF ¶¶ 60-61; 3/16 Tr. (Martin) at 252:14-23, 261:8-11, 263:18-24; *Flick* at Table 4.]

[19] This Opinion will refer to DTX-2052, which is the English version of the paper, as "*Frankus*."

Based on his conclusions and proposed changes, Dr. Martin summarized his interpretation of the tramadol pharmacophore with the following depiction:



[*See* DFOF ¶ 62.]

Having identified the tramadol pharmacophore, Dr. Martin opined that the prior art would have motivated a POSA to make the following changes to the molecule [*see generally* DFOF ¶¶ 63-78; 3/16 Tr. (Martin) at 261:17-271:2]:

1. Dr. Martin opined that it was known that the meta-hydroxy group on the aromatic oxygen showed more analgesic activity than the meta-methoxy group. [*See* DFOF ¶¶ 51-54; 3/16 Tr. (Martin) at 247:2-252:13; *Flick* at Table 5, DTX-834_0012 ("The free m-hydroxyl group gives the best strengthening of action . . . .").]
2. Dr. Martin proposed replacing the bridge carbon hydroxyl with a hydrogen, which he opined was known to result in no significant loss of analgesic activity. [*See* DFOF ¶¶ 64-66; 3/16 Tr. (Martin) at 262:7-263:17; DTX-834_0012 ("The bridge

carbon in 1-position on the cyclohexane ring can have a hydroxyl group as the fourth substituent, and with only slight loss of activity, a halogen atom. A hydrogen radical also leads to only a slight loss of activity . . . .").] Dr. Martin suggested that the motivation to make this change would be to simplify the molecule. [3/16 Tr. (Martin) at 262:19-263:15.]

3. Finally, Dr. Martin proposed opening the cyclohexane ring. [*See* DFOF ¶¶ 67-78 3/16 Tr. (Martin) at 263:18-286:6; *Flick*; DTX-736 ("*Sevcik*"); DTX-739 ("*Spassov*").]

Plaintiffs presented evidence that a POSA would not have been motivated to make these modifications. The Court addresses Dr. Martin's proposed modifications and Plaintiff's evidence below.

i. Chemical modifications generally

Plaintiffs' expert testified that a conservative estimate of the modifications that a POSA could have made to tramadol presents almost half a million different possible compounds. [PFOF ¶ 292; 3/22 a.m. Tr. (Roush) at 102:8-103:17; 3/22 p.m. Tr. (Roush) at 82:4-83:18.] This estimate is only a small selection of the possible modifications that a POSA would have considered. [PFOF ¶ 292; 3/22 a.m. Tr. (Roush) at 102:8-103:17.] The prior art references that guided Dr. Martin investigated only about thirty individual compositions, which would not have illuminated to a POSA the biological effect that would arise from many other modifications. [PFOF ¶ 293; 3/10 Tr. (Buschmann) at 215:21-216:7; 3/22 a.m. Tr. (Roush) at 103:18-104:12, 105:8-14; 3/17 Tr. (Martin) at 108:3-14; *Flick.*] Plaintiffs presented evidence of other references that did investigate other such modifications that Dr. Martin does not appear to have considered. [PFOF ¶ 295; 3/22 a.m. Tr. (Roush) at 107:17-109:8; PTX-1055 at 396.] Lastly, Dr. Buschmann explained that the *Flick* reference, on which Dr. Martin relied, investigated mixtures of stereoisomers of the studied

compounds without separating the compounds based on their stereochemistry. [PFOF ¶ 294; *Flick*; 3/10 Tr. (Buschmann) at 217:4-218:8; 3/16 Tr. (Martin) at 233:4-13.]

ii. Aromatic Oxygen

Dr. Martin's proposed change regarding the substitution of the aromatic oxygen is encompassed within his analysis of the lead compound selection. [*See supra* Section IV.A.i.2.a.ii.] The Court concluded that it would not have been obvious to select S,S-ODMT from the mixture of tramadol and its metabolites. [*Id.*] Accordingly, the Court does not find it would have been obvious to reduce the methoxy group on the aromatic oxygen to a hydroxy group.

iii. The bridge carbon hydroxyl group

Dr. Martin testified that *Flick* demonstrated that removing the bridge carbon hydroxyl group resulted in no substantial loss of analgesic activity. [*See* DFOF ¶¶ 64-65; 3/16 Tr. (Martin) at 262:7-263:15; *Flick* at Table 4.] Defendants posited that a POSA would have been motivated to make this change to simplify the molecule, in keeping with the opioid tradition of simplifying analgesics based on morphine. [*See* DFOF ¶ 66; 3/16 Tr. (Martin) at 262:19-263:15.] Plaintiffs, however, presented evidence that researchers had made many changes to morphine, not limiting themselves to "simplifying" the molecule. [PFOF ¶ 255; 3/22 a.m. Tr. (Roush) at 72:23-73:17; 3/17 Tr. (Martin) at 99:5-10.] Furthermore, Dr. Roush testified that while the removal of the hydroxyl group impacted the analgesic activity slightly, it also made the molecule almost twice as toxic. [PFOF ¶¶ 325; 3/22 a.m. Tr. (Roush) at 130:9-133:2; *Flick* at Table 4.] Finally, Dr. Martin admitted that the bridge carbon hydroxyl group tends to stabilize a conformation resembling tramadol due to the hydrogen bond with the tertiary amine, so a POSA would likely have been motivated to retain that group rather than reducing it to hydrogen. [PFOF ¶ 326; 3/17 Tr. (Martin) at 104:3-105:2.] Thus Defendants have not proven by clear and convincing evidence that a POSA would have been motivated to remove the bridge carbon hydroxyl group.

iv. The cyclohexane ring

Regarding the cyclohexane ring, Dr. Martin opined that it would have been obvious to a POSA to undergo the following analysis based on the prior art:

(1) First, a POSA would have learned from *Flick* not to make the cyclohexane ring bigger or smaller. [*See* DFOF ¶ 68; 3/16 Tr. (Martin) at 261:10-11; *Flick* at Table 4.]

(2) Next, a POSA would have decided not to complicate the molecule by adding substituents to the cyclohexane ring. [*See* DFOF ¶ 69; 3/16 Tr. (Martin) at 266:18-267:10.]

(3) Therefore, a POSA would have instead been motivated to open the cyclohexane ring and prepare linear analogs of tramadol [*see* DFOF ¶ 70; 3/16 Tr. (Martin) at 267:11-269:15] by either cleaving one of the bonds in the ring ("scission") [*see* DFOF ¶ 71; 3/17 Tr. (Martin) at 18:13-22:21] or by removing one of the carbons in the ring ("excision") [*see* DFOF ¶ 71; 3/16 Tr. (Martin) at 270:24-271:2].

(4) Having decided to open the cyclohexane ring, a POSA would have avoided scission of a carbon-carbon bond in the cyclohexane ring because such an approach would not allow the methyl groups in the resulting open-chain molecule to occupy the same spatial positions. [*See* DFOF ¶¶ 72-73; 3/17 Tr. (Martin) at 20:7-22:21.]

(5) Thus, a POSA would have chosen excision as the method of opening the cyclohexane ring, and would have determined that excising one of two possible carbons in the cyclohexane ring would produce compounds that

would be likely to exhibit analgesic behavior. [*See* DFOF ¶¶ 74-77; 3/17 Tr. (Martin) at 23:1-24:19; DTX-739.]

(6) Finally, a POSA would have known, based on prior art references and Newman projections which carbon to excise. [*See* DFOF ¶¶ 76-78; 3/17 Tr. (Martin) at 23:1-24:19; *see also* 3/17 Tr. (Martin) at 7:8-14:5.]

In response to Dr. Martin's opinions regarding the cyclohexane ring, Dr. Roush testified for Plaintiffs that a POSA would not have opened the ring to make linear compounds in the first place. [*See generally* PFOF ¶¶ 300-309; 3/22 a.m. Tr. (Roush) at 79:7-24, 109:9-116:17.] Dr. Roush further testified that, even if a POSA were to open the ring, a POSA would not have been motivated to cleave a carbon-carbon bond in the ring (scission) or to remove a carbon (excision). [*See generally* PFOF ¶¶ 310-315; 3/22 a.m. Tr. (Roush) at 116:23-123:4.] Dr. Roush also testified that a POSA would not have found Dr. Martin's references to present a compelling motivation to modify tramadol. [*See generally* PFOF ¶¶ 316-24; 3/22 a.m. Tr. (Roush) at 123:5-133:21.]

First, it was known that the cyclohexane ring in tramadol restricts the conformational options that the molecule has, thereby improving its propensity to bind to receptors. [PFOF ¶¶ 301, 303-04; 3/22 a.m. Tr. (Roush) at 79:7-24, 109:25-111:20, 114:1-22; PTX-871 at JN_NUCYNTA_1656858 ("A central tenet in structure-based design is that the binding affinity of a ligand will be improved if its conformational motion can be restricted to that of the bound state."); PTX-1055 at 390-91 ("From a structural point of view, cyclohexane forms the common element of a variety of analgesics that are otherwise difficult to classify. The alicyclic ring system serves to restrict conformational options in all derivatives that contain it . . . ."); 3/17 Tr. (Martin) at 80:8-81:20.] Examples were known in the art of more flexible analogues of cyclic analgesics having poorer analgesic activity. [PFOF ¶¶ 307-08; 3/22 a.m. Tr. (Roush) at 115:1-116:17;

PTX-185.] In fact, of the molecules investigated in *Flick*—the paper which Defendants consider "[t]he most relevant prior art reference for the SAR of tramadol and related compounds" [*see* DFOF ¶ 45]—none were linear molecules. [PFOF ¶ 302; *Flick*; 3/10 Tr. (Buschmann) at 216:16-217:3, 3/17 Tr. (Martin) at 38:23-25, 108:15-18, 110:4-9.]

Second, Plaintiffs presented evidence of the numerous possibilities that existed (and lack of guidance from the prior art regarding those possibilities) had a POSA decided to open the cyclohexane ring. [PFOF ¶ 310; 3/22 a.m. Tr. (Roush) at 116:23-117:15.] A POSA would have had a choice of at least three bonds to cleave (five if not concerned with maintaining the stereochemistry). [PFOF ¶¶ 311-312; 3/22 a.m. Tr. (Roush) at 117:16-118:10; Roush Demonstrative at 29-34.] A POSA would have also had a choice of at least two carbons to excise. [PFOF ¶¶ 314-315; 3/22 a.m. Tr. (Roush) at 120:21-123:4.] And, once the ring was open, a POSA would have had a choice of substituting or removing carbons or other groups. [PFOF ¶ 313; 3/22 a.m. Tr. (Roush) at 117:3-119:2.]

Third, Plaintiffs presented evidence that the linear compounds tested by the *Spassov* and *Nazarov* references on which Dr. Martin relied would not have motivated a POSA to open the cyclohexane ring. The *Spassov* compounds were not tested for, or known to have, analgesic activity. [PFOF ¶ 316; 3/22 a.m. Tr. (Roush) at 123:5-124:17; PTX-61.] Regarding *Nazarov*, Plaintiffs presented evidence that the one compound shown to have biological activity possessed the bridge carbon hydroxyl group (which Dr. Martin proposed replacing), possessed a benzene ring lacking a hydroxyl substituent (unlike tramadol), was shown to have pharmacological properties distinct from analgesia, and involved a stereoselective synthesis that would have produced the wrong stereochemistry. [PFOF ¶¶ 317-321; 3/22 a.m. Tr. (Roush) at 124:18-130:8; PTX-54 at ACT-TAP0016872-73; 3/17 Tr. (Martin) at 31:10-36:7.] Plaintiffs also note that, while

the Nazarov paper was available to the authors of *Flick*, it did not motivate those researchers to investigate linear compounds. [PFOF ¶ 322; 3/17 Tr. (Martin) at 38:5-25.]

In light of the evidence set forth, Defendants have not proven clearly and convincingly that it would have been obvious to a POSA based on the prior art to make the modifications necessary to go from tramadol to tapentadol.

3. The '593 patent is not obvious

Having reviewed the evidence presented by the parties, the Court finds that Defendants' lead compound contentions derive from a knowledge of the claimed inventions and the starting point the inventors actually took rather than a view of the options available to a POSA in 1994. [Plaintiffs' Conclusions of Law ("PCOL") ¶¶ 630-631.] Defendants have failed to clearly and convincingly show that a POSA would have selected tramadol (or any of its individual enantiomers, *O*-desmethyl metabolites, or any combination thereof) as lead compounds for developing a new analgesic as of July 23, 1994. [PCOL ¶ 628.] Defendants have also failed to clearly and convincingly show that the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify tramadol to make tapentadol hydrochloride with a reasonable expectation of success. The Court, therefore, finds that Defendants have failed to meet their burden of proving by clear and convincing evidence that any of the asserted claims of the '593 patent are obvious under 35 U.S.C. § 103.

ii. '593 Patent Utility

Defendants have challenged the utility of the '593 patent. [PTO ¶¶ 1465, 1168-1181.] To prove that the '593 patent lacks utility, Defendants must demonstrate that the patent contains inadequate evidence of pharmacological activity. *See Fujikawa*, 93 F.3d at 1564. On this issue, Defendants presented the expert testimony of Dr. Christian Wolf and Dr. Jeffrey Mogil. Plaintiffs presented the expert testimony of Dr. Michael Ossipov.

Defendants' utility argument proceeds in two parts. First, Defendants contend that the '593 patent contains no testing to support the "desired pharmacological response." Second, Defendants contend that the testing that is contained within the '593 patent specification is insufficient to convince one of skill in the art to a reasonable probability that the compound of the asserted claims exhibits any pharmacological response. The Court addresses these arguments in turn.

1. The "desired pharmacological response"

Defendants contend that, as a matter of law, the '593 patent must contain "testing to support 'the underlying object of the present invention.'" [*See* Defs. Br. at 11.] Defendants suggest that the underlying object was "to 'provide substances with an analgesic effect, which are suitable for the treatment of severe pain without giving rise to the side effects which are typical of opioids.'" [*See* Defs. Br. at 11.] Defendants alternatively suggest that the underlying object was "a pronounced analgesic effect which is significantly enhanced compared with that of tramadol." [*See* DFOF ¶ 508.] Either way, Defendants contend that, because the '593 patent undisputedly does not contain side effect testing or comparative testing to tramadol, its utility has not been demonstrated. [DFOF ¶¶ 507, 508; 3/23 Tr. (Ossipov) at 169:11-172:8; 3/11 Tr. (Mogil) at 257:10-20, 266:14-19; 3/22 p.m. Tr. (Roush) at 107:7-22.]

Plaintiffs argue, however, that the utility stated in claim 8 is treatment of pain in mammals. [Pls. Br. at 27; *see* PFOF ¶ 359.] While Defendants rely on specification statements about the "object of the invention," the asserted claims do not make any reference to side effects or tramadol. [*See id.*; *see also* '593 patent at claims 8, 61, 117, and 147.] *Raytheon*, 724 F.2d at 956 (the claims "define the invention to be tested for utility"). The Court agrees with Plaintiffs that the utility of the asserted claims is analgesia. Accordingly, the lack of side effect testing or comparative testing to tramadol in the '593 patent does not lead to the conclusion that the patent lacks utility.

2. The testing in the patent

Defendants contend that, even acknowledging the utility of the asserted claims as analgesia, the testing in the specification of the patent is insufficient to establish analgesia. [*See* Defs. Br. at 11.] Plaintiffs presented evidence that the '593 patent discloses that the asserted claims have utility through its discussion of *in vivo* test data from the mouse writhing model. [PFOF ¶ 337; '593 patent at 21:53-22:40.] Defendants argue that the mouse writhing test, which is undisputedly the only test for analgesia disclosed in the patent, is not reasonably indicative of analgesia. [*See* DFOF ¶ 514-532; *see generally* 3/11 Tr. (Mogil) at 256:19-277:15.] Defendants also contend that, while the '593 patent contains mouse writhing test data for some of the compounds disclosed, it contains no data regarding the analgesic activity of the compound of Example 25 in the '593 patent, which is the compound claimed in asserted claims 61, 117, and 147. (Defs. Br. at 11; *see generally* DFOF ¶¶ 510, 512-513; *see generally* 3/11 Tr. (Mogil) at 262:10-264:15; 3/17 Tr. (Wolf) at 142:7-23.]

a. The reliability of the mouse writhing test, generally

Plaintiffs presented evidence that the mouse writhing test is a reliable, fundamental, and industry standard test for detecting compounds with antinociceptive analgesic activity. [PFOF ¶ 337; 3/23 Tr. (Ossipov) at 119:9-120:1; Friedichs Depo. at 166:13-16, 201:6-13.] Scientific publications recognize the mouse writhing test as a widely used, reliable animal model for identifying compounds with antinociceptive analgesic activity, and the model has been recognized as one of the three most reliable animal models for nociceptive pain. [PFOF ¶ 339; 3/23 Tr. (Ossipov) at 119:9-120:1; PTX-929; PTX-746; DTX-165; DTX-170.] Defendants' own expert, Dr. Mogil, agreed that the mouse writhing test was commonly used in 1994. [PFOF ¶ 340; 3/11 Tr. (Mogil) at 299:4-7.]

Dr. Mogil's testimony included extensive criticism of the mouse writhing test itself. One criticism was that the mouse writhing test could produce false positives due to non-responsiveness of some test subjects to the irritant. [*See* PFOF ¶ 360; 3/11 Tr. (Mogil) at 305:15-24.] A second criticism was the non-specificity of the mouse writhing test due to writhing inhibition caused by non-analgesics. [*See* PFOF ¶ 361; DFOF ¶¶ 521-524; 3/11 Tr. (Mogil) at 267:5-273:10; DTX-170 at Table 3; DTX-1576_0022; DTX-165_0003 ("Because of the lack of specificity, caution is required in interpreting the results, until other tests have been performed.").] A third criticism was the sensitivity of the test to analgesic manipulations, which renders the test susceptible to confounding factors such as stress-induced analgesia, whereby stress itself can reduce pain. [*See* PFOF ¶ 362; DFOF ¶¶ 525-526; 3/11 Tr. (Mogil) at 273:11-276:22; DTX-166_0009-10, DTX-1576_0013, DTX-177_0002.] A fourth criticism was the potential for confounding responses, such as motor impairment and sedation, which can inhibit writhing activity without producing analgesia. [*See* PFOF ¶ 364; DFOF ¶ 527; 3/11 Tr. (Mogil) at 276:23-277:15; DTX-1576_0020 ("[A] decrease in the number of writhes is not indicative of antinociception if it is accompanied by gross motoric disturbances such as muscle relaxation or paralysis.").] And a fifth criticism was the potential for difficulty in counting writhes. [*See* PFOF ¶ 365; *see also* 3/11 Tr. (Mogil) at 258:14-18; 3/23 Tr. (Ossipov) at 126:14-21.]

In response to Dr. Mogil's criticisms of the mouse writhing test, Plaintiffs demonstrated (on cross examination of Dr. Mogil and through the testimony of Dr. Ossipov) that these concerns would be alleviated by a competent technician. [PFOF ¶ 365; 3/23 Tr. (Ossipov) at 157:14-19.] Such a technician would be able to administer the test without inducing stress [PFOF ¶ 362; 3/23 Tr. (Ossipov) at 120:2-21, 151:24-154:9], would be able to apply consistent criteria to count the writhes of a mouse, and would have no difficulty identifying nonresponsiveness, non-specificity,

and motor impairment. [PFOF ¶¶ 360-365; 3/11 Tr. (Mogil) at 304:8-305:15; 3/23 Tr. (Ossipov) at 154:10-155:23.]

Dr. Mogil also criticized the '593 patent for relying solely on the mouse writhing test without providing evidence of additional testing to confirm the mouse writhing test conclusions, as Defendants contend would be standard practice in scientific publications. [*See* PFOF ¶ 366; DFOF ¶¶ 514-519; 3/11 Tr. (Mogil) at 254:3-259:12 269:18-270:22, DTX-1576_0011, 0022.] Defendants presented evidence of scientific literature stating that "no model is reliably predictive" and inferences should be made "only through the judicious use of complimentary models of nociception and assessments of motoric function." [DFOF ¶ 517; DTX-1576_0011, 0022).] Defendants also elicited testimony from the experts concerning the value of having multiple complimentary models of pain to test for analgesia. [DFOF ¶¶ 514, 516, 531; 3/11 Tr. (Mogil) at 254:3-259:12; 3/23 Tr. (Ossipov) at 181:20-196:2.] However, the law does not require that a patent's disclosure meet the same standard as a peer-reviewed journal publication. *See* 35 U.S.C. § 112. In any event, Plaintiffs provided evidence of scientific publications containing only mouse writhing test data. [PFOF ¶ 366; 3/23 Tr. (Ossipov) at 229:3-230:18, 150:24-151:9; PTX-746 at JN_NUCYNTA_0749749.] Furthermore, despite his criticism of the mouse writhing test on the stand, Dr. Mogil admitted that he has used the mouse writhing test and in his past writing he has called the writhing test "the only major nociceptive test largely developed, and still used, on mice." [PFOF 340; 3/11 Tr. (Mogil) at 309:25-310:3, 311:24-312:1; DTX-166_0018.]

b. The mouse writhing test, as applied to the '593 patent

The '593 patent explains that the "analgesic effectiveness of the compounds according to the invention" was investigated in the "phenylquinone-induced writhing test," and it provides information regarding that testing, including the number of mice that received each dose, the type of mice used, and the testing procedure. [PFOF ¶ 342; '593 patent at 21:55-67.] The patent

discloses data from the mouse writhing test for many of the compounds disclosed, including a summary table disclosing test results for 24 compounds. [FOF ¶ 343 '593 patent at 22:15-40.] The summary table reports ED_{50} values for 18 compounds within the claimed class of compounds. [PFOF ¶ 344; '593 patent at 22:3-40; 3/23 Tr. (Ossipov) at 128:14-17.] The remaining six entries in the summary table report the percent by which the number of writhes was reduced for mice given a 25 mg/kg dose of the test compound. [PFOF ¶ 349; '593 patent at 22:15-40.] A POSA in 1994 would have appreciated that the summary table of mouse writhing data in the '593 patent discloses test results for over 800 mice.[20] [PFOF ¶ 35; 3/23 Tr. (Ossipov) at 144:20-145:4.] The ED_{50} values in the table were calculated "with a 95% confidence level"[21] using software that performs regression analysis. [PFOF ¶ 347; '593 patent at 22:3-10; 3/23 Tr. (Ossipov) at 123:21-124:1.] A control group was used to generate the values in the table (*i.e.*, the values were generated "by comparison with mice tested in parallel to which only phenylquinone had been administered"). [PFOF ¶¶ 348-49; '593 patent at 22:3-40; 3/23 Tr. (Ossipov) at 123:10-20, 124:16-125:4).] A dose dependent response in the mouse writhing test is strong evidence of antinociception, and the ED_{50} values reported in the '593 patent provide this strong evidence. [PFOF ¶ 346; 3/23 Tr. (Ossipov) at 129:13-21.]

As stated in the '593 patent, "[a]ll of the compounds according to the invention which were investigated exhibited a pronounced analgesic effect." [PFOF ¶ 351; '593 patent at 22:11-13.] Plaintiffs' expert, Dr. Ossipov, testified that he is very confident that all the tested

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[20] The patent discloses that there were ten mice per dose. With a minimum of three dose groups, plus a control group, for each of the eighteen ED_{50} values (40 mice each), and a 25 mg/kg dosing level group, plus a control group, for each of the six tested for percent inhibition (20 mice each), the table represents a minimum of 840 mice. [PFOF ¶ 350; '593 patent at 21:60-61; 3/23 Tr. (Ossipov) at 123:3-9, 125:5-8.]

[21] A 95% confidence level indicates a 95% probability that a repeated experiment would contain an ED_{50} value between the confidence intervals. [PFOF ¶ 347; 3/23 Tr. (Ossipov) at 128:18-23.]

compounds investigated in the summary table demonstrated the inhibition of nociceptive pain. [PFOF ¶ 343; 3/23 Tr. (Ossipov) at 124:8-15.]

The compounds covered by the asserted claims of the '593 patent all have the same core chemical structure, the structure illustrated in claim 8. [PFOF ¶ 341; *see* '593 patent).] Defendants did not present evidence of a single compound without analgesic activity that has a structure that would be covered by any of the asserted claims. [*See* PFOF ¶ 358.] Accordingly, a POSA would have had a reasonable expectation that Example 25 (tapentadol hydrochloride) would have a dose-dependent antinociceptive effect due to its structural similarity to the family of compounds that demonstrated analgesic activity.[22] [PFOF ¶ 357; 3/23 Tr. (Ossipov) at 149:5-15; PCOL ¶¶ 609-610.] *See Glaxosmithkline LLC v. Baner Pharmacaps, Inc.*, No. 11-046, 2013 U.S. Dist. LEXIS 112440, at *78 (D. Del. Aug. 9, 2013) ("[A] specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented *must* be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter *unless* there is reason for one skilled in the art to question the objective truth of the statement of utility or its scope." (citation omitted)), *aff'd*, 744 F.3d 725 (Fed. Cir. 2014); Manual of Patent Examining Procedure § 2107.02(I) ("Where an applicant has established utility for a species that falls within an identified genus of compounds, and presents a generic claim covering the genus, as a general matter, that claim should be treated as being sufficient under 35 U.S.C. 101. Only where it can be established that other species clearly encompassed by the claim do not have utility should a

[22] The parties presented evidence concerning declarations submitted to the USPTO during prosecution of the '737 patent, containing at least some data obtained after the original filing date of the patent. [*See* PFOF ¶¶ 352-356; DFOF ¶¶ 533-543.] The parties dispute whether post-filing data may be used to establish utility and whether the patentees should be entitled to the 1994 priority date. [PCOL ¶ 611; DCOL ¶¶ 510-512]. Because the Court finds that the data presented in the '593 patent specification is sufficient to support the utility of the asserted claims, the Court makes no findings as to the admissibility of the prosecution declarations on the question of utility.

rejection be imposed on the generic claim."); *see also, e.g.*, *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995) ("[A]pplicants provided . . . test results showing that several compounds within the scope of the claims exhibited significant [pharmacological activity] . . . . Such evidence alone should have been sufficient to satisfy applicants' burden."); *In re Jolles*, 628 F.2d 1322, 1327 (C.C.P.A 1980) (finding that the Board of Patent Appeals and Interferences "erred . . . by failing to give sufficient weight to the similarity of the remaining claimed derivatives to the derivative [that had been tested] . . . .").

3. The asserted claims of the '593 patent do not lack utility

Based on the evidence presented, the Court finds that Defendants have not met their burden of clearly and convincingly proving that the asserted claims of the '593 patent lack utility under 35 U.S.C. § 101.

iii. '593 Patent Written Description and Original Patent

Defendants contend that asserted claims 61, 117, and 147 of the '593 patent lack written description under 35 U.S.C. § 112. [PTO ¶¶ 1464, 1155-62.] Defendants further contend that those same claims in the '593 patent do not meet the "original patent" requirement set forth in 35 U.S.C. § 251. [PTO ¶¶ 1163-1167.] To prove that the '593 patent lacks written description under 35 U.S.C. § 112, Defendants bear the burden of demonstrating by clear and convincing evidence that a POSA would not have understood from the disclosure within the patent specification that the inventor "had possession" of the tapentadol hydrochloride claimed in claims 61, 117, and 147. *See Ariad*, 598 F.3d at 1351. Similarly, to prove that the '593 patent fails to meet the "original patent" requirement of 35 U.S.C. § 256, Defendants must clearly and convincingly show that the tapentadol hydrochloride of reissued claims 61, 117, and 147 was not taught by the original patent's description. *See Antares*, 771 F.3d at 1361-62.

On this issue, Defendants presented the expert testimony of Dr. Christian Wolf, who opined that the '593 patent does not contain "structural data" that would allow a POSA to conclude that the inventors possessed the compound claimed in claims 61, 117, and 147. [*See generally* DFOF ¶¶ 552-558; *see also* Defs. Br. at 15; 3/17 Tr. (Wolf) at 149:22-150:16.] Dr. Wolf also opined on mistakes in the original and reissue patent specifications and the prosecution history. [*See generally* DFOF ¶¶ 558, 561-66; *see also* Defs. Br. at 15-16; 3/17 Tr. (Wolf) at 154:18-155:22; 156:25-160:18.] Based on these mistakes, Defendants' argue that from the alleged "numerous irreconcilable discrepancies about the identity of the compound of Example 25 in the specification . . . a POSA would conclude the inventors did not know what they possessed, let alone the ultimately claimed . . . species." [*See* Defs. Br. at 15.]

Plaintiffs contend that the subject matter of claims 61, 117, and 147 is adequately disclosed and that those claims satisfy the requirements of the original patent rule. On this issue, Plaintiffs presented the testimony of Dr. Roush, who opined on the chemical structure drawn in conjunction with Example 25 and the disclosure of the routine chemistry steps that a POSA could follow to synthesize the depicted molecule. [PFOF ¶ 385; 3/22 p.m. Tr. (Roush) at 8:8-9:1; *see also* PCOL ¶ 652; Pls. Br. at 32-33.] It is undisputed that the drawing in Example 25 is a correct depiction of the compound claimed in claims 61, 117, and 147, and that the drawing and the synthetic steps have not changed over the lifetime of the prosecution and reissue of the patent. [PCOL ¶ 653; 3/17 Tr. (Wolf) at 208:5-20; 3/10 Tr. (Buschmann) at 57:9-12, 63:15-22, 67:2-7.] Furthermore, Plaintiffs presented the testimony of Dr. Buschmann, an inventor of the '593 patent, who provided credible testimony to explain each of the alleged "discrepancies." [3/10 Tr. (Buschmann) at 57:22-61:6, 61:19-62:18, 63:23-67:1.]

1. Sufficiency of the disclosure

The structural formula depicted in conjunction with Example 25 and designated as "-21" is undisputedly tapentadol hydrochloride, the compound claimed in claims 61, 117, and 147. [PFOF ¶ 377; 3/16 Tr. (Steed) at 52:19-53:7; 3/17 Tr. (Wolf) at 155:23-156:2.] The structure includes three dimensional indicators indicating the molecule's stereochemistry. [PFOF ¶ 379; 3/22 p.m. Tr. (Roush) at 134:23-135:8.] Defendants' expert, Dr. Wolf, admitted that a structure can be sufficient to describe a molecule to a POSA without analytical structural data, assuming that a POSA could look into the specification and find evidence that the inventors did invent what they claimed they invented. [*See* PFOF ¶ 380; 3/17 Tr. (Wolf) at 178:10-18.] Plaintiffs' expert, Dr. Roush, discussed that evidence in the specification, testifying that a POSA would rely on the chemical structure drawn and also on the synthesis steps disclosed as part of the detailed reaction scheme. [PFOF ¶ 383; 3/22 p.m. Tr. (Roush) at 11:13-12:14.]

Dr. Wolf testified that a POSA could verify whether he or she had prepared the structure depicted in Example 25 using analytical techniques that were well known, such as Nuclear Magnetic Resonance ("NMR") and Infrared ("IR") spectroscopy. [PFOF ¶ 381; 3/17 Tr. (Wolf) at 185:5-186:3.] Defendants argue that such techniques should have been disclosed in the patent specification. [Defs. Br. at 15.] Although Dr. Wolf cited three references discussing the types of structural data that can be used to identify chemical compounds, none of those references purports to contain any statement about the law of written description as it pertains to patents in the chemical field. [PFOF ¶ 382; 3/17 Tr. (Wolf) at 186:16-18, 186:25-187:21.]

In light of the evidence presented, the Court finds that the combination of the depicted structure in Example 25 with the collection of synthetic steps consistent with that final structure was sufficient to indicate to a POSA that the patentees were in possession of the invention claimed in claims 61, 117, and 147.

2. Discrepancies in the disclosure

Defendants argue that, notwithstanding the structural drawing and the synthetic steps in Example 25, discrepancies in the disclosure of the '593 patent would indicate to a POSA that the inventors were not in possession of the tapentadol hydrochloride claimed in claims 61, 117 and 147. Specifically, Defendants presented evidence that the melting point and optical rotation data disclosed for the compound of Example 25 would indicate to a POSA that the steps of Example 25 do not result in tapentadol hydrochloride and do not result in a compound that is the enantiomer of Example 24 as the drawn structure of Example 25 indicates. [*See* DFOF ¶ 558; 3/17 Tr. (Wolf) at 149:22-150:16, 154:8-155:22.] Defendants also rely on mistakes made in the "R" and "S" stereochemistry descriptors, which were written as "(1S,2S)" in the original patent application, amended to "(1R,2S)" during prosecution leading to the issuance of the original '737 patent, and reissued as "(1R,2R)" in the '593 patent. [DFOF ¶¶ 561-566; 3/17 Tr. (Wolf) at 156:25-160:18; 3/10 Tr. (Buschmann) at 133:7-16, DTX-950_034.] These mistakes, Defendants argue, would prevent a POSA from concluding that the inventors were in possession of the claimed invention—tapentadol hydrochloride.

This Court construed the claim term "(–)-(1R,2R)-3-3(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride (–21)" to mean "the chemical compound (–)-(1R,2R)-3-3(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride depicted by the structural formula identified by the number (–21) in Example 25 of the RE593 patent." [ECF No. 332.] In doing so, the Court declined to adopt Defendants' proposed construction for the term, through which Defendants sought to incorporate limitations requiring a specific melting point and optical rotation. [PFOF ¶ 375; ECF No. 332.]

It is undisputed that the compounds depicted by the structural formulas drawn in Examples 24 and 25 are enantiomers. [PFOF ¶ 386; 3/17 Tr. (Wolf) at 192:25-193:1.] Dr.

Buschmann testified about the discrepancy between the melting points, stating that the patent drafter incorrectly transcribed the melting point from his laboratory notebook. [3/10 Tr. (Buschmann) at 61:11-18.] Dr. Roush testified that the optical rotation discrepancy between the compounds of Example 24 and 25 was likely within the range of measurement error, and was certainly not large enough to make a POSA question that they were enantiomers. [3/22 p.m. Tr. (Roush) at 17:12-19:14.] As for the "R" and "S" stereochemistry descriptors, Dr. Buschmann explained the reasonable mistake that resulted in the incorrect naming of the molecule in the original application and the issued '737 patent, a mistake that was ultimately corrected in the '593 patent. [3/10 Tr. (Buschmann) at 57:22-61:6, 61:23-62:18, 63:23-67:1.] In light of the evidence presented about the structural formula and the synthetic steps, the Court finds that the mistakes and/or discrepancies in the description of Example 25 would not cause a POSA to question that the inventors had in fact invented the molecule depicted by the drawn structure, which is undisputedly tapentadol hydrochloride claimed in claims 61, 117, and 147.

3. The asserted claims of the '593 patent satisfy the written description and original patent requirements

This Court finds that the disclosure of the synthetic steps and the structural formula of Example 25 in the original application is sufficient to meet the written description and original patent requirements. A POSA would understand that the inventors possessed the tapentadol hydrochloride depicted by the drawn molecule at the time the original application was filed. Therefore, Defendants have not met their burden of proving by clear and convincing evidence that the '593 patent lacks written description under 35 U.S.C. § 112 or fails to satisfy the original patent requirement under 35 U.S.C. § 251.

iv. '593 Patent Enablement

Defendants contend that asserted claim 8 is not enabled in accordance with the requirements of 35 U.S.C. § 112. [PTO ¶¶ 1192-1207.] To prove that claim 8 is not enabled, Defendants bear the burden of demonstrating by clear and convincing evidence that the disclosure of the '593 patent would not teach a POSA "how to make and use the full scope of the claimed invention without undue experimentation." *See Martek*, 579 F.3d at 1378. On this issue, Defendants presented the testimony of Dr. Wolf and Dr. Mogil. Plaintiffs argue that the full scope of claim 8 has been enabled by the specification. On this issue, Plaintiffs presented the testimony of Dr. Ossipov.

Claim 8 encompasses over 11 million compounds, which correspond to over 600 million salts. [DFOF ¶ 571; 3/17 Tr. (Wolf) at 164:13-165:10.] Defendants contend that the analgesic activity of new compounds must be determined empirically for each new compound. [*See* DFOF ¶ 576; 3/11 Tr. (Mogil) at 291:4-11; Friedrichs Depo. at 214:17-215:5; 3/23 Tr. (Ossipov) at 210:4-10.] Defendants therefore posit that in order to make and use the full scope of claim 8, a POSA would need to first synthesize, purify, and identify each of the compounds, and then perform appropriate animal model testing on a compound-by-compound basis to assess purported analgesic activity, a process which would require 10-12 days per compound. [*See* DFOF ¶ 572; 3/11 Tr. (Mogil) at 286:19-287:17; 3/17 Tr. (Wolf) at 163:21-169:7.] It is undisputed that, if such a process were required to enable the claim, that process would require years to perform and billions of mice. [DFOF ¶ 572; 3/11 Tr. (Mogil) at 287:8-17; 3/23 Tr. (Ossipov) at 158:16-22, 209:12-212:7.]

However, this Court is not persuaded that the enablement law requires the making and testing of every one of the 11 million species in genus claim 8. *See In re Bundy*, 642 F.2d 430, 434 (C.C.P.A. 1981) ("Requiring specific testing of the thousands of prostaglandin analogs encompassed by the present claim in order to satisfy the how-to-use requirement of § 112 would

delay disclosure and frustrate, rather than further, the interests of the public."); *In re Angstadt*, 537 F.2d 498, 502-03 (C.C.P.A. 1976) ("To require [disclosure of a test with every species covered by the claim] would apparently necessitate a patent application or applications with 'thousands' of examples or the disclosure of 'thousands' of catalysts along with information as to whether each exhibits catalytic behavior . . . ." (footnote omitted)). As a practical matter, it would be "absurd" to require the testing of every single compound in genus claim 8. [PFOF ¶ 369; 3/23 Tr. (Ossipov) at 158:16-159:5.] "Such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments [and] would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed." *Angstadt*, 537 F.2d at 502-03.

Rather, the law requires that a POSA be able to practice the full scope of the claims without undue experimentation. To meet that requirement, Plaintiffs presented evidence that a POSA would be able to make and test any compound encompassed by genus claim 8 as a matter of routine experimentation. [PFOF ¶¶ 372-73; 3/23 Tr. (Ossipov) at 159:6-14.] In fact, Defendants' experts admitted that the work required to test and synthesize each compound would be routine. [PFOF ¶ 373; 3/11 Tr. (Mogil) at 317:9-20.]

Plaintiffs also presented evidence that a representative number of the compounds encompassed within claim 8 were tested and all exhibited antinociceptive activity, and that a POSA would reasonably believe that other structurally similar compounds in the same family would have antinociceptive effects. [PFOF ¶ 369; 3/23 Tr. (Ossipov) at 149:7-15.] Defendants have not identified any compound within the class of compounds covered by claim 8 that lacks nociceptive activity. [*See* PFOF ¶ 371.] Nor have Defendants identified any compounds within genus claim 8

that would be difficult to make or test, considering the guidance provided by the patent. [*See* PFOF ¶¶ 372-73; 3/23 Tr. (Ossipov) at 159:6-14.]

In light of the evidence presented, Defendants have not met their burden of proving by clear and convincing evidence that claim 8 is not enabled.

B. '364 PATENT – INVALIDITY

Plaintiffs have asserted claims 1, 2, 3, and 25 of the '364 patent. Defendants contend that each of these claims is invalid.

Independent claim 1 and dependent claims 2 and 3 are each directed to a specific crystalline form of tapentadol hydrochloride, namely polymorph Form A. [*See* '364 patent at 18:66-67, 19:5-6, 19:11-12.] The claims are drafted such that the crystalline Form A is described in terms of its X-ray diffraction pattern:

> The invention claimed is:
>
> **1**. A crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride exhibiting at least X-ray lines (2-theta values) in a powder diffraction pattern when measured using Cu K_α radiation at 15.1±0.2, 16.0±0.2, 18.9±0.2, 20.4±0.2, 22.5±0.2, 27.3±0.2, 29.3±0.2 and 30.4±0.2.
>
> **2**. The crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride according to claim **1** exhibiting at least X-ray lines (2-theta values) in a powder diffraction when measured using Cu K_α radiation at 14.5±0.2, 18.2±0.2, 20.4±0.2, 21.7±0.2 and 25.5±0.2.
>
> **3**. The crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride according to claim **1** exhibiting an X-ray pattern (2-theta values) in a powder diffraction when measured using Cu K_α radiation essentially the same as that provided in FIG. **1**.

['364 patent at 18:65-19:15.]

Claim 25 is directed to a pharmaceutical composition comprising crystalline Form A of tapentadol hydrochloride, described in terms of its X-ray diffraction pattern.

> **25**. A solid pharmaceutical composition comprising, as an active ingredient, a crystalline Form A of (–)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride exhibiting at least X-ray lines (2-theta values) in a powder diffraction pattern when measured using Cu K_α radiation at 15.1±0.2, 16.0±0.2, 18.9±0.2, 20.4±0.2, 22.5±0.2, 27.3±0.2, 29.3±0.2 and 30.4±0.2, and at least one suitable additive or auxiliary substance.

['364 patent at 20:56-63.]

i. Inherent Anticipation

Defendants contend that the asserted claims of the '364 patent are invalid under 35 U.S.C. § 102(b) as inherently anticipated by Example 25 of the '737 patent. [PTO ¶ 1469.] To prove that the '364 patent is inherently anticipated, Defendants bear the burden of proving by clear and convincing evidence that Example 25 "necessarily and inevitably" produces the claimed invention, Form A of tapentadol hydrochloride. *See Schering*, 339 F.3d at 1379.

Defendants argue that polymorphic Form A of tapentadol hydrochloride in the asserted claims, is inherently anticipated because "Example 25 of the '737 patent describes a procedure for making tapentadol hydrochloride crystals that inevitably results in at least some Form A." [Defs. Br. at 18.] On this issue, Defendants presented the testimony of Dr. Jonathan Steed and Dr. Adam Matzger. Plaintiffs respond that Defendants have not proven that the procedure set forth in Example 25 necessarily and inevitably results in Form A. On this issue, Plaintiffs presented the testimony of Dr. Joel Bernstein and Dr. William Roush.

It is undisputed that the '737 patent (including Example 25) does not explicitly mention polymorphs and it does not disclose the crystal form of any chemical compound, including tapentadol hydrochloride. Ultimately, the dispute on this issue is whether Defendants have met their burden of proving by clear and convincing evidence that the practice of the procedure set forth in Example 25 "necessarily and inevitably" results in the production of polymorphic Form A

of tapentadol hydrochloride. *See Schering*, 339 F.3d at 1379. For the reasons that follow, the Court finds that Defendants have failed to meet that heavy burden.

1. The procedure set forth in Example 25 of the '737 patent

While the invention claimed in the '364 patent is a specific polymorphic form—namely, Form A—of tapentadol hydrochloride, Example 25 of the '737 patent describes a procedure for synthesizing tapentadol hydrochloride without reference to the polymorphic form being synthesized. The Court begins by discussing that procedure, which contains three steps:[23]

(1) Step 1 involves a series of sub-step reactions in which compound (-1) is reacted under the specified conditions to synthesize compound (-22).[24] ['737 patent at 18:51-19:2.]

(2) Step 2 involves a series of sub-step reactions in which compound (-22) is reacted under the specified conditions to synthesize compound (-23).[25] ['737 patent at 19:18-47.]

[23] The '593 patent does not explicitly disclose the three steps of Example 25 but instead states that they are identical to the three steps of Example 24, with the only difference being the starting material. The starting material for Example 25 is compound (-1), chemically named (–)-(2S,3S)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol hydrochloride. Compound (-1) is the enantiomer of (+1), which is the starting material for Example 24. Accordingly, to convert the procedure of Example 24 to the procedure of Example 25, each "(+)" becomes a "(–)"and each "R" becomes an "S", and vice versa.

[24] The chemical name of compound (-22) is (–)-(2S,3S)-[3-Chloro-3-(3-methoxyphenyl)-2-methylpentyl]-dimethylamine hydrochloride.

[25] The chemical name of compound (-23) is (–)-(2S,3S)-[3-(3-methoxyphenyl)-2-methylpentyl]-dimethylamine hydrochloride.

(3) Step 3 involves a series of sub-step reactions in which compound (-23) is reacted under the specified conditions to synthesize compound (-21),[26] which is tapentadol hydrochloride. ['737 patent at 19:49-67.]

[*See* 3/15 Tr. (Steed) at 191:19-193:19; Steed Demonstrative 4.] The tapentadol hydrochloride product is not formed until the end of Step 3 of the three-step synthesis described in Example 25. [DFOF ¶ 1009; 3/15 Tr. (Steed) at 190:20-191:11, 193:11-19.]

In the first sub-step of Step 3, compound (-23) is dissolved in hydrobromic acid, at which point it is no longer a crystalline solid because it is in solution. [DFOF ¶ 109; '737 patent at 19:52-53; 3/10 Tr. (Buschmann) at 176:8-21.] Once the compound is in solution, the Step 3 sub-step reactions first result in the free base form of tapentadol (*i.e.*, tapentadol without the hydrochloride) in solution. [DFOF ¶ 1010; 3/15 Tr. (Steed) at 193:11-19.] The final sub-step reaction in Step 3 (addition of trimethylchlorosilane/water to the solution) is the point in the synthesis at which the tapentadol hydrochloride product crystallizes out of the solution. [DFOF ¶ 1010; 3/15 Tr. (Steed) at 191:4-11, 193:20-25; 3/21 Tr. (Bernstein) at 262:17-23.]

2. Evidence presented on inherent anticipation

On the issue of inherent anticipation, the parties presented evidence of samples of tapentadol hydrochloride that were purportedly synthesized in accordance with the procedure of Example 25. The Court addresses these samples as follows.

a. The University of Wisconsin

In support of their inherent anticipation contention, Defendants commissioned scientists at the University of Wisconsin to perform a synthesis that Defendants contend is consistent with the

[26] The chemical name of compound (-21) is (–)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride.

procedure of Example 25. The University of Wisconsin scientists' task was "to reproduce step three of Example 25." [PFOF ¶ 417; 3/16 Tr. (Steed) at 32:6-19, 33:16-20.] Dr. Steed testified as to the University of Wisconsin scientists' performance of each of the sub-step reactions in Step 3, which resulted in the crystallization of the white powder tapentadol hydrochloride product sample. [DFOF ¶¶ 1019-1022; DTX-298; 3/15 Tr. (Steed) at 206:22-213:10; Steed Demonstratives 6-7.] The XRPD analysis that was performed on the product sample shows that the University of Wisconsin scientists produced a mixture of Form A and Form B—*i.e.*, they produced some Form A tapentadol hydrochloride crystals and some Form B tapentadol hydrochloride crystals. [DFOF ¶ 1023; DTX-297; 3/15 Tr. (Steed) at 215:13-217:20; 3/22 a.m. Tr. (Bernstein) at 6:8-11.] This result, Defendants contend, is proof that performing the procedure of Example 25 produces Form A of tapentadol hydrochloride in anticipation of the '364 patent.

In challenging Defendants' inherent anticipation evidence, Plaintiffs contend that the University of Wisconsin scientists did not faithfully follow the procedure of Example 25 because they only performed Step 3 of the synthesis and did not start at the beginning with Step 1. [PFOF ¶ 416; 3/15 Tr. (Steed) at 195:18-196:3, 205:14-18.] Plaintiffs contend that, in general, a faithful reproduction requires going back to the beginning of the procedure and starting where the inventor started because each step in the procedure can affect the nature of the final product. [*See* PFOF ¶¶ 422-23; 3/21 Tr. (Bernstein) at 238:15-18, 238:22-239:5; 3/16 Tr. (Steed) at 28:11-16.] In this case, Plaintiffs' expert testified that a faithful reproduction would have required completing each of the steps in Example 25. [*See* PFOF ¶ 422; 3/22 p.m. Tr. (Roush) at 42:22-43:2.] As discussed below, Plaintiffs presented evidence of syntheses in which a Grünenthal technician performed all of the steps of Example 25. [*See infra.*] Because the University of Wisconsin's synthesis did not

begin at Step 1, Plaintiffs contend it was "a truncated 'reproduction' . . . unfaithful to Example 25" [*see* Pls. Br. at 36] and is, therefore, not proof of inherent anticipation.

Defendants responded to Plaintiffs' criticism of the University of Wisconsin sample by offering Dr. Steed's explanation of the reasoning behind Defendants' decision to only commission the performance of Step 3. Dr. Steed explained that Defendants commissioned only Step 3 (and not Steps 1 and 2) because the starting material for Step 3 is known and is immediately placed into solution at the beginning of Step 3, at which point the sample does not have a crystal structure. [*See* DFOF ¶¶ 1008-1009; '737 patent at 19:52-53; 3/15 Tr. (Steed) at 191:4-24, 193:11-19; 3/10 Tr. (Buschmann) at 176:8-21.] The remainder of Step 3 occurs in solution and the crystallized tapentadol hydrochloride does not form until the very last sub-step reaction of Step 3. [DFOF ¶ 1010; 3/15 Tr. (Steed) at 191:4-11, 193:20-25; 3/21 Tr. (Bernstein) at 262:17-23.] Accordingly, Defendants contend that Step 3 is "the only one that's relevant in terms of defining the polymorphic form and of course the conditions under which it occurs." [*See* DFOF ¶ 1010; 3/15 Tr. (Steed) at 194:8-10, 205:19-206:1.]

Ultimately, the parties have offered competing views as to whether the University of Wisconsin faithfully performed the procedure of Example 25. It is Defendants' burden to prove inherent anticipation by clear and convincing evidence. The record reflects only one synthesis by the University of Wisconsin scientists, which consisted of less than all of the steps enumerated in the patent and produced a mixture of Form A and Form B crystals. Plaintiffs contend that the University of Wisconsin testing is insufficient given its shortcomings, particularly in light of the remainder of the record.

b. Grünenthal technician Marita Müeller

In further opposition to Defendants' inherent anticipation position, Plaintiffs presented evidence of their own samples of tapentadol hydrochloride synthesized using what they contend

was the procedure of Example 25. Grünenthal technician Marita Müeller made four attempts (three in 2002 and one in 2009) to synthesize tapentadol hydrochloride in accordance with the procedure of Example 25. [PFOF ¶ 393; 3/10 Tr. (Gruss) at 257:17-24.] Ms. Müeller began at the beginning of Example 25 and performed each step of the synthesis. [PFOF ¶ 394; 3/22 a.m. Tr. (Roush) at 27:9-28:13.] It is undisputed that two of Ms. Müeller's syntheses (her first and third syntheses) produced tapentadol hydrochloride samples that contained only Form B. [PFOF ¶ 394; 3/16 Tr. (Steed) at 44:19-22; 3/16 Tr. (Matzger) at 112:11-14; 3/22 p.m. Tr. (Roush) at 29:7-23.] In 2002, and again at trial, Dr. Gruss reviewed the results of XRPD analysis from Ms. Müeller's tapentadol hydrochloride samples and concluded that both of Ms. Müeller's samples produced only Form B with no Form A. [PFOF ¶¶ 397-98; 3/10 Tr. (Gruss) at 259:21-260:3, 260:15-262:22; PTX-491_C.] The expert witnesses agreed with Dr. Gruss's conclusions. [PFOF ¶¶ 399-400, 401, 409; 3/21 Tr. (Bernstein) at 222:12-228:10; Bernstein Demonstrative at 13-17; DTX-491_C; 3/16 Tr. (Steed) at 7:17-8:18.] Thus, Plaintiffs contend, following the procedure of Example 25 can produce tapentadol hydrochloride that is only Form B.

Defendants, however, challenge Ms. Müeller's syntheses as unfaithful to Example 25. Defendants' expert, Dr. Steed, reviewed the records of Ms. Müeller's work and testified that, in his opinion, Ms. Müeller made mistakes in her synthetic process that rendered her syntheses unfaithful to Example 25. [DFOF ¶¶ 1045-46; 3/15 Tr. (Steed) at 218:11-219:9, 220:22-221:5.] Plaintiffs, responded by presenting evidence Dr. Steed's criticisms were inaccurate or irrelevant. [*See, e.g.,* PFOF ¶ 394; 3/22 p.m. Tr. (Roush) at 27:9-28:13.]

Specifically, Dr. Steed first identified problems with the amount and character of Ms. Müeller's starting material [3/15 Tr. (Steed) at 221:11-18; PTX-567_T at GRT-NUC00110768_T] but he later admitted that the experiment was appropriately scaled [PFOF ¶ 404; 3/16 Tr. (Steed)

at 42:2-5]. Second, Dr. Steed noted problems with the drying step which could result in bromide impurities [DFOF ¶ 1049; 3/15 Tr. (Steed) at 224:25-225:25] but Dr. Roush explained that the drying was sufficient and would not result in impurities [PFOF ¶ 406; 3/22 p.m. Tr. (Roush) at 32:22-33:11]. Third, Dr. Steed testified that Ms. Müeller failed to premix TMCS (trimethylchlorosilane) and water in the final crystallization step such that hydrochloric acid was not generated and impurities were introduced [DFOF ¶ 1050; 3/15 Tr. (Steed) at 226:1-25; PTX-567_T] but Dr. Roush testified that it would have been unsafe to premix the TMCS and water and that adding them separately would not change the reaction [PFOF ¶ 407; 3/22 p.m. Tr. (Roush) at 34:21-35:25]. Fourth, Dr. Steed noted that at the end of Ms. Müeller's synthesis, when crystals did not fall out of the solution spontaneously, she improvised by immersing the mixture in an ice bath to get a solid. [*See* DFOF ¶ 1051; 3/15 Tr. (Steed) at 227:1-14; Müeller Depo. at 63:14-24, 64:25-65:2, 65:5-11, 66:4-19.] But Dr. Roush testified that stirring in an ice bath is a standard laboratory procedure in order to obtain crystals. [PFOF ¶ 408; 3/22 p.m. Tr. (Roush) at 36:12-38:1.]

Defendants also presented the testimony of Drs. Steed and Matzger that the beige or yellow color of Ms. Müeller's tapentadol hydrochloride product samples was indicative of an impure product. [DFOF ¶¶ 1052-53, 1056; DTX-1202; DTX-1206; 3/10 Tr. (Buschmann) at 128:4-18; Müeller Depo. at 68:6-9, 78:1-5; PTX-567_T at GRT-NUC00110768_T; DTX-10003_0015; 3/16 Tr. (Matzger) at 99:7-14; 3/15 Tr. (Steed) at 227:15-19, 228:19-21.] However, Dr. Roush confirmed that color is not necessarily indicative of an impure product. [3/22 p.m. Tr. (Roush) at 29:24-30:21.] Furthermore, there is no color identified in Example 25. [PFOF ¶ 414; 3/16 Tr. (Matzger) at 131:24-132:1.]

Defendants do not dispute that Ms. Müeller's syntheses resulted in tapentadol hydrochloride or that it was Form B. [*See* 3/16 Tr. (Steed) at 7:17-8:22.] Defendants' criticisms of Ms. Müeller's work largely focused on impurities. [*See, e.g.*, 3/15 Tr. (Steed) at 218:11-219:9; 3/16 Tr. (Matzger) at 111:1-4, 18-21.] Defendants have posited the theory that the presence of impurities can cause a synthesis to result in Form B rather than Form A and, therefore, Ms. Müeller's work was not a faithful reproduction of Example 25 because it contained too many impurities. [*See, e.g.*, 3/15 Tr. (Steed) at 194:11-22; 3/21 Tr. (Bernstein) at 256:21-257:18; *see also* DFOF ¶¶ 1060-78; DTX-1158_0002-03; DTX-1242; 3/21 Tr. (Bernstein) at 268:3-6, 271:20-272:14, 274:14-19, 277:11-20; 3/10 Tr. (Buschmann) at 201:23-202:2; 3/15 Tr. (Steed) at 194:11-22; DTX-1242_0013; DTX-1075_0008; DTX-1279_0003-04; 3/16 Tr. (Matzger) at 84:25-85:22, 87:18-22, 88:7-21.] Defendants argue that when Example 25 is faithfully performed, the product will be largely free of impurities and Form A will result. [*Id.*]

However, Plaintiffs emphasize that Example 25 does not contain a purity limitation. [PFOF ¶ 414; 3/16 Tr. (Matzger) at 131:12-21.] Indeed, Defendants' experts admitted that a POSA performing Example 25 would expect to get some impurities because all chemical samples have impurities and they were unable to provide a "firm answer" on how much impurities would be too much to constitute a faithful reproduction of Example 25. [PFOF ¶¶ 412-13; 3/16 Tr. (Steed) at 21:14-25, 34:18-19, 3/16 Tr. (Matzger) at 114:22-24, 115:11-13, 116:14-24, 118:4-18.] Thus, Plaintiffs contend, Defendants' impurities theory is a red herring that does not impact whether or not the reproduction of Example 25 was faithful. [*See* Pls. Br. at 37.]

Similar to the University of Wisconsin sample discussed above, the parties have offered extensive competing evidence as to whether Ms. Müeller's syntheses were faithful reproductions of Example 25. Notwithstanding Defendants' challenges, Ms. Müeller's syntheses, during which

she performed all of the steps of Example 25 and produced Form B, weigh against a determination that Defendants have proven inherent anticipation by clear and convincing evidence.

c. '364 patent Example 2 starting material

There is one additional tapentadol hydrochloride sample on which Defendants rely to demonstrate inherent anticipation. That sample is the internal Grünenthal sample that was the starting material for '364 patent Example 2 ("Ex. 2 Starting Material"), which Defendants point to as a sample of Form A prepared according to Example 25. [DFOF ¶¶ 1024-28; DTX-144_0007-09; DTX-1001_0005, 13-14 (Tables 1-3); 3/11 Tr. (Gruss) at 56:11-14, 62:24-63:1; '364 patent at 5:39-41.] However, as discussed, the parties have differing views on what constitutes a faithful performance of Example 25. [*See supra*.] Given the dearth of evidence as to the execution of the process for preparing the Ex. 2 Starting Material, the Court does not find this sample to be sufficient evidence that performing Example 25 necessarily and inevitably produces Form A.

3. Defendants' evidence does not carry their burden on inherent anticipation

"[I]f the teaching of the prior art can be practiced in a way that yields a product lacking the allegedly inherent property, the prior art in question does not inherently anticipate." *Cephalon, Inc. v. Watson Labs., Inc.*, 939 F. Supp. 2d 456, 465 (D. Del. 2013). Thus it is insufficient for Defendants to demonstrate that performing Example 25 ***can*** produce Form A; rather, they must show by clear and convincing evidence that performing Example 25 ***necessarily and inevitably*** produces Form A—*i.e.*, that Example 25 cannot be performed without producing Form A. *See Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047-48 (Fed. Cir. 1995) (affirming the district court's finding of no inherent anticipation where testing evidence demonstrated that the prior art example "could yield crystals of either polymorph").

Defendants have posited that Example 25 produced Form A crystals on two occasions—the University Wisconsin's sample and the Ex. 2 Starting Material. Defendants have failed to put

forth sufficient evidence to meet their burden of showing that Example 25 necessarily and inevitably produces Form A crystals. In fact, the University of Wisconsin's synthesis generated a mixture of Form A crystals and Form B crystals, thus suggesting that the prior art example could yield crystals of either the claimed polymorph or a different polymorph. *See Cephalon*, 939 F. Supp. 2d at 465. Defendants have not clearly convinced this Court that Example 25 cannot be performed without producing Form A. Moreover, Ms. Müeller performed what Plaintiffs have argued was a faithful reproduction of Example 25 and got what Defendants admit was a sample of only Form B tapentadol hydrochloride. [*See supra.*]

Under the law, even if Defendants have shown that following the procedure of Example 25 ***can*** produce Form A tapentadol hydrochloride, that showing would be insufficient to meet their burden on inherent anticipation. *Cephalon*, 939 F. Supp. 2d at 465. The evidence presented at trial by both parties leaves this Court unconvinced that practicing the procedure of Example 25 will ***necessarily and inevitably*** result in Form A. *See Glaxo*, 52 F.3d at 1047-48; *Cephalon*, 939 F. Supp. 2d at 470 ("[T]he court concludes that the defendants have not met their burden of demonstrating that [the prior art example] necessarily and inevitably results in [the claimed polymorph form] and, therefore, have not proved invalidity by inherent anticipation."). Accordingly, the Court finds that the '364 patent is not inherently anticipated by Example 25 of the '737 patent.

ii. Obviousness

Defendants allege that the asserted claims of the '364 patent are invalid for obviousness under 35 U.S.C. § 103. [PTO ¶¶ 1470, 1246-62.] To prove that the '364 patent is obvious, Defendants bear the burden of proving by clear and convincing evidence that the invention of the '364 patent—polymorphic Form A of tapentadol hydrochloride—would have been obvious to a POSA in 2004 at the time of the invention. *See KSR*, 550 U.S. 398.

Defendants contend that Form A of tapentadol hydrochloride would have been obvious in view of the '737 patent in combination with common knowledge in the field about polymorph screening such as found in FDA Guidance [DTX-290] and a 1995 article about polymorph screening published by Dr. Stephen Byrn (the "Byrn article") [DTX-755]. On this issue, Defendants presented the testimony of Dr. Steed. Plaintiffs argue that the claims of the '364 patent were not obvious because polymorphism and the claimed Form A are fundamentally unpredictable. [PTO ¶¶ 697-716; Pls. Br. at 38.] On this issue, Plaintiffs presented the testimony of Dr. Joel Bernstein.

1. Obviousness analysis

As discussed above, the obviousness inquiry requires analysis of four factors: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness. *See Graham*, 383 U.S. at 17-18.

a. The scope and content of the prior art

In analyzing the question of obviousness, the Court must first look at the scope and content of the prior art. *See Graham*, 383 U.S. at 17-18. In this case, the Court evaluates the disclosure of the '737 patent as well as the prior art knowledge about crystalline forms and polymorph screening.

i. The '737 patent

The '737 patent discloses many compounds, one of which is tapentadol hydrochloride. [PFOF ¶ 450; 3/21 Tr. (Bernstein) at 209:14-21; 3/22 a.m. Tr. (Bernstein) at 18:7-17.] The '737 patent states that tapentadol hydrochloride is made in crystalline form, but it does not discuss the crystal structure. [DFOF ¶ 1502; 3/15 Tr. (Steed) at 253:17-21; 3/21 Tr. (Bernstein) at 220:9-12.] The word "polymorph" does not appear in the '737 patent.

ii. Knowledge about crystal forms

The crystal form landscape for a particular compound can include polymorphs, solvates, hydrates, and polymorphs of solvates and hydrates. [PFOF ¶ 442; 3/21 Tr. (Bernstein) at 211:1-212:17.] Dr. Bernstein testified that about 30 to 35% of all compounds are polymorphic. [PFOF ¶ 446; 3/21 Tr. (Bernstein) at 202:23-203:1.] However, it is impossible to predict whether a compound will have multiple crystalline forms, how many it will have, and which forms it will have. [PFOF ¶¶ 443-47; 3/21 Tr. (Bernstein) at 197:6-14 ("[N]o crystal form is predictable."), 200:15-201:19 ("[T]here is no, no molecular feature which can be used as a predictor of polymorphism."), 204:19-205:25; PTX-681 at 241 ("[T]he state of our knowledge and understanding of the phenomenon of polymorphism is still such that we cannot predict with any degree of confidence if a compound will be polymorphic, prescribe how to make possible (unknown) polymorphs, or predict what their properties might be."); DTX-930_0022 ("Unlike salts, which for the most part can be prophetically claimed based on an understanding of the chemical structure of the compound and its ionization constants, the existence and identity of hydrates, solvates, co-crystals and polymorphs have defied prediction."); PTX-693 at JN_NUCYNTA_0064169 ("One of the continuing scandals in the physical sciences is that it remains in general impossible to predict the structure of even the simplest crystalline solids from a knowledge of their chemical composition.").]

iii. Polymorph screening

As early as 1987, the FDA had issued guidelines indicating that "[a]ppropriate analytical procedures should be used to determine whether (or not) polymorphism occurs." [DFOF ¶ 1503; DTX-290_0037; 3/15 Tr. (Steed) at 253:25-255:8.] Such appropriate measures include polymorph screening. [3/15 Tr. (Steed) at 253:21-24; *see also* DFOF ¶ 1504; DTX-755_0001 ("Interest in the subject of pharmaceutical solids stems in part from the [FDA]'s drug substance guideline that

states 'appropriate' analytical procedures should be used to detect polymorphic, hydrated or amorphous forms of the drug substance.").]

Dr. Steed testified that screening for polymorphs is a routine part of pharmaceutical companies' drug development. [3/15 Tr. (Steed) at 253:21-24.] Dr. Buschmann testified that, regardless of regulatory guidelines, it was important to know if tapentadol hydrochloride was polymorphic "not only [for] the regulatory bodies, it was important for any further developments that, to have knowledge of solid form characteristics." [DFOF ¶ 1506; 3/10 Tr. (Buschmann) at 162:16-163:4; *see also* 3/11 Tr. (Gruss) at 78:1-19.] Once tapentadol hydrochloride entered clinical development, Grünenthal considered it "important also to take consideration of the so-called solid phase of the compound intended for oral use," which included "investigat[ing] the hydrochloride salt if different polymorphs may exist." [DFOF ¶ 1503; 3/10 Tr. (Buschmann) at 77:17-78:4.] By 2000, Grünenthal generally understood that pharmaceutical companies "take consideration of polymorphism when they are developing pharmaceutical compounds." [DFOF ¶ 1510; 3/11 Tr. (Gruss) at 77:1-19.]

A POSA would have understood as of June 2004 how to conduct a polymorph screen and there were publications that provided guidance on how to do such a screen. [*See* DFOF ¶¶ 1514, 1520; 3/15 Tr. (Steed) at 255:9-14.] Dr. Gruss understood at that time that polymorph screening was a common technique that involved using different common solvents and temperatures to test for polymorphs. [DFOF ¶ 1515; 3/10 Tr. (Gruss) at 228:15-21 ("[P]olymorph investigation is to apply various parameters on the crystallization like temperature ranges, like various solvents to extend as broad as possible range of investigations in order to understand and characterize the compounds or the compound under consideration.").] Dr. Bernstein has written that "[c]rystallization from solution is one of the first laboratory skills that chemists acquire, and

applying variations to the conventional methods has been the traditional strategy in the search for polymorphs." [DFOF ¶ 1516; PTX-1037 at 3.] Dr. Bernstein has also written that "[o]ne traditional strategy for screening a compound for polymorphic behavior involves the trial of a variety of solvents and solvent mixtures." [DFOF ¶ 1519; PTX-1041 at 252.]

Defendants presented the Byrn article as evidence of the knowledge in the art about common solvents and techniques that should be used in polymorph screens. [DFOF ¶ 1520; DTX-755.] The Byrn article explains steps to detect polymorphism. [DFOF ¶ 1521; DTX-755.] The Byrn article states that "[t]he first step in the polymorphs decision tree is to crystallize the substance from a number of different solvents in order to attempt to answer the question: Are polymorphs possible?" [DFOF ¶ 1522; DTX-755_0002.] The Byrn article specifically lists certain solvents to use in the recrystallization experiments, including "water, methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, ethyl acetate, hexane and mixtures if appropriate." [*Id.*] Figure 1 of the article is a "Flowchart/decision tree for polymorphs." [DFOF ¶ 1521; DTX-755_0002.] The first question in the decision tree is "Polymorphs Discovered?" [*Id.*] To answer this question, the paper states "Different Recrystallizing Solvents (different polarity) – vary temperature, concentration, agitation, pH." [*Id.*] Figure 1 also identifies techniques (including XRPD) that can be used to "Test for Polymorphs." [*Id.*]

b. The level of ordinary skill in the art

The parties have proposed substantially similar definitions of a POSA for the '364 patent. All parties agree that a POSA would be a chemist, chemical engineer, or someone in a similar field who has experience in development, preparation, and characterization of polymorphic forms of compounds. [*See* PFOF ¶ 390; 3/16 Tr. (Matzger) at 69:24-70:16.]

c. The differences between the claimed subject matter and the prior art

The claimed subject matter is a polymorph form of tapentadol hydrochloride, which is one of the many compounds disclosed in the '737 patent. There is nothing in particular in the '737 patent that would have motivated a POSA studying crystal structure to select tapentadol hydrochloride from amongst the many compounds disclosed in the '737 patent. [PFOF ¶ 451; 3/16 Tr. (Steed) at 50:5-10.]

Had a POSA chosen to study the crystal form of tapentadol hydrochloride (from amongst the compounds in '737 patent), its crystal structure could have taken many forms. Had a POSA specifically decided to screen for polymorphs of tapentadol hydrochloride, a POSA would not have been able to look at the structure of tapentadol hydrochloride and predict whether it is polymorphic. [PFOF ¶ 452; 3/10 Tr. (Gruss) at 267:13-21 ("Q. Could the polymorphism of Tapentadol have been predicted from the chemical structure? A. Not to my understanding it could have not been predicted at that point in time."); 3/21 Tr. (Bernstein) at 206:3-7; 3/16 Tr. (Steed) at 50:15-20.] If it had been known that tapentadol hydrochloride was polymorphic, a POSA could not have predicted how many crystal forms it would have. [PFOF ¶ 453; 3/21 Tr. (Bernstein) at 220:23-221:3; 3/16 Tr. (Steed) at 51:2-5.] Finally, if it had been known that tapentadol had two polymorph forms, a POSA could not have predicted the structure, properties, or relative stability of any of the forms. [PFOF ¶ 454; 3/21 Tr. (Bernstein) at 221:1-11; 3/16 Tr. (Steed) at 51:6-10.]

Defendants contend that it was straightforward for Grünenthal to ask SSCI (a company founded by the same Dr. Byrn who authored the Byrn article) to "produce as many new forms of [tapentadol hydrochloride] as possible." [DFOF ¶¶ 1523-1524; 3/22 a.m. Tr. (Bernstein) at 23:6-10; 3/11 Tr. (Gruss) at 19:8-15.] Defendants presented evidence suggesting that SSCI followed known procedures (including using eight of the nine solvents listed in the Byrn article and different cooling and evaporation conditions) to conduct the polymorph screen and arrive at

the conclusion that tapentadol hydrochloride had two polymorphic forms—Form A and Form B. [DFOF ¶¶ 1525-1526; DTX-755_0002; DTX-1087_0018-19; DTX-1001_0014-15; 3/22 a.m. Tr. (Bernstein) at 28:14-29:5; 3/15 Tr. (Steed) at 257:23-259:1.] Defendants argue that "a routine polymorph screen, like the one described in the Byrn article, would have revealed Form A of tapentadol hydrochloride" as one of the two polymorphs. [DFOF ¶ 1528; 3/15 Tr. (Steed) at 259:18-260:2.]

Plaintiffs, however, presented evidence that the Byrn article merely summarized the initial question as whether a compound was polymorphic or not, condensing the many variables listed in other prior art references into a few lines. [PFOF ¶ 461; DTX-930_0003; 3/22 a.m. Tr. (Bernstein) at 44:5-45:12; DTX-755.] Plaintiffs also presented evidence that, while "solution crystallization" is a known technique that may be used to explore the polymorph landscape, it is a technique that includes a large variety of conditions that could be appropriate for a particular polymorph screen, including solvent, temperature, stirring, cooling rate, seeding, and whether an anti-solvent is used. [PFOF ¶ 459; 3/21 Tr. (Bernstein) at 214:12-215:8.] The variability of these conditions produces a huge number of possible choices that must be made during the course of a polymorph screen. [PFOF ¶ 457; 3/21 Tr. (Bernstein) at 213:20-214:10.] Ultimately, there is no way to know how a screen will proceed before beginning to experiment and a POSA has no way of knowing whether more than one form will exist or what the physical properties of the forms are. [PFOF ¶ 464; 3/21 Tr. (Bernstein) at 218:20-24, 219:21-221:11.]

In sum, Plaintiffs demonstrated that, while each individual technique performed during a polymorph screen may be routine, polymorph screening consists of an unpredictable application of those routine techniques. [*See* PCOL ¶ 668.] Plaintiffs further showed that the results of the polymorph screen—*i.e.*, the determination of the structure and properties of the polymorph forms

of tapentadol hydrochloride—would have been impossible to predict. [PFOF ¶ 452; 3/10 Tr. (Gruss) at 267:13-21; *see also* PFOF ¶¶ 443-47; 3/21 Tr. (Bernstein) at 197:6-14, 200:15-201:19, 204:19-205:25; PTX-681 at 241; DTX-930_0022; PTX-693 at JN_NUCYNTA_0064169.] As "predictability is a touchstone of obviousness," *Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009), Defendants have failed to meet their burden of demonstrating that the specific polymorph Form A of tapentadol hydrochloride was obvious. *See Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1358 (Fed. Cir. 2008) ("To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on . . . 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.").

d. Secondary considerations of nonobviousness

Neither party focused on secondary considerations of nonobviousness for the '364 patent. Accordingly, this factor does not impact the analysis.

2. Obviousness in Polymorph Patent Cases

In making this obviousness challenge to the '364 patent, Defendants are the latest in a line of defendants who have argued that newly discovered polymorphs should not be patentable under the law of obviousness. *See, e.g.*, *Cephalon*, 939 F. Supp. 2d at 490; *Merck & Cie v. Watson Labs., Inc.*, 125 F. Supp. 3d 503 (D. Del. 2015), *rev'd on other grounds*, 822 F.3d 1347 (Fed. Cir. 2016); *Takeda Pharm. Co. v. Handa Pharm., LLC*, Case No. C-11-00840, 2013 U.S. Dist. LEXIS 187604, at *232-33 (N.D. Cal. Oct. 17, 2013). In each case the defendants contended that a POSA would have been motivated to discover the claimed polymorph, and in each case the court rejected this argument. *Id.* In *Cephalon*, the court specifically noted that "for a patent challenger to establish obviousness, it is insufficient to allege a general motivation to discover an undefined solution that could take many possible forms." 939 F. Supp. 2d at 500; *see also Innogenetics, N.V. v. Abbott*

Labs., 512 F.3d 1363, 1373-74 (Fed. Cir. 2008) ("[K]knowledge of a problem and motivation to solve it are entirely different from motivation to combine particular references to reach the particular claimed method."). In *Takeda*, the court stated that "here the invention involved the selection from a broad range of available but unpredictable techniques to try to create a previously non-existent crystalline compound whose structure could not be predicted." 2013 U.S. Dist. LEXIS 187604, at *233.

Defendants attempt to distinguish the present case by arguing that "[e]ach court that has declined to find polymorph screening renders polymorph patent claims invalid has lacked the benefit of the Byrn article, or any article that evidences how the patentee followed the specific and express teachings of the prior art . . . ." [*See* DCOL ¶ 1014.] However, the Byrn article was published in 1995, long before many of the cases discussed above. [*See* DTX-755.] Moreover, while it is undisputed in this case that methods for conducting polymorph screening were known in the art, the relevant question is whether such knowledge renders the patent obvious in what courts have described as the "decidedly unpredictable field" of polymorphism. *See Cephalon*, 939 F. Supp. 2d at 501-02.

Defendants attempt to discredit Dr. Bernstein's testimony by noting his opinion that "no polymorph patent can ever be obvious" "[b]ecause [polymorphism] is not predictable." [DFOF ¶ 1530; 3/22 a.m. Tr. (Bernstein) at 30:23-31:19.] While this Court does not speak on the hypothetical question of whether every polymorph patent is nonobvious, the Court notes that Defendants' argument appears to imply the opposite extreme—that every polymorph patent is obvious. This Court does not make such a finding, which would contravene the findings of other district courts and the Federal Circuit. Accordingly, the Court finds that the asserted claims of the '364 patent are not obvious.

iii. Utility

Defendants allege that the asserted claims of the '364 patent are invalid for failure to meet the utility requirement of 35 U.S.C. § 101. [PTO ¶¶ 1471, 1288-95.] To prove that the '364 patent lacks utility, Defendants bear the burden of clearly and convincingly demonstrating that the disclosure does not provide adequate evidence of the benefit of Form A of tapentadol hydrochloride. *See Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 925 (Fed. Cir. 2011).

Specifically, Defendants contend that the statement of utility in the '364 patent is vague and insufficient. [*see* Defs. Br. at 31; DFOF ¶¶ 2001-2013.] Alternatively, Defendants argue that the '364 does not demonstrate the superior stability of Form A over Form B, which is the stated utility. [*See* Defs. Br. at 32-33; DFOF ¶¶ 2014-27.] On this issue, Defendants presented the testimony of Dr. Matzger. Plaintiffs respond that the '364 patent has clear utility under the relevant standard. On this issue, Plaintiffs presented the testimony of Dr. Bernstein.

To establish utility, an application need only "show that an invention is useful" and "disclose a use which is not so vague as to be meaningless." *Fisher*, 421 F.3d at 1371. The '364 patent discloses several uses for Form A, such as providing "new solid forms of [tapentadol hydrochloride] useful in the treatment or inhibition of pain." ['364 patent at 1:42-45.] The '364 patent explicitly references the '737 patent [*see* '364 patent at 1:46], which teaches that tapentadol hydrochloride is useful for treating pain. [*See supra* Section IV.A.ii.] In 2004, it was generally known in the art that tapentadol hydrochloride was useful as an analgesic. [PFOF ¶ 466; DTX-260_0072; 3/22 a.m. Tr. (Bernstein) at 20:12-21:7.] Furthermore, there is no dispute that Form A of tapentadol hydrochloride is useful as an analgesic. [PFOF ¶ 465; 3/16 Tr. (Matzger) at 121:15-17; 3/21 Tr. (Bernstein) at 195:23-196:3.]

In addition to being useful as an analgesic, the '364 patent states:

> Crystalline Form A according to the invention has the same pharmacological activity as Form B but is more stable under ambient conditions. It can be advantageously used as active ingredient in pharmaceutical compositions."

['364 patent at 4:13-17.] Defendants contend that this statement is ambiguous because the terms "stable" and "ambient conditions" are not defined in the patent. [*See* DFOF ¶¶ 2003, 2006-12.] However, the Court understands these terms the same way all of the witnesses appeared to understand the terms—that Form A is the form that tends to persist (and that Form B will tend to convert to Form A) at room temperature. [*See* 3/15 Tr. (Steed) at 234:3-6 ("Q. What evidence have you seen that form A is the stable form at room temperature and that form B converts to form A at that temperature? A. The evidence is abundant."); 3/16 Tr. (Matzger) at 107:6-11 ("Q. Now, Doctor, in your opinion, is Form A of tapentadol hydrochloride the more stable form? A. Yes, of pure tapentadol hydrochloride, I think there's little question that it's the more stable form. Q. And it's more stable at room temperature? A. Yes."); 3/21 Tr. (Bernstein) at 268:3-6 ("Q. And in terms of impurities, when we're looking at the forms B and A, you agree that in fact form A is the stable form at room temperature, correct? A. That's correct."); 3/10 Tr. (Gruss) at 226:14-18 ("It is crystalline form A, Tapentadol hydrochloride, which is thermodynamically[27] stable at room temperature and more stable than the other known form B. Q. More stable than form B. Is that what you are saying? A. Yes.").]

Defendants also contend that thermodynamic stability is not necessarily useful. [*See* Defs. Br. at 32; DFOF ¶ ¶¶ 2014-22.] Defendants support this argument with evidence suggesting that the less stable form of a compound could be more pharmaceutically desirable in some instances [*see* DFOF ¶¶ 2014-20] and they contend that there is nothing in the '364 patent to suggest that

[27] *See* Errata to Trial Transcripts, ECF No. 511-1 at 10.

the more stable form of tapentadol hydrochloride is the more useful form for pharmaceutical activity [*see* DFOF ¶¶ 2020-21]. Defendants' argument, however, appears to import a requirement into the patent statute that the claimed invention be "better" than the prior art—a requirement which the Federal Circuit has declined to find in the statute. *See Demaco Corp. v. F. Von Langsdorff Licensing, Ltd.*, 851 F.2d 1387, 1390 (Fed. Cir. 1988) ("The patent statute does not require that a patentable invention be superior to all prior devices."). Moreover, Dr. Matzger admitted that in order to establish utility, the '364 patent need not establish that Form A is superior to Form B. [PFOF ¶ 470; 3/16 Tr. (Matzger) at 121:11-14.]

Lastly, Defendants contend that, even if stability is the utility of the invention, the disclosure of the '364 patent does not contain sufficient data to support the statement that Form A is more stable. [*See* Defs. Br. at 33; DFOF ¶¶ 2023-26.] However, Example 16 of the '364 patent demonstrates that Form A converts to Form B between 40 and 50 degrees Celsius (which is above room temperature)—and thus Form A is more stable at room temperature. [PFOF ¶ 471; '364 patent at 18:53-57; 3/16 Tr. (Matzger) at 80:14-18, 122:17-25; 3/21 Tr. (Bernstein) at 196:4-197:1.] Dr. Steed agreed with this conclusion; he concluded from Example 16 that Form A and Form B are an "enantiotropic pair," with Form A being stable at room temperature and Form B being stable at higher temperatures. [PFOF ¶ 473; 3/15 Tr. (Steed) at 234:13-235:21.] Thus, Example 16 of the '364 patent provides the evidence to support the statement in the patent that Form A is more stable.

For the foregoing reasons, the Court finds that Defendants have not met their burden of proving by clear and convincing evidence that the asserted claims of the '364 patent lack utility.

C. '364 PATENT – UNENFORCEABILITY

i. Unclean Hands

Defendants contend that Plaintiffs should be barred from enforcing the '364 patent under the doctrine of unclean hands. [PTO ¶¶ 1468, 1263-1287.] On this issue, Defendants bear the burden of demonstrating clearly and convincingly that the patentees intentionally engaged in misconduct during prosecution of the patent that would render it inequitable for the patent to be enforced. *See Therasense*, 649 F.3d 1276.

Specifically, Defendants argue that Grünenthal's inequitable misconduct before the USPTO was the fundamental reason the patent was granted. [*See* Defs. Br. at 34.] The '364 patent represents that Grünenthal had "surprisingly found" "a new form (Form A) of [tapentadol] hydrochloride which is different from the form already known (Form B) obtained by the procedure described in example 25 of U.S. Patent No. 6,248,737 and U.S. Pat. No. 6,344,558 as well as EP 693 475 B1." [DFOF ¶ 2028; '364 patent at 1:58-63; *see also* DTX-87_0009 ("[T]he new crystalline form A is distinct from the hitherto known crystalline form disclosed in US patent nos. 6,248,737 and 6,344,558, referred to in the application as crystalline form B.").] In the "statement of reasons for allowance" of the '364 patent, the USPTO Examiner stated:

> The crystalline form recited in the instant claims and supported by the instant Figures and throughout the specification is novel and nonobvious over the closest prior art disclosed in United States Patent no. 6,248,737. In the instant case, Applicant's[*sic*] compared the form of the closest prior art with the new crystalline form. As claimed, the new crystalline form is novel and nonobvious over the prior art form in view of the evidence provided in the instant specification.

[DFOF ¶ 2029; DTX-1361_0006.] Defendants contend that Grünenthal withheld information and provided misleading information that calls into question the veracity of the statement in the patent

and the Examiner's conclusions. Plaintiffs respond that Grünenthal did not act with unclean hands in procuring the '364 patent. [PTO ¶¶ 721-756.]

1. Presence of Form A in Grünenthal samples

Defendants contend that Form A was present in samples of tapentadol hydrochloride prepared at Grünenthal and SSCI and that it was misleading for Grünenthal to withhold that information from the USPTO. [*See* Defs. Br. at 34-35; DFOF ¶ 2035; DTX-1060; DTX-1088; DTX-1087_0016; DTX-1075; DTX-1242_0013; 3/16 Tr. (Matzger) at 84:24-88:21; *see also* 3/16 Tr. (Matzger) at 140:4-141:7.] However, as questions of novelty and obviousness are dependent on public disclosures and uses, the presence of Form A in non-public internal samples would not have formed the basis for the Examiner to reject the claims of the '364 patent. *See* 35 U.S.C. § 102 ("A person shall be entitled to a patent unless—[]the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention . . . ."). The relevant patentability question regarding the '364 patent, as discussed extensively above, is whether Example 25 necessarily and inevitably produces Form A. [PCOL ¶ 694; PFOF ¶ 482; 3/16 Tr. (Matzger) at 155:12-16.] The Examiner noted that the patentee had distinguished Form A from the form in the prior art Example 25. [DFOF ¶ 2029; DTX-1361_0006.] Plaintiffs presented evidence demonstrating that Grünenthal believed that Example 25 produced Form B [*See supra* (Marita Müeller's syntheses)], which is consistent with what Grünenthal told the Examiner. Defendants have not presented evidence showing that during prosecution Grünenthal believed that Example 25 would produce Form A and intentionally withheld that information. [*See* PCOL ¶ 694.]

2. Figure 4 in the '364 patent

Defendants contend that Grünenthal misleadingly implied that the Form B XRPD pattern in the '364 patent was generated from a tapentadol hydrochloride sample synthesized using the

procedure of Example 25 of the '737 patent, when in fact it was not.[28] [*See* Defs. Br. at 34-35.] However, the patent states only that Figure 4 is the XRPD pattern for Form B [*see* DFOF ¶ 2032; '364 patent at Fig. 4 ("XRPD pattern of Form B")], which it undisputedly is. [*See* PFOF ¶ 486; 3/16 Tr. (Matzger) at 135:24-136:17.]

The '364 patent does not say that Figure 4 is the XRPD pattern for a sample produced by the procedure of Example 25 of the '737 patent, nor does the '364 patent say that Figure 4 is the XRPD pattern for a sample discussed in any of its specific examples. Defendants appear to contend that those statements are implied by the language of some of the examples in the patent that discuss Form B having been prepared according to Example 25 of the '737 patent. [*See, e.g.*, [DFOF ¶¶ 2030-31; '364 patent at 7:35-37, 8:1-17.] Defendants also appear to ask this Court to infer deceptive intent on the part of Grünenthal for making those implied statements. [*See* DFOF ¶ 2041.] On the evidence presented and under the relevant standard for showing unclean hands, the Court does not make such findings.

Moreover, the law is clear that to find unclean hands, "deceptive intent must be 'the single most reasonable inference drawn from the evidence.'" *Ohio Willow Wood*, 813 F.3d at 1358. Here, Dr. Fischer (an inventor of the '364 patent) testified that his choice of the representative Form B pattern to be included in the patent application was not based on deceptive intent but rather his judgment as to "which were the best ones [he] had at that point in time." [*See* PFOF ¶ 488; Fischer Depo. at 292:1-10; *see also* PFOF ¶ 487; 3/16 Tr. (Matzger) at 129:13-19 (conceding that

[28] It is undisputed that the XRPD pattern of Figure 4 was generated from a sample of tapentadol hydrochloride that was not prepared according to Example 25 of the '737 patent. [DFOF ¶ 2033; 3/16 Tr. (Matzger) at 89:19-90:6; DTX-146_0022-23 (Requests for Admission Nos. 21 and 22); DTX-39_0067 (Responses to 30(b)(6) topics).]

a POSA would choose a pattern with good signal to noise ratio).] Accordingly, the Court does not find that the source of Figure 4 forms a basis for unclean hands.

3. Example 2 in the '364 patent

Defendants contend that the '364 patent is misleading because its described methods for preparing samples "were never actually performed as written in the specification." [*See* DFOF ¶ 2037.] Defendants specifically point to Example 2 in the '364 patent, which begins with "tapentadol hydrochloride [] prepared according to example 25." [DFOF ¶ 2038; '364 patent at 5:39-41.]

Defendants appear to argue that, although the Ex. 2 Starting Material was demonstrated to be Form A [*see supra* ('364 patent inherent anticipation)], Example 2 misleadingly implies that it was Form B [*see* DFOF ¶¶ 2037-38]. However, Example 2 in the '364 patent states only that the starting material was tapentadol hydrochloride, not that it was Form B. [*See* '364 patent at 5:39-41.] Moreover, the first step of Example 2 was to dissolve the tapentadol hydrochloride in acetone, at which point the tapentadol hydrochloride in solution is no longer in crystalline form. [PFOF ¶ 491; '364 patent at 5:41-45; 3/16 Tr. (Matzger) at 139:22-25; 140:1-140:3; *see also*; 3/21 Tr. (Bernstein) at 293:10-24.] As there is no false or misleading statement in the patent, the Court does not find that Example 2 forms a basis for unclean hands.

4. Raman Spectroscopy

Defendants contend that, though several examples in the '364 patent conclude by saying that the form produced "was proven by . . . RAMAN microscopic analysis," that procedure was not actually done. [DFOF ¶ 2040; 3/16 Tr. (Matzger) at 137:10-138:14; 159:10-19.] Dr. Matzger distinguished between "RAMAN spectroscopy" (which was done) and "RAMAN microspectroscopy or microscopy" (which Dr. Matzger asserted was not done). [DFOF ¶ 2040; 3/16 Tr. (Matzger) at 159:8-19.]

For the following reasons, however, the Court does not find that the '364 patent's statement about "RAMAN microscopic analysis" provides a basis for a finding of unclean hands. Other than Dr. Matzger's unexplained testimony that there is a difference between "RAMAN spectroscopy" and "RAMAN microspectroscopy," there is no other evidence in the record discussing what the difference is. Furthermore, to the extent there is a difference between the two, the record contains insufficient evidence for the Court to conclude that Grünenthal made an intentional misrepresentation. Ultimately, the sparse record on this issue does not allow Defendants to meet their burden on the defense of unclean hands.

In light of the foregoing, the Court finds that Defendants have not met their burden of clearly and convincingly proving that the '364 patent is unenforceable due to unclean hands.

D. '130 PATENT – INFRINGEMENT

Plaintiffs have asserted claims 1 and 2 of the '130 patent against all Defendants. Plaintiffs have also asserted claims 3 and 6 of the '130 patent against Alkem only.

Independent claim 1 and dependent claim 2 of the '130 patent are directed to a method of treating polyneuropathic pain by administering tapentadol hydrochloride:

> What is claimed is:
>
> **1.** A method of treating polyneuropathic pain in a subject suffering therefrom, said method comprising administering to said subject an effective polyneuropathic pain inhibiting amount of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol
> or a pharmaceutically acceptable salt thereof.
>
> **2.** A method according to claim **1**, comprising administering a hydrochloride salt of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol.

['130 patent at 18:65-19:15.]

Dependent claim 3 and independent claim 6 of the '130 patent are directed to a method of treating a specific type of polyneuropathic pain—namely diabetic polyneuropathy or diabetic polyneuropathic pain—by administering tapentadol hydrochloride.

> 3. A method according to claim 1, wherein said polyneuropathic pain is diabetic polyneuropathic pain.
>
> 6. A method of treating diabetic polyneuropathy in a subject suffering therefrom, said method comprising administering to said subject a pharmacologically effective amount of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol
> or a pharmaceutically acceptable salt thereof.

['130 patent at 18:10-11, 18:16-21.]

i. **Induced Infringement under 35 U.S.C. § 271(b)**

Plaintiffs allege that by selling their tapentadol hydrochloride extended release tablet products, Defendants will induce infringement of the '130 patent in violation of 35 U.S.C. § 271(b). To prove induced infringement of claims 1 and 2, Plaintiffs bear the burden of demonstrating by a preponderance of the evidence that Defendants possess specific intent to encourage others to administer tapentadol hydrochloride to treat polyneuropathic pain.[29] *See AstraZeneca*, 633 F.3d at 1056. [*See* '130 patent, claims 1 and 2.] Plaintiffs must prove that Defendants possess the specific intent to actively encourage physicians, pharmacists, or patients to infringe the patent—not merely evidence that Defendants will describe a way of infringing or permit infringement. *See Takeda*, 785 F.3d at 630-31; *AstraZeneca*, 633 F.3d at 1056; *see also Shire LLC v. Amneal Pharm., LLC*, No. 11-3781, 2014 U.S. Dist. LEXIS 85369, at *15-16 (D.N.J.

[29] Similarly, to prove induced infringement by Alkem of claims 3 and 6, Plaintiffs must demonstrate that Alkem specifically intends to encourage others to administer tapentadol hydrochloride to treat DPN. [*See* '130 patent, claims 3 and 6.]

June 23, 2014) (finding that a permitted use is not necessarily an encouraged use), *aff'd and reversed on other grounds*, 802 F.3d 1301 (Fed. Cir. 2015).

In determining whether Defendants possess the requisite specific intent, it is the actions of the Defendants—in this case, the instructions in the label itself—that must be evaluated. *See Takeda*, 785 F.3d at 634. Information outside the label (*e.g.*, a physician's knowledge) is not sufficient to meet the standard. *See id.* at 631 ("The label must encourage, recommend, or promote infringement."); *see also United Therapeutics Corp. v. Sandoz, Inc.*, No. 12-1617, 2014 U.S. Dist. LEXIS 121573, at *55 (D.N.J. Aug. 29, 2014) ("If some physicians nonetheless choose to prescribe [the defendant's product] for [the patented method] . . . , the Court finds that they will do so based on their own independent belief that [prescribing the defendant's product for the patented method] provides a benefit for their patients. [The defendant]'s label does not instruct them to do so. It is not enough that a user following the instructions may end up practicing the patented method." (internal quotation marks omitted)).

1. Actavis[30]

To prove that Actavis is liable for induced infringement, Plaintiffs must demonstrate that Actavis possesses specific intent to encourage the use of its tapentadol hydrochloride extended release product for the treatment of polyneuropathic pain. Plaintiffs' evidence of this specific intent must be directed to Actavis's actions—*i.e.*, the instructions Actavis has placed in the label of its product. *See Takeda*, 785 F.3d at 634.

[30] For convenience, this section of the Opinion is drafted with resepect to Defendant Actavis. The factual findings and legal conclusions in this section also apply to Defendant Roxane. The Court will address separately the additional information contained within Roxane's label. [*See infra.* Section IV.D.i.2.]

a. Actavis's label does not encourage treatment of polyneuropathic pain.

Actavis's proposed label carves out Indication 2 but Indication 1 remains in the label. [PTO ¶ 66.] The label states:

> Tapendadol extended-release is an opioid agonist indicated for the management of:
>
> - Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

[DFOF ¶ 2558; DTX-1653_0124; 3/11 Tr. (Weinberger) at 183:11-16.] In addition to carving out Indication 2 from its proposed label, Actavis has carved out all other references to neuropathic pain or neuropathy that are contained in the NUCYNTA® ER label. [DFOF ¶ 2559; DTX-1653.] Thus, Actavis's proposed label does not contain the words "neuropathic pain," "neuropathy," "polyneuropathic pain," or "polyneuropathy." [DFOF ¶ 2560; 3/11 Tr. (Weinberger) at 186:4-14; 3/14 p.m. Tr. (Brown) at 112:12-21.] Actavis's proposed label does not contain information about DPN clinical trials. [DFOF ¶ 2561; DTX-1653.] The only clinical trial summary in Actavis's proposed label is the CLBP study. [*Id.*]

Plaintiffs contend that, despite Actavis having carved out Indication 2 (the DPN indication) and all references to neuropathic pain from its label, Actavis still specifically intends for its product to be used to treat polyneuropathic pain. As support for this contention, Plaintiffs note that polyneuropathic pain often manifests as severe chronic pain and that it is likely that some doctors, pharmacists, and patients will use Actavis's tapentadol hydrochloride extended release product to treat polyneuropathic pain. [PFOF ¶ 221; 3/14 p.m. Tr. (Brown) at 40:18-41:23; 3/21 Tr. (Buvanendran) at 41:9-11; 3/11 Tr. (Weinberger) at 186:21-23, 226:23-227:8.] Actavis responds that, under the law of inducement, its knowledge that some physicians, pharmacists, and patients may use its product in a manner that infringes the '130 patent is insufficient to meet the specific

intent requirement for induced infringement. [*See* Defs. Br. at 39; DFOF ¶¶ 2564-65, 2569; DCOL ¶¶ 2502-2507.] Actavis further contends that, to the contrary, its act of carving out Indication 2 and references to neuropathic pain is evidence of the opposite intent—*i.e.*, intent *not* to induce. [*See* DFOF ¶ 2563.] *See Otsuka Pharm. Co., LTD. v. Torrent Pharm. Ltd.*, 99 F. Supp. 3d 461, 485 (D.N.J. 2015) ("The fact that . . . [the d]efendants actively and voluntarily removed any reference to the allegedly infringing indication, in turn, belies any suggestion that these [d]efendants acted with the specific intention to encourage infringement. Indeed, this affirmative action would seem to negate any reasonable inference of an active intent to induce infringement.").

Plaintiffs cannot meet their burden on induced infringement merely by showing that Actavis knows its product will be used to treat polyneuropathic pain. "This would seem to too easily transform that which we have held is 'legally irrelevant'—mere knowledge of infringing uses—into induced infringement." *Takeda*, 785 F.3d at 632 (citation omitted). Accordingly, Plaintiffs assert two theories as to how Actavis's label evidences specific intent to encourage infringement. Plaintiffs' first theory is that, despite the carve-out of the DPN indication, Actavis still intends for its product to be used to treat DPN because DPN is encompassed by Indication 1. [*See* PFOF ¶¶ 226, 228.] Plaintiffs' second theory is that, even with the carve-out, the inclusion of CLBP in the label is evidence that Actavis intends for its product to be used to treat polyneuropathic pain. [PFOF ¶¶ 222-225.] To support these theories, Plaintiffs rely on the testimony of Dr. Michele Brown.[31] Actavis responds by relying on the testimony of Drs.

[31] Defendants elicited testimony from Dr. Brown on cross examination concerning her professional connections with Depomed and Janssen. [*See* DFOF ¶¶ 2570-2573.] Dr. Brown was formerly a member of Janssen's Speakers' Bureau, she is currently a member of Depomed's Speakers' Bureau, and she has testified as an expert for Depomed in other cases. [DFOF ¶¶ 2573; 3/15 Tr. (Brown) at 4:20-5:6, 14:1-25.] As part of her relationship with Depomed, one of her specific responsibilities has been to educate other practitioners about Depomed's NUCYNTA® products. [DFOF ¶ 2571; 3/15 Tr. (Brown) at 6:2-13:5.]

Weinberger and Buvanendran. For the following reasons, the Court does not find either of Plaintiffs' theories persuasive.

i. Actavis's label does not contain evidence that Actavis intends for its product to be used to treat DPN

Plaintiffs contend that, despite Actavis having carved out Indication 2 (the DPN indication) from its label, Actavis still intends for its product to be used in the treatment of DPN. However, Plaintiffs have not pointed to anything in Actavis's label that could be construed as evidence of intent for the product to treat DPN. Instead, as illustrated below, Plaintiffs' evidence on this point focuses on their own NUCYNTA® ER label rather than Actavis's label. *See Takeda*, 785 F.3d at 634 (noting that, for a finding of inducement, the label of the allegedly infringing product must encourage infringement). Indeed, Dr. Brown admitted that her opinions relied on her knowledge of the exact information that Actavis carved out (*i.e.*, the presence of the DPN indication and the summary of DPN studies in the NUCYNTA® ER label).[32] [DFOF ¶ 2575; 3/14 p.m. Tr. (Brown) at 79:8-11, 80:6-81:5, 104:25-106:2; 3/15 Tr. (Brown) at 39:22-41:22.]

For example, Plaintiffs assert (and heavily rely on the notion) that that treatment of DPN is an "on-label"[33] use of Actavis's product even though Actavis's product only contains

[32] As previously noted, Defendants presented testimony of Dr. Brown's professional relationship with Depomed, particularly regarding the NUCYNTA® products. In addition to arguing that this relationship impeaches Dr. Brown's credibility, Defendants contend that, because she has intimate knowledge of and familiarity with NUCYNTA® and tapentadol hydrochloride, her opinions about Actavis's label are not reflective of how an ordinary physician would read the labels. [*See* DFOF ¶ 2574.] *See Acorda Therapeutics Inc. v. Apotex Inc.*, No. 07-4937, 2011 U.S. Dist. LEXIS 102875, at *54 (D.N.J. Sept. 6, 2011) ("[The doctor]'s analysis was not that of a[n] ordinary doctor, who [the plaintiff] alleges will directly infringe the claims. [The doctor] is a paid member of the [plaintiff's] Speakers' Bureau with knowledge of this drug far beyond the information in the label. . . . [He] has substantially more knowledge of what conclusions to draw from the label."), *aff'd per curiam*, 476 F. App'x 746 (Fed. Cir. 2012).

[33] The term "on-label use" refers to a "use[] that [is] approved by the FDA." *See In re Plavix Mktg., Sales Practices & Prods. Liab. Litig.*, 123 F. Supp. 3d 584, 604 (D.N.J. 2015) ("[A] drug

Indication 1. [*See* PFOF ¶ 64 ("The treatment of DPN falls within Tapentadol ER's first indication . . . ."); 3/11 Tr. (Haeussler) at 125:17-23, 126:11-15.] However, to support this assertion, Plaintiffs do not point to Actavis's label but rather their own original NUCYNTA® ER label, which only contained Indication 1. [*See* PFOF ¶¶ 54, 59, 62, 66, 73, 221; 3/11 Tr. (Haeussler) at 116:22-117:1, 126:24-127:23; 3/14 p.m. Tr. (Brown) at 95:17-22, 80:6-81:5, 82:11-14.]

The Court does not find Plaintiffs' reliance on its own original NUCYNTA® ER label persuasive for two reasons. First, as discussed above, Indication 1 was supported in the original NUCYNTA® ER label by the very DPN study that Actavis has specifically carved out of its label. [PFOF ¶¶ 61-62; PTX-1499 at JN_NUCYNTA_0273457-59; 3/11 Tr. (Haeussler) at 121:17-122:16.] Second, Actavis has presented extensive evidence that when NUCYNTA® ER was only approved for Indication 1, DPN was an "off-label"[34] use that could not be promoted by Janssen. [DFOF ¶¶ 2538-44; 3/11 Tr. (Haeussler) at 140:16-24; DTX-1674_0001 ("[Indication 1] is only for moderate to severe chronic pain in adults. That is the only thing that can be said when discussing the indication. In the US, the commercial team is prohibited for promoting for a specific indication example for LBP or OA or DPN unless you have that as an indication statement."); DTX-1419_0008 ("While some are using tapentadol to treat chronic low back pain, many more are treating conditions off-label. [Such off-label c]onditions include DPN, . . . postherpetic neuralgia, ..."); DTX-1419_0025 ("Specifically, the [DPN] indication: Eases concerns for HCPs already or considering prescribing Nucynta for DPN and other neuropathic conditions off-label.").]

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prescribed for its on-label use—by definition—means that the prescription is medically reasonable for its intended purpose by virtue of the FDA approval process.").

[34] If a use is not "on-label," it is referred to as "off-label." Although a doctor may prescribe a drug for an off-label use, a pharmaceutical company may not promote its drug for off-label uses. *See* 21 U.S.C. § 331.

In fact, Janssen paid approximately $50 million dollars to conduct the study necessary to get approval for Indication 2 so that it would be able to promote NUCYNTA® ER to treat DPN [DFOF ¶ 2544; 3/11 Tr. (Haeussler) at 148:6-149:9], which is compelling evidence that NUCYNTA® ER was not previously indicated for DPN.

Defendants have also argued that Plaintiff's decision not to assert claims 3 and 6 of the '130 patent (which are directed to treatment of DPN) against Actavis suggests that Plaintiff does not believe Actavis's label promotes the product for treatment of DPN. [*See* 4/27 Sealed Tr. at 64:3-13, 65:7-66:10.] At the very least, the fact that Actavis has specifically carved out Indication 2 (and "actively and voluntarily removed any reference to" DPN) is evidence that Actavis does not specifically intend to encourage the use of the product for the treatment of DPN. *See Otsuka*, 99 F. Supp. 3d at 485.

ii. Inclusion of the CLBP study in the label is not evidence that Actavis intends for its product to be used to treat polyneuropathic pain

The only clinical study that appears in Actavis's label is the CLBP study that appeared in the original NUCYNTA® ER label as one of two studies supporting the approval of Indication 1. [DFOF ¶ 2561; DTX-1653.] In the context of the approval of Indication 1, that CLBP study appears to have been considered by the FDA, and in fact by Janssen itself, to be a study of nociceptive pain. [*See* DFOF ¶ 2527; 3/11 Tr. (Haeussler) at 116:22-24; 152:5-154:19; DTX-2007_0006 (emphasis added); *see also* DTX-2007_000107.] In light of this characterization, the Court does not find the presence of that study in Actavis's label to be evidence that Actavis specifically intends the drug to be used for polyneuropathic pain.

Specifically, in the FDA's feedback to Janssen about the two studies supporting Indication 1, the FDA stated that "the efficacy of Tapentadol ER in the treatment of chronic pain was established from two positive adequate and well-controlled trials (Studies 11 and 15) . . . ."

[DTX-2007_0007.] Study 11 was a study of patients with CLBP and Study 15 was a study of patients with DPN. [DTX-2007_000105.] As characterized by the FDA's Primary Clinical Reviewer, these two studies had "different populations (LBP and DPN), and different types of pain (nociceptive pain and neuropathic pain)." [DTX-2007_000107.] Accordingly, in its Medical Review, the FDA noted:

> Based on the Clinical Review of Dr. Eric Brodsky, dated 8/19/10, the efficacy of Tapentadol ER in the treatment of chronic pain was established from two positive adequate and well-controlled trials (Studies 11 and 15) with supportive evidence from Study 8. The two positive trials had . . . ***different populations (low back pain [LBP] and painful diabetic peripheral neuropathy [DPN]), and different types of pain (nociceptive and neuropathic)***, thereby providing heterogeneous designs and populations for study of Tapentadol ER.

[DFOF ¶ 2527; DTX-2007_0006 (emphasis added).] Thus, the FDA's characterization of the two studies was that: Study 11, which studied CLBP, was a study of nociceptive pain; and Study 15, which studied DPN, was a study of neuropathic pain. [*Id.*] Plaintiff's fact witness for issues related to regulatory approval of the NUCYNTA® products, Dr. Haeussler, confirmed that the FDA considered the CLBP study to be a study of nociceptive pain in the context of granting approval for Indication 1. [DFOF ¶ 2528; 3/11 Tr. (Haeussler) at 152:5-154:19.]

In addition to the FDA's and Janssen's characterizations of the CLBP study, Defendants presented scientific evidence that the study was of nociceptive pain. The study was conducted to investigate efficacy in subjects with moderate to severe chronic low back pain, but these patients were not screened for neuropathic pain before participating. [DFOF ¶ 2522; PTX-1186 at § 14.1; DTX-1660_0003; 3/14 p.m. Tr. (Brown) at 119:15-17.] The CLBP study was described in detail in a paper published in 2010 by Robert Bunyak, *et al.*, which stated that the CLBP study did not investigate efficacy of tapentadol ER for neuropathic pain. [DFOF ¶ 2524; DTX-1660 ("*Bunyak*").] Defendants presented evidence that, because the study only included information on

the effectiveness for CLBP in patients in the general population without establishing whether any of them had a neuropathic component, a physician likely would not make any assessment of whether Actavis's product was useful for neuropathic pain based on the CLBP study in Actavis's label. [DFOF ¶ 2566; 3/11 Tr. (Weinberger) at 189:3-6, 191:20-192:8.] Thus, this Court does not find the CLBP study in the label to be evidence of Actavis's intent to encourage the use of its product to treat polyneuropathic pain.

Further support for Actavis's position is found in the fact that the FDA appears generally to consider CLBP to be non-neuropathic. In a 2014 draft Guidance for Industry publication by the FDA regarding analgesic indications, the FDA stated that "[n]on-neuropathic pain conditions . . . include chronic low back pain . . . ." [DFOF ¶¶ 2534; DTX-2064_00010; *cf.* DFOF ¶ 2534; PTX-3004 at 18 (March 2016 statement by the Centers for Disease Control and Prevention ("CDC") that "muscular back pain" is nociceptive pain).] Dr. Buvanendran confirmed that CLBP is primarily a form of nociceptive pain.[35] [DFOF ¶ 2532; 3/21 Tr. (Buvanendran) at 42:6-8.]

The Court recognizes that Plaintiffs have presented evidence concerning the estimated percentage of CLBP patients who suffer from a neuropathic component. [*See, e.g.*, DFOF ¶ 2524; DTX-1660_0016.; DFOF ¶ 2525; DTX-1664_0006.] This estimated percentage varies in the literature, with some estimates ranging as high as 55%. [DFOF ¶ 2533; PTX-872 ("*Morlion*") ("approximately 20-55%")[36]; DTX-1662_0001 (estimate of 20-35%); DTX-1664_0002 (estimate

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[35] Moreover, Dr. Buvanendran testified that to the extent CLBP patients suffer from a neuropathic component, it is overwhelmingly mononeuropathic in nature rather than polyneuropathic. [3/21 Tr. (Buvanendran) at 42:8-14.]

[36] Plaintiffs cite the *Morlion* reference for the proposition that "[u]p to at least 83% of CLBP patients have a polyneuropathic pain component." [*See* PFOF ¶ 225.] What *Morlion* actually states is that "approximately 20-55% of patients with chronic LBP have a >90% likelihood of a neuropathic pain component, and, in an additional 28% of patients, a neuropathic pain component is suspected." [PTX-872 at JN_NUCYNTA_1656869.] *Morlion* does not provide compelling evidence for the higher end of Plaintiffs' range.

of 37%).] However, Plaintiffs' evidence on this point is unpersuasive for the following reasons. First, it is noteworthy that Plaintiffs' evidence about CLBP does not appear to sufficiently distinguish between polyneuropathic pain (which would infringe) and mononeuropathic pain (which would not infringe). [*See* DFOF ¶ 2533.] Second, and more critically, the literature confirms that even CLBP patients who may be suffering from a neuropathic component are still suffering from pain that is primarily nociceptive. [*See* DFOF ¶ 2533; *Morlion* at JN_NUCYNTA_1656870 ("Overall, 80-90% of patients with LBP are thought to experience pain arising from a nociceptive mechanical cause.").] Ultimately, Plaintiffs' evidence estimated that pure neuropathic causes are thought to account for only 5-15% of low back pain and that number may be higher for chronic low back pain. [DFOF ¶ 2533; *Morlion* at JN_NUCYNTA_1656870.] Again, however, this estimate does not appear to account for CLBP patients suffering from mononeuropathic pain, treatment of which would not infringe the '130 patent.

At most, Plaintiffs' evidence suggests that CLBP patients, in the abstract, can have a neuropathic component to their pain. However, Defendants' evidence directly addressed the specific CLBP study in Actavis's label, demonstrating that it has been characterized as a study of nociceptive pain by Janssen and the FDA. [*See supra.*] Defendants have also raised doubts that a physician would consider prescribing a product for polyneuropathic pain based solely on the CLBP study in Actavis's label. [*See supra.*] Defendants presented evidence that, despite Plaintiffs' presentation of percentage estimates for neuropathic components, CLBP is generally considered to be nociceptive in nature. [*See supra.*] Finally, Actavis's act of removing the DPN indication and any reference to DPN from its label is evidence that Actavis does not intend for its product to be used to treat polyneuropathic pain. [*See supra.*] Thus, on the evidence in the record, Plaintiffs

have not demonstrated that the presence of the CLBP study in Actavis's label is evidence that Actavis specifically intends for its product to be used to treat polyneuropathic pain.

b. Actavis's tapentadol hydrochloride extended release product will not induce infringement of the '130 patent.

In light of the factual findings above, the Court starts with the legal premise that to find inducement, "[t]he label must encourage, recommend, or promote infringement." *Takeda*, 785 F.3d at 631. Descriptions of an infringing method are insufficient. *Id.* ("The question is not just whether instructions 'describ[e] the infringing mode,' but whether the 'instructions teach an infringing use of the device *such that* we are willing to infer from those instructions an affirmative intent to infringe the patent.'" (citation omitted)). Because Plaintiffs have not pointed to such evidence in Actavis's label, Plaintiffs have not met their burden.

Plaintiffs argue that the *Takeda* case (and other cases on which Defendants rely) is inapposite because it involved an off-label use of the drug, whereas in this case the infringing use of Actavis's product to treat polyneuropathic pain would allegedly be an on-label use. However, because Actavis's label contains only Indication 1 supported only by the CLBP study, the Court is not persuaded that treatment of polyneuropathic pain is an on-label use of Actavis's product in this case.[37] [*See supra* Section IV.D.i.1.a.i.] Accordingly, the Court does not find that Plaintiffs' distinction between on-label and off-label provides a convincing or helpful framework in this case.

Moreover, even assuming this is a case where the infringing use is on-label for Actavis's product, Plaintiffs cite no case law for the proposition that the mere fact that a use is on-label ends

[37] This can be contrasted with the Court's statement made in denying Roxane's Motion for Summary Judgment of Noninfringement of the '130 Patent that "Indication 2 [] is merely a subset of Indication 1 . . . ." [ECF No. 390.] In that context, the label at issue included both indications as well as two DPN studies, neither of which appears in the current carved out versions of Actavis's or Roxane's label.

the inducement inquiry. Indeed, Defendants cite the *Shire* case from this district, which stands for the opposite proposition—that a "permit[ted]" on-label use is not necessarily an encouraged use. *Shire*, 2014 U.S. Dist. LEXIS 85369, at *15-16. In *Shire*, the plaintiff held a patent to a method of treatment comprising administering a drug "with intake of food." *Id.* The defendants' proposed label stated that "the products may be taken 'with or without food.'" *Id.* As the court stated:

> The problem is that the statement that the medication may be taken with or without food cannot be reasonably understood to be an instruction to engage in an infringing use. As [the d]efendants contend, it is indifferent to which option is selected. At most, it may be understood to permit an infringing use, but permission is different from encouragement.

Id. at 16.

The *Shire* case is informative on the issue presented in this case. As the instruction in Actavis's label only instructs the user to administer the drug to treat severe chronic pain, which undisputedly includes nociceptive pain, it cannot reasonably be understood to be an instruction to engage in the infringing use of administering the drug to treat polyneuropathic pain. *See id.* at 15-16. Thus, even if the label permits administration for polyneuropathic pain, permission is different from encouragement. *Id.*

Plaintiffs rely heavily on the language of the Federal Circuit in *AstraZeneca LP v. Apotex, Inc.*, where the court stated:

> [T]he district court found that [the defendant] had the requisite specific intent to induce infringement because [the defendant] ***included instructions in its proposed label that will cause at least some users to infringe*** the asserted method claims."

633 F.3d, 1042, 1060 (Fed. Cir. 2010) (emphasis added). Plaintiffs contend that Actavis's label fits this description. However, even if "some users" may use Actavis's product to treat polyneuropathic pain in a way that infringes, as discussed above, the Court does not agree that Actavis's label "includes instructions . . . that will ***cause***" those users to infringe. *See id.* (emphasis

added). In *Apotex*, the court determined that following the label instruction to "titrat[e] down from the recommended starting doses ***would necessarily lead to [the infringing]*** once-daily usage." *See id.* at 1049 (emphasis added). Here, on the other hand, doctors can and likely will follow the instructions on Actavis's label to prescribe Actavis's product for noninfringing purposes, such as treating nociceptive and mononeuropathic pain. [*See infra* Section IV.D.ii (Contributory Infringement).] Furthermore, to the extent doctors prescribe Actavis's product for infringing polyneuropathic pain treatments, it will not be because they have been encouraged by Actavis's label to do so. *See Shire*, 2014 U.S. Dist. LEXIS 85369, at *15-16; *see also Takeda*, 785 F.3d at 632.

Plaintiffs have also directed the Court's attention to the recent decision from the District of Delaware in *GlaxoSmithKline LLC v. Teva Pharmaceuticals USA, Inc.*, No. 14-878, 2016 U.S. Dist. LEXIS 94438 (D. Del. July 20, 2016), where the magistrate judge addressed similar facts to this case—namely, inducement by a drug label indication that was alleged to overlap with a carved out indication. In that case, the magistrate judge explicitly rejected the defendant's argument that a finding of induced infringement should be legally precluded any time a defendant files a Section viii statement and carves out its label. *Id.* at *42-43. Instead, the magistrate judge determined at the motion to dismiss phase that, accepting all of the allegations in the complaint as true, the plaintiff had stated a claim for inducement that was plausible and should have the opportunity to present evidence of the defendant's specific intent to induce infringement through further stages of the case. *Id.* at *37-52.[38]

[38] The Court notes that in *GlaxoSmithKline*, the defendant had taken specific actions to promote the product, including issuing press releases and marketing the product as AB rated. *Id.* at *26-37. This may be contrasted with the instant case.

This Court agrees fully with the conclusion in *GlaxoSmithKline* that the mere fact that Actavis has carved out Indication 2 from its label does not preclude Plaintiff's claim for inducement as a matter of law. Indeed, that is why this case was not terminated at the motion to dismiss or summary judgment stages. [*See* Case No. 15-6797, ECF No. 55 and 56 (Opinion and Order denying Motion to Dismiss); Case No. 14-3941, ECF Nos. 195 and 196 (Opinion and Order denying motion for summary judgment of noninfringement).] Like the magistrate judge in *GlaxoSmithKline*, this Court declined to dismiss Plaintiffs' claims or grant summary judgment in favor of Defendants, thus allowing Plaintiffs the opportunity to put forth evidence at trial of Actavis's specific intent to encourage the use of their products for the treatment of polyneuropathic pain.[39] At this point, however, this case has advanced through trial and Plaintiffs had the burden of presenting evidence of that specific intent. As discussed above, Plaintiffs failed to meet that evidentiary burden.

Plaintiffs cite case law for the proposition that the label need not use the exact words in the patent to induce infringement. [*See* PCOL ¶ 559 (citing *In re Omeprazole Patent Litig.*, 258 F. Supp. 2d 221, 235 (S.D.N.Y. 2001); *L.A. Biomedical Res. Institute v. Eli Lilly & Co.*, No. 13-8567, 2014 U.S. Dist. LEXIS 185431 (C.D. Cal. May 12, 2014); *Bone Care Int'l, L.L.C. v. Roxane Labs., Inc.*, No. 09-285, 2012 U.S. Dist. LEXIS 80450 (D. Del. June 11, 2012)).] Specifically, Plaintiffs quote language from *Omeprazole* indicating that the "absence of direct instruction on infringement . . . does not foreclose finding of active inducement." [*Id.*] Plaintiffs' quote, however, is truncated

[39] In denying Actavis's Motion to Dismiss, this Court declined to "engage in specific fact-finding" as to the instructions in Actavis's label and allowed Plaintiff's declaratory judgment claim for inducement to proceed. [Case No. 15-6797, ECF No. 55 at 11-12.] Similarly, in denying Roxane's Motion for Summary Judgment of Noninfringement, the Court concluded that Plaintiffs' evidence of intent raised "questions of fact that Roxane may explore at trial." [Case No. 14-3941, ECF No. 195 at 11-12.]

and omits the end of the *Omeprazole* court's sentence: "where the intended use of products would be readily apparent to the customer." *Omeprazole*, 258 F. Supp. 2d at 235 (citing *Mendenhall v. Astec Indus., Inc.*, 887 F.2d 1094 (Fed. Cir. 1989)). This Court does not require "magic words" in the label for a finding of inducement. *See Omeprazole*, 258 F. Supp. 2d at 234-35. What is required, however, is a showing that Actavis intends its customers to use the product to treat polyneuropathic pain because that use is readily apparent to the customer from the label—as discussed above, Plaintiffs have failed to make such a showing.

Similarly, Plaintiffs cite *Bone Care* and *L.A. Biomedical*, where the courts found that even though the label did not use the exact terms of the patent, there was inducement. However, in those cases, the courts first determined that the use of the product to treat a symptom in a manner consistent with the label would directly result in the patented treatment of the underlying condition. *Bone Care*, 2012 U.S. Dist. LEXIS 80450, at *33; *L.A. Biomedical*, 2014 U.S. Dist. LEXIS 185431, at *14 ("Therefore, a once daily dosage of [the drug] to treat ED in these patients results directly in treatment of the underlying penile fibrosis and the performance of the patented method."). Here, by contrast, nociceptive pain and neuropathic pain are distinct types of pain. [*See* PFOF ¶¶ 81-91; 3/23 Tr. (Ossipov) at 160:4-14.] Noninfringing uses of Actavis's product to treat nociceptive pain or mononeuropathic pain can be entirely distinct from uses of the product to treat polyneuropathic pain. [*See id.*] Thus, Plaintiffs have not demonstrated that use of Actavis's product in a manner consistent with Actavis's label will result directly in the infringing treatment of polyneuropathic pain.

Lastly, during her testimony, Plaintiffs' expert (Dr. Brown) was asked the following question by Plaintiffs' counsel:

> What would the label look like if somebody wanted to avoid infringement of the '130 patent, in your opinion?

[3/15 Tr. (Brown) at 92:10-11.] Dr. Brown responded:

> I would put under limitations of use to prescribe this for everything but polyneuropathic pain.

[3/15 Tr. (Brown) at 92:12-13.] Dr. Brown's opinion on this matter, however, does not alter the law of inducement. As the Federal Circuit said in *Takeda*, "[t]his turns the legal test on its head." 785 F.3d at 632 n.4. It is Plaintiffs' burden to demonstrate by a preponderance of the evidence that Actavis's proposed label encourages infringement. *See id.* It is not Actavis's burden to demonstrate affirmative steps taken to make sure that others avoid infringement. *Id.*

In light of the evidence that has been presented and the relevant case law, this Court finds that Plaintiffs have failed to meet their burden of proving induced infringement by a preponderance of the evidence against Actavis.

2. Roxane

Similar to Actavis's label, Roxane's label carves out Indication 2, leaving only Indication 1:

> Tapentadol Extended-Release Tablets are an opioid agonist indicated for the management of:
>
> - moderate to severe chronic pain in adults
>
> when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

[PTO ¶ 102; DFOF ¶ 2550; DTX-1566.] Additionally, Roxane's label contains only the CLBP study but not the DPN studies. [PTO ¶ 102; DFOF ¶ 2549; DTX-2020; DTX-1566; DTX-1568.] Accordingly, regarding the indications and the clinical studies, the Court's conclusions regarding Roxane's inducement are identical to those described above with respect to Actavis. Roxane's label, however, contains two additional pieces of information to which Plaintiffs point as evidence

of Roxane's intent to encourage the use of its product for the treatment of polyneuropathic pain. The Court addresses those pieces of information as follows.

The first place where Roxane's label differs from Actavis's is that, even though Roxane's label only describes the CLBP study, it states that "the efficacy of Tapentadol ER was studied in five studies." [DFOF ¶ 2576; PTX-923.] Dr. Brown opined that a clinician would read this sentence and would then "pull the studies and [] would find the DPN." [DFOF ¶ 2576; 3/15 Tr. (Brown) at 25:19-26:24.] However, this theory of specific intent has been rejected by courts in this district. *See United Therapeutics*, 2014 U.S. Dist. LEXIS 121573, at *49-50 (rejecting the argument that "a scholarly scavenger hunt—which *may* be incited by a reference in [the defendant's] proposed label, which *may* be undertaken by some physicians, and *may* ultimately result in a discovery which leads some physicians [to directly infringe], despite [the defendant's] carve out—may constitute evidence of [the defendant's] intent to induce physicians to engage in infringing conduct" suffices for purposes of induced infringement); *see also Otsuka Pharm. Co., LTD. v. Torrent Pharm. Ltd.*, 99 F. Supp. 3d 461, 493 (D.N.J. 2015) (citing *United Therapeutics*, 2014 U.S. Dist. LEXIS 121573).

The second piece of additional information in Roxane's label is the disclaimer, which reads:

> *Information describing the use of Tapentadol Extended Release Tablets in patients with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy is approved for Janssen Pharmaceuticals, Inc. However, due to Janssen Pharmaceuticals, Inc.'s marketing exclusivity rights, this drug is not labeled with that information.*

[PFOF ¶ 229; PTX-923 at ROXtap00087161.] Plaintiffs contend that this is evidence of intent because this "language would lead any reasonable prescriber to conclude that Roxane's generic product . . . safely and effectively treats DPN, but excludes a DPN indication for a non-medical reason: Janssen's 'market exclusivity.'" [Pls. Br. at 8.] Roxane argues the opposite extreme—

that this disclaimer is explicit evidence of its intent not to infringe. [Defs. Br. at 36-37.] Ultimately, the Court finds that this disclaimer cuts both ways and constitutes the sort of language that the Federal Circuit has said "cannot be combined with speculation about how physicians may act to find inducement." *Takeda*, 785 F.3d at 632. The Federal Circuit has indicated that the Court should not "look outside the label to understand the alleged implicit encouragement in the label." *Id.* at 634. While Roxane's disclaimer notes the infringing DPN use of the product, it states that the product is "***not*** labeled with that information"—*i.e.*, one would have to look outside the label to understand how to administer the product for that use. Thus, the disclaimer by itself is insufficient to encourage the use of Roxane's product to treat polyneuropathic pain.

In light of the conclusions drawn above with respect to Actavis, and the Court's conclusion that the additional information in Roxane's label does not evidence intent to induce infringement, the Court finds that Plaintiffs have failed to meet their burden of proving induced infringement by a preponderance of the evidence against Roxane.

3. Alkem

Unlike Roxane and Actavis, Alkem has not carved Indication 2 or the DPN studies out of its label. Rather, Alkem's proposed label provides that Alkem's product is indicated for management of neuropathic pain associated with DPN, which is a common type of polyneuropathic pain:

> Tapentadol extended release tablets are opioid agonist indicated for the management of:
>
> - pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
>
> - neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

[PFOF ¶¶ 204, 207; PTX-224 at ALK_TAP_36275; 3/14 p.m. Tr. (Brown) at 50:21-24.] Alkem's label also includes the two DPN studies that appear in the NUCYNTA® ER label. [PFOF ¶ 209; PTX-225 at ALK_TAP_36298-36301.]

Alkem is aware of the '130 patent and the scope of its claims covering treatment of polyneuropathic pain and DPN. [PFOF ¶ 205; PTX-220 at ALK_TAP_36173, 36178; 3/14 p.m. Tr. (Brown) at 62:8-22.] Plaintiffs presented evidence that Alkem's label, including Indication 2 for neuropathic pain associated with DPN, reflects Alkem's specific intent to instruct a physician to prescribe the product to treat DPN, which is a type of polyneuropathic pain. [3/14 p.m. Tr. (Brown) at 66:7-18.] Plaintiffs also pointed to the presence of DPN clinical studies in Alkem's label as further evidence of Alkem's specific intent to encourage the administration of its product to treat DPN. [3/14 p.m. Tr. (Brown) at 66:19-67:8.] In light of the evidence presented by Plaintiffs regarding Indication 2 and the DPN clinical studies, the Court finds that Alkem will knowingly encourage physicians, pharmacists, and patients to administer its tapentadol hydrochloride extended release product to treat DPN. [PCOL ¶ 569.] Alkem has not presented evidence that undercuts this finding. [*See* PFOF ¶ 202.] Accordingly, the Court finds that Plaintiff has met its burden of demonstrating by a preponderance of the evidence that Alkem will "knowingly induce[] infringement and possess[] specific intent to encourage another's [direct] infringement." *AstraZeneca*, 633 F.3d at 1056; *Takeda*, 785 F.3d at 630-31 ("Inducement can be found where there is [e]vidence of active steps taken to encourage direct infringement."). Thus, Alkem will induce infringement of claims 1, 2, 3, and 6 of the '130 patent because it knows and intends for its products to be used in a manner that infringes the patent.

ii. <u>Contributory Infringement under 35 U.S.C. § 271(c)</u>

To prove contributory infringement, Plaintiff must prove by a preponderance of the evidence that: (1) somebody (*e.g.*, physicians, patients, and pharmacists) will directly infringe the

'130 patent by administering Defendants' products to treat polyneuropathic pain; (2) Defendants have knowledge of the '130 patent; (3) Defendants' products have no substantial non-infringing uses; and (4) Defendants' products are a material part of the invention of the '130 patent. *See Fujitsu*, 620 F.3d at 1326. Here, the first factor is satisfied because Defendants do not appear to dispute the likelihood that their products will be administered by at least some physicians, patients, and pharmacists to treat polyneuropathic pain. [*See* PFOF ¶¶ 213, 230; 3/14 p.m. Tr. (Brown) at 61:5-13, 69:8-25, 84:6-22, 99:12-21.] As to the second factor, Defendants are aware of the '130 patent. [PTO ¶¶ 63, 90, 99.] Regarding the fourth factor, the invention of the '130 patent is treatment of polyneuropathic pain with tapentadol hydrochloride—thus, each Defendant's tapentadol hydrochloride product is a material part of the invention. [PFOF ¶ 231; 3/14 p.m. Tr. (Brown) at 91:16-24, 100:7-14.]

The evidence presented at trial focused largely on the third factor of contributory infringement—whether there are substantial non-infringing uses of Defendants' products. A non-infringing use is substantial if it is "not unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental." *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1327 (Fed. Cir. 2009). In the context of pharmaceutical products, a substantial non-infringing use must be one for which the product is authorized to be sold—*i.e.*, it must be on-label.[40] *Eli Lilly*, 435 F. App'x at 927. Thus, in this case, substantial noninfringing uses include uses for severe chronic pain that is not polyneuropathic. [3/14 p.m. Tr. (Brown) at 85:10-13.]

It is undisputed that non-infringing uses of Defendants' products exist—Dr. Brown admitted that treatment of severe chronic nociceptive pain and treatment of severe chronic mononeuropathic pain would both be noninfringing uses of the products. [DFOF ¶ 3006; 3/23 Tr.

[40] It should be noted that all three Defendants' products will contain Indication 1.

(Brown) at 59:13-20.] Dr. Brown also conceded that the labeling for Defendants' products instruct users to administer the products for pain that is not polyneuropathic. [DFOF ¶ 3005; 3/14 p.m. Tr. (Brown) at 129:22-25.] Therefore, to meet their burden on contributory infringement, Plaintiffs attempted to demonstrate that such non-infringing uses are not substantial—*i.e.*, that the majority of the on-label uses for Defendants' products will infringe the patents.

Plaintiffs argue that uses of Defendants' products to treat nociceptive and mononeuropathic pain would be rare and insubstantial. [*See* PFOF ¶¶ 232-33.] Dr. Brown testified that nociceptive pain is most often acute (rather than chronic) and typically is treated with as-needed medication (rather than around-the-clock chronic pain medication). [3/14 p.m. Tr. (Brown) at 70:17-22, 85:13-17.] Dr. Brown also testified that mononeuropathic pain, such as diabetic mononeuropathic pain, is rare as compared to polyneuropathic pain. [PFOF ¶ 233; 3/14 p.m. Tr. (Brown) at 70:23-71:1, 72:12-18, 85:18-20.] Therefore, Plaintiffs contend that most conditions that present severe chronic pain, and are thus on-label for Defendants' products, are polyneuropathic in nature—*i.e.*, the products do not have substantial non-infringing uses.

Defendants' experts, however, presented extensive evidence of substantial noninfringing uses for Defendants' products. Dr. Weinberger testified that he has, in his own practice, used tapentadol hydrochloride extended release tablets to treat pain that is not polyneuropathic. [DFOF ¶ 3009; 3/11 Tr. (Weinberger) at 204:8-13.] Dr. Buvanendran testified that in his practice he has used long-acting opioids to treat severe chronic pain conditions that are non-neuropathic. [DFOF ¶¶ 3013-3014; 3/21 Tr. (Buvanendran) at 47:1-6.] Such conditions include nociceptive conditions such as chronic non-healing ulcers, chronic ureter and kidney or bladder obstructions, osteoarthritis, and rheumatoid arthritis. [DFOF ¶¶ 3013-3014; 3/21 Tr. (Buvanendran) at 107:21-108:8, 111:22-112:21,] Dr. Weinberger and Dr. Buvanendran also presented a number of

conditions that they opined could be treated with Defendants' products that would be noninfringing because they are nociceptive or mononeuropathic. [PFOF ¶¶ 234-235; 3/11 Tr. (Weinberger) at 204:14-205:11; Weinberger Demonstrative at 18; 3/21 Tr. (Buvanendran) at 44:5-47:11, 106:23-107:6.] While Plaintiffs' expert, Dr. Brown, testified that many of the conditions identified by Dr. Weinberger and Dr. Buvanendran were acute pain conditions [PFOF ¶ 234; 3/14 p.m. Tr. (Brown) at 85:21-91:8], Dr. Brown conceded that treatment of rheumatoid arthritis and osteoarthritis would be two uses that would be noninfringing. [DFOF ¶ 3010; 3/11 Tr. (Weinberger) at 204:16-25; 3/14 p.m. Tr. (Brown) at 89:2-5.]

In discussing the noninfringing pain conditions identified by Defendants' experts, Plaintiffs contend that these pain conditions are very uncommon, such that they do not constitute "substantial" noninfringing uses. [*See* PFOF ¶¶ 246-248; 3/23 Tr. (Brown) at 9:9-10:8 (providing estimates of less than 5% for patients suffering from purely nociceptive or mononeuropathic components of the Defendants' identified conditions).] However, Dr. Buvandendran and Dr. Weinberger both testified that treating the conditions they identified with tapentadol hydrochloride extended release drugs would not be "unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental" uses of the drugs. *See Vita-Mix*, 581 F.3d at 1327. [*See* DFOF ¶ 3011; 3/11 Tr. (Weinberger) at 205:12-206:21.]

For the reasons identified above, Plaintiffs have failed to meet their burden of demonstrating that Defendants' products will contribute to infringement of the asserted claims of the '130 patent.

E. '130 PATENT – INVALIDITY

i. Anticipation

Defendants contend that the asserted claims of the '130 patent are invalid under 35 U.S.C. § 102(b) as anticipated by the '737 patent. [PTO ¶¶ 1456, 1304, 1321-1324.] To prove that

the '130 patent is anticipated, Defendants bear the burden of proving by clear and convincing evidence that the '737 patent discloses every element of the claimed invention, administering tapentadol hydrochloride to treat polyneuropathic pain.

Defendants contend that the '737 patent anticipates the claimed invention because it discloses tapentadol hydrochloride and describes it as being "suitable for the treatment of severe pain," which will necessarily include a subpopulation with polyneuropathic pain. [Defs. Br. at 50; DFOF ¶¶ 3502, 3504; '737 patent at 1:52-55; 3/21 Tr. (Buvanendran) at 78:8-79:2, 79:21-80:6.] On this issue, Defendants presented the testimony of Dr. Buvanendran. Plaintiffs respond that the '737 patent does not anticipate the asserted claims because it does not disclose, explicitly or inherently, the polyneuropathic pain element of the asserted claims. [Pls. Br. at 47-48; PFOF ¶¶ 503-507.] On this issue, Plaintiffs presented the testimony of Dr. Brown and Dr. Ossipov.

It is undisputed that the '737 patent does not explicitly mention polyneuropathic pain. Ultimately, the dispute on this issue is whether Defendants have met their burden of proving by clear and convincing evidence that the disclosure of "severe pain" in the '737 patent discloses, explicitly or inherently, the treatment of polyneuropathic pain. [DFOF ¶ 3502; 3/21 Tr. (Buvanendran) at 78:8-79:2.]

The question of "[w]hat a prior art reference discloses in an anticipation analysis is a factual determination . . ." *Tegal Corp. v. Tokyo Electron Am., Inc.*, 257 F.3d 1331, 1345-46 (Fed. Cir. 2001). Furthermore, "in order to anticipate, a prior art disclosure must also be enabling, such that one of ordinary skill in the art could practice the invention without undue experimentation." *Novo Nordisk Pharm., Inc. v. Bio-Technology Gen. Corp.*, 424 F.3d 1347, 1355 (Fed. Cir. 2005).

Defendants argue that "severe pain" in the '737 patent teaches the claimed polyneuropathic pain. [DFOF ¶¶ 3502, 3504; '737 patent at 1:52-55; 3/21 Tr. (Buvanendran) at 78:8-79:2, 79:21-

80:6.] On cross examination, Dr. Brown admitted that in an abstract sense, severe pain can include polyneuropathic pain, polyneuropathic pain has always been a form of severe pain, and some of the population of patients with severe pain would have polyneuropathic pain. [DFOF ¶¶ 3505-07; 3/23 Tr. (Brown) at 48:22-49:17.] Dr. Ossipov made similar admissions, outside the context of the '737 patent. [3/23 Tr. (Ossipov) at 214:8-220:16.]

Plaintiffs argue, however, that the disclosure of "pain" in the '737 patent is limited to nociceptive pain. [Pls. Br. at 47-48.] Plaintiffs emphasize that the '737 patent never mentions the word "polyneuropathic pain" or the treatment thereof. [PFOF ¶ 504; 3/23 Tr. (Brown) at 11:11-19; 3/21 Tr. (Buvanendran) at 79:21-23.] Dr. Buvanendran admitted that "the '737 patent does not explicitly or necessarily disclose polyneuropathic pain or the treatment [of] polyneuropathic pain . . . ." [PFOF ¶ 504; 3/21 Tr. (Buvanendran) at 118:17-20.]

Plaintiffs further point out that the context of the '737 patent makes clear that the word "pain" referred only to nociceptive pain. First, the only test data for pain treatment disclosed in the '737 patent is from the mouse writhing test, which is a purely nociceptive pain model. [PFOF ¶ 505; 3/23 Tr. (Brown) at 12:4-11; 3/23 Tr. (Ossipov) at 116:15-22, 120:19-121:4, 172:6-8, 238:6-22; 3/11 Tr. (Mogil) at 266:17-19, 298:19-23; 3/21 Tr. (Buvanendran) at 117:19-23.] And second, the state of the art prior to the filing of the '130 patent was such that when a physician "discussed opioids in regard to the treatment of severe pain at that time, [s/he] did think nociceptive pain." [PFOF ¶ 506; 3/23 Tr. (Brown) at 12:12-24; 3/23 Tr. (Ossipov) at 116:23-117:20.]

Dr. Brown and Dr. Ossipov both testified that the context of the '737 patent was essential to their understanding of what that patent meant by the word "pain," as distinct from their understanding of what "pain" means in an abstract sense. [3/23 Tr. (Brown) at 39:24:-40:3 ("Q. Now, Doctor, you'll agree that the '737 patent describes using tapentadol hydrochloride to treat

severe pain, correct? A. It uses it in the context of what I said earlier in regard to the writhing test and our understanding in 1994."), 86:21-87:23 ("[W]hen I said it in the entire grand scheme of the world, pain can include neuropathic and nociceptive pain, but when you're looking at the specific confines of the '737 patent, we're talking about severe pain in the context of a writhing test, which is a test of nociceptive pain, and we're talking about using an opioid analgesic to treat that pain, which is consistent with what I thought in 1997. So, again, in the context of the '737 patent, I again feel that it's a model of nociceptive pain. . . . [T]he writhing test is very important in the context here."); 3/23 Tr. (Ossipov) at 160:4-14 ("The ['737] patent only shows data for nociceptive pain, so that shows that you have compounds that are antinociceptive . . . . So, no, you can't make that jump from an antinociceptive agent in a writhing test to being effective in polyneuropathic pain. There's absolutely no connection. It's a completely different mechanism.").] Furthermore, Dr. Ossipov testified that in the absence of any context to specifically indicate neuropathic pain, when the term "pain" is used, a POSA would "default to nociceptive pain." [3/23 Tr. (Ossipov) at 226:25-227:4; *see also* 3/23 Tr. (Ossipov) at 221:22-223:1 ("It's not specified what type of pain. . . . But again, somebody in my field, in preclinical research, seeing pain at that time would be thinking of nociceptive pain.").]

Defendants contend that Dr. Brown "impermissibly" limited the meaning of the term "severe pain" in the '737 patent. [*See* DFOF ¶ 3508.] Defendants further argue that Plaintiffs' infringement position against Actavis and Roxane requires this Court to read the word "pain" in Indication 1 of the labels to include polyneuropathic pain and, thus, Plaintiffs should not be heard to argue that the word "pain" in the '737 patent is limited to only nociceptive pain. [*See* Defs. Br. at 53; DFOF ¶ 4014; 3/14 p.m. Tr. (Brown) at 103:11-104:9; 3/15 Tr. (Brown) at 72:24-73:4.] However, as discussed above, the Court has found that the word "pain" in the labels is insufficient

to demonstrate specific intent to encourage treatment of polyneuropathic pain. [*See supra.*] Moreover, the Court finds persuasive Dr. Ossipov's and Dr. Brown's testimony that a POSA would have understood the term "severe pain" in the '737 patent to be nociceptive pain.[41]

The Court further notes that the '737 patent does not appear to enable the practice of the asserted claims of the '130 patent—namely, administration of tapentadol hydrochloride for the treatment of polyneuropathic pain. There is no discussion of polyneuropathic pain in the '737 patent and there is no evidence provided regarding the efficacy of tapentadol hydrochloride for treatment of polyneuropathic pain or other considerations (*e.g.*, side effects) regarding its use. Accordingly, having not enabled the asserted claims, the '737 patent cannot anticipate the asserted claims. *See Novo Nordisk*, 424 F.3d at 1355.

Defendants bear the burden of proving anticipation by clear and convincing evidence. The Court finds that Defendants have not met their burden of proving that the '737 patent anticipates the asserted claims of the '130 patent.

ii. Obviousness-type Double Patenting

Defendants contend that the asserted claims of the '130 patent are invalid under the judicially-created doctrine of obviousness-type double patenting. [PTO ¶¶ 1458, 1426-1439.] To prove that the claims of the '130 patent are invalid for obviousness-type double patenting, Defendants bear the burden of proving by clear and convincing evidence that the asserted claims

[41] In sum, the interpretation of the word "pain" is at issue for both the infringement and validity issues of the '130 patent. In each instance, the Court interprets the word "pain" in the context of the document in which it appears and the relevant legal issue. In the context of evaluating induced infringement, the Court does not find that the word "pain" in Actavis's and Roxane's labels evidences intent to encourage use of the products for treatment of polyneuropathic pain. Here, in the context of evaluating anticipation, the Court is not clearly convinced that a POSA would have understood "pain" in the prior art '737 patent to include polyneuropathic pain because the context of the document indicates that the pain is nociceptive.

of the '130 patent are not patentably distinct from an earlier expiring patent claim that Plaintiff also owns. *Amgen*, 580 F.3d at 1374. In this case, Defendants contend that the asserted claims of the '130 patent are not patentably distinct from claim 117 of the '593 patent. [*See* DFOF ¶¶ 4006-4055.] On this issue, Defendants presented the testimony of Dr. Buvanendran.

Plaintiffs offer two alternative responses to Defendants' double patenting contentions. Plaintiffs first contend that, as a matter of law, the doctrine of obviousness-type double patenting cannot apply to claim 117 of the '593 patent. [*See* PCOL ¶ 706; PFOF ¶ 509.] Alternatively, Plaintiffs contend that the asserted claims of the '130 patent are patentably distinct from claim 117. [*See* PFOF ¶¶ 510-531.] On this issue, Plaintiffs presented the testimony of Dr. Brown.

1. Applicability of the doctrine of obviousness-type double patenting to claim 117

As a threshold issue, Plaintiffs contend that, as a matter of law, the doctrine of obviousness-type double patenting is not applicable in this case. Claim 117 in the '593 patent (*i.e.*, the earlier claim) was a claim added during the reissue prosecution of the '593 and did not issue until April 24, 2007, which was one month after the filing of the '130 patent. [*See* PFOF ¶ 509; 3/21 Tr. (Buvanendran) at 118:21-121:8.] Thus, Plaintiffs argue, claim 117 "did not exist at the time of filing of the '130 patent" and thus cannot serve as the "earlier" claim in the obviousness-type double patenting analysis. [*Id.*]

Plaintiffs' argument is inconsistent with the law and with the purpose of the obviousness-type double patenting doctrine. The Federal Circuit has explicitly stated that "the doctrine of obviousness-type double patenting continues to apply where two patents that claim the same invention have different expiration dates." *Abbvie*, 764 F.3d at 1374. In other words, it is the date the patent expires—rather than the date it is filed or issued—that determines whether the doctrine can be applied. *See id.* This interpretation is consistent with the purpose of the doctrine, which is to prevent a patent holder from extending the term of the monopoly by obtaining additional patent

claims that are not patentably distinct. *Id.*; *see also id.* at 1373 ("The ban on double patenting ensures that the public gets the benefit of the invention after the original period of monopoly expires.").

According to the Orange Book, the claims of the '593 patent (including claim 117) expire on August 5, 2022 and the claims of the '130 patent do not expire until September 22, 2028. [DFOF ¶ 4004.] Both the '593 patent and the '130 patent are commonly owned by the same entity, Grünenthal. [PFOF ¶ 4005; *see* '593 patent; '130 patent.] Accordingly, since claim 117 in the '593 patent is a claim in a patent that expires earlier than the asserted claims of the '130 patent, and both patents are owned by the same entity, claim 117 may be properly viewed as the "earlier" claim for purposes of the obviousness-type double patenting inquiry.

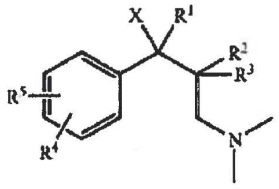
2. Application of the doctrine of obviousness-type double patenting

To evaluate obviousness-type double patenting, the Court must first identify the differences between the earlier claim (claim 117 of the '593 patent) and the later claim (claim 1 of the '130 patent). *Abbvie*, 764 F.3d at 1374. The Court must then determine whether those differences render the later claim patentably distinct from the earlier claim. *Id.*

a. The differences between the two claims

Claim 117 of the '593 patent depends from independent claim 8 of the '593 patent, and therefore includes all the elements of claim 8. *See* 35 U.S.C. § 112(d) "A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers."). Defendants demonstrated that the full claim 117 (including the limitations of claim 8) reads as follows:

> A method of treating a mammal suffering from pain, said method comprising administering to said mammal an effective analgesic amount of 1-phenyl-3-dimethyl-aminopropane compound corresponding to formula I



wherein the compound is (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylropyl-phenol hydrochloride (-21).

[DFOF ¶ 4008; *see* 3/21 Tr. (Buvanendran) at 51:8-13.] Dr. Buvanendran placed this rewritten claim 117 side-by-side with claim 1 of the '130 patent for purposes of comparison:

'593 Patent, Claim 117 (1994)	'130 Patent, Claim 1 (2007)
[Claim 8] **A method of treating a mammal suffering from pain,** **said method comprising administering to said mammal an effective analgesic amount** **of a 1-phenyl-3-dimethyl-aminopropane compound ...** **[Claim 117]** **wherein the compound is (–)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride (–21)**	**A method of treating polyneuropathic pain in a subject suffering therefrom,** **said method comprising administering to said subject an effective polyneuropathic pain inhibiting amount** **of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol or a pharmaceutically acceptable salt thereof**

[*See* 3/21 Tr. (Buvanendran) at 51:14-52:12; Buvanendran Demonstrative at 30.]

As demonstrated by the side-by-side comparison, when directly compared, there are three differences between claim 117 of the '593 patent and claim 1 of the '130 patent. [DFOF ¶ 4009; 3/21 Tr. (Buvanendran) at 51:14-52:12.] Two differences are that claim 117 of the '593 patent refers to treating a "mammal" with an "analgesic amount" while claim 1 of the '130 patent refers to treating a "subject" with a "pain inhibiting amount." [DFOF ¶ 4010; 3/21 Tr. (Buvanendran) at

51:19-52:1, 52:8-12.] It is undisputed that these differences do not render claim 1 of the '130 patent patentably distinct from claim 117 of the '593 patent. [*Id.*]

The third difference is that claim 117 of the '593 patent refers to treating "pain" while claim 1 of the '130 patent refers to treating "polyneuropathic pain." [DFOF ¶ 4010; 3/21 Tr. (Buvanendran) at 52:2-12.] The essence of the dispute on the issue of obviousness-type double patenting is whether this difference between "pain" and "polyneuropathic pain" renders claim 1 of the '130 patent patentably distinct from claim 117 of the '593 patent.

b. Whether the later claim is patentably distinct

i. Defendants' first argument – "pain" is an umbrella term

Defendants first contend that the term "pain" in claim 117 of the '593 patent is an umbrella term which includes both the concepts of nociceptive pain and neuropathic pain. [*See* DFOF ¶ 4011; 3/21 Tr. (Buvanendran) at 52:13-24.] This argument is similar to Defendants' position regarding anticipation of the '130 patent by the '737 patent—*i.e.*, that the term "pain" includes and teaches "polyneuropathic pain." With respect to anticipation, the Court has determined that, in light of the context provided by the '737 patent, a POSA would have understood the term "pain" as "nociceptive pain." [*See supra* Section IV.E.i.] As the disclosure of the '593 patent is essentially identical to the disclosure of the '737 patent, the Court's conclusion remains the same with respect to obviousness-type double patenting.

The Court notes that in the anticipation context above, the analysis was limited to what was disclosed within the four corners of the prior art '737 patent, *see Advanced Display*, 212 F.3d at 1282, whereas the obviousness inquiry allows Defendants to present evidence from other prior art references as to how a POSA would have understood the term "pain" at the time of the filing of

the '130 patent.[42] [*See* DFOF ¶¶ 4011-4021.] As such, Defendants argue that a POSA in 1994 would have understood the term "pain" to refer to a genus that includes the species of nociceptive pain (including somatic and visceral) and neuropathic pain (including mononeuropathic and polyneuropathic). [*See* DFOF ¶ 4019; 3/21 Tr. (Buvanendran) at 52:13-24.] Defendants point to prior art suggesting that the term "pain" referred to both nociceptive and neuropathic pain. [*See* PFOF ¶¶ 4015-4017; DTX-1576.] In a reference published in 1989, Dr. Donna L. Hammond discussed the nomenclature used to discuss pain, referring both to nociceptive pain and neuropathic pain. [DFOF ¶¶ 4015-16; DTX-1576_0004.] Dr. Brown and Dr. Ossipov have also conceded that, in the abstract sense, the term "pain" includes both nociceptive and neuropathic pain. [3/23 Tr. (Brown) at 86:21-23.]

Nevertheless, much like the Court's conclusion with respect to anticipation, the Court finds Defendants' evidence is limited to how Dr. Hammond, Dr. Brown, and Dr. Ossipov would have understood the meaning of the term "pain" in an abstract sense. That evidence is ancillary to the question of what "pain" means ***in claim 117 of the '593 patent.*** [*See supra* Section IV.E.i.] The Court concludes that Defendants' outside evidence does not outweigh the evidence presented as to the context of the '593 patent—namely, the nociceptive mouse writhing test that provides the only evidence of analgesia in the '593 patent disclosure. [*See* PFOF ¶ 505; 3/23 Tr. (Brown) at 12:4-11; 3/23 Tr. (Ossipov) at 116:15-22, 120:19-121:4, 172:6-8, 238:6-22; 3/11 Tr. (Mogil) at 266:17-19, 298:19-23; 3/21 Tr. (Buvanendran) at 117:19-21.] Accordingly, the Court finds that

[42] The parties essentially agree that a POSA with respect to the '130 patent would have had a working knowledge of, and experience in a field related to, neuropathic pain and treatment thereof. [PFOF ¶ 498; 3/21 Tr. (Buvanendran) at 30:3-17.] Defendants presented evidence that a POSA would have understood the term "pain" the same way in 1994 (at the time of the filing date of the '593 patent) and in 2007 (at the time of the filing date of the '130 patent). [DFOF ¶ 4013; 3/21 Tr. (Buvanendran) at 53:6-10.]

the term "pain" in claim 117 of the '593 patent is limited to nociceptive pain and therefore does not encompass all of the subject matter of the asserted claims of the '130 patent.

ii. Defendants' second argument – nociceptive pain renders obvious polyneuropathic pain

Defendants alternatively argue that even if the term "pain" in claim 117 of the '593 patent only refers to nociceptive pain, a POSA reading that claim in March 2007 (the filing date of the '130 patent) would have found it obvious to use the compound tapentadol hydrochloride to treat polyneuropathic pain. [*See* DFOF ¶ 4022; 3/21 Tr. (Buvanendran) at 59:17-23.] Defendants contend that a POSA would have known that tapentadol hydrochloride was an opioid derivative and by March 2007, there was substantial literature establishing that opioids were effective for treating polyneuropathic pain. [DFOF ¶¶ 4023-24; 3/21 Tr. (Buvanendran) at 59:24-60:9.]

Defendants presented evidence of a 2002 internal Grünenthal report in which Dr. Christoph wrote: "Thus, the old dogma of lacking efficacy of opioids in the treatment of neuropathic pain holds no longer true." [DFOF ¶ 4027; DTX-1030_0015; 3/14 a.m. Tr. (Christoph) at 101:19-23.] In that same report, Dr. Christoph noted that "several studies have proven efficacy of opioids in neuropathic pain conditions (Rowbotham et al., 1991; Dellemijn and Vanneste, 1997; Sindrup et al., 1999)." [DFOF ¶ 4027; DTX-1030_0015; 3/14 a.m. Tr. (Christoph) at 99:1-13.] Defendants also presented a 2003 internal Grünenthal report in which the inventors of the '130 patent wrote:

> Although there is a large consensus concerning the effectiveness of opioids in nociceptive pain, their efficacy in neuropathic pain was debatable until recent years (Portenoy, 1996; Dellmijn, 1999). However, several studies have proven efficacy of opioids in neuropathic pain condition (Dellmijn & Vanneste, 1997; Sindrup *et al*, 1999).

[DFOF ¶ 4026; PTX-454 at 14.]

In addition to internal Grünenthal documents, Defendants pointed to prior art studies investigating the efficacy of opioids in treating neuropathic pain. [*See* DFOF ¶¶ 4035-4047;

PTX-1141 (March 2005 study by Gilron et al. confirming the findings of earlier studies showing the efficacy of opioids in the treatment of neuropathic pain); 3/21 Tr. (Buvanendran) at 62:23-63:10; DTX-1609 (2004 treatment algorithm published by Namaka et al. showing opioids, including tramadol, as a second line treatment for neuropathic pain); 3/21 Tr. (Buvanendran) at 63:13-64:4; PTX-1131 (2005 treatment algorithm published by Finnerup discussing the use of opioids such as morphine, oxycodone, and tramadol for the treatment of polyneuropathic pain); DTX-1603 (2005 review article by Freeman studying the opioid oxycodone for treating diabetic neuropathy and describing efficacy of opioids, including tramadol, for treatment of polyneuropathic pain); DTX-1599 (2006 article by Baron reviewing more than 25 years of studies concerning the treatment of neuropathic pain, including opioids like tramadol, morphine, and oxycodone); 3/21 Tr. (Buvanendran) at 64:12-65:22.] Dr. Buvanendran testified that as a clinical practitioner he prescribed opioids in his practice to treat polyneuropathic pain. [DFOF ¶ 4048; 3/21 Tr. (Buvanendran) at 66:4-10.] Finally, Defendants presented evidence of studies that specifically investigated the efficacy of tramadol (*i.e.*, Grünenthal's predecessor drug and the drug from which tapentadol was derived) in treating polyneuropathic pain. [*See* DFOF ¶¶ 4028-4047; DTX-1605 (June 1998 study by Harati, et al. concluding that "tramadol was significantly more effective than placebo for treating the pain of diabetic neuropathy" and "[t]ramadol is an alternative to tricyclic drugs or anticonvulsants for treating the pain of diabetic neuropathy"); 3/23 Tr. (Brown) at 94:20-95:1; DTX-916 (2006 study by Hollingshead, et al. concluding that "tramadol is an effective treatment for neuropathic pain"); 3/21 Tr. (Buvanendran) at 62:11-14; DTX-1609; PTX-1131; DTX-1603; DTX-1599.]

Plaintiffs presented evidence, however, that the standard was not to prescribe opioids for neuropathic pain because neuropathic pain was generally considered to be unresponsive to opioids.

[PFOF ¶ 513; 3/23 Tr. (Brown) at 14:5-8.] Notwithstanding the discrete studies identified by Defendants above, Plaintiffs' evidence demonstrated that POSAs saw neuropathic pain as refractory to opioids (*i.e.*, either the opioid would be ineffective or would require very high doses to be effective). [PFOF ¶ 513; 3/23 Tr. (Brown) at 14:6-8, 15:4-11.] Because of this, opioids were known to show only limited effectiveness in treating neuropathic pain conditions because "they relatively quickly were reaching levels of side effects because you needed to—they needed to be dosed higher than in normal nociceptive pain conditions." [3/14 a.m. Tr. (Christoph) at 103:19-23; 3/23 Tr. (Brown) at 15:4-11.] Prescribing opioids at higher doses can cause serious problems in patients, including side effects (like nausea, vomiting, and constipation). [PFOF ¶ 514; 3/23 Tr. (Brown) at 15:12-25.] High doses of opioids can also cause destruction, dysfunction, or sensitivity of the normal nociceptive pain pathways, which can lead to conditions like hyperalgesia (where a person experiences pain at a different level and manner than a normal person would experience). [PFOF ¶¶ 514-15; 3/23 Tr. (Brown) at 15:15-16:10.]

Defendants contend that Dr. Brown's conclusion about the effectiveness of tramadol and other opioids for treating polyneuropathic pain was based only on her own clinical experience and not a review of the literature. [*See* DFOF ¶ 4034; 3/23 Tr. (Brown) at 20:16-18.] Defendants further contend that Dr. Brown improperly focused on side effects and quality of life to discount the published clinical evidence about efficacy of opioids for treating polyneuropathic pain. [*See* DFOF ¶ 4050.] The asserted claims in the '130 patent, however, are for methods of "*treating*" polyneuropathic pain. Plaintiffs presented evidence demonstrating that the effective treatment of polyneuropathic pain involves many considerations other than simply identifying a drug that exhibits efficacy in lowering a patient's pain score. [3/21 Tr. (Buvanendran) at 95:15-18; 3/23 Tr. (Brown) at 24:2-11.]

Plaintiffs also presented evidence of literature before, and even after, the 2007 filing date of the '130 patent suggesting that there was controversy surrounding the usefulness of opioids in treating neuropathic pain. [PFOF ¶¶ 519-530; DTX-1609 (Namaka et al. explained that "usefulness of narcotics [or opioids] in the treatment of chronic neuropathic pain is often debated and not very well studied"); DTX-1401 (2007 article by Dworkin et al. explaining that "[t]he management of patients with chronic [neuropathic pain] is complex and response to existing treatments is often inadequate. Even with well-established [neuropathic pain] medications, effectiveness is unpredictable, dosing can be complicated, analgesic onset is delayed, and side effects are common."); PTX-3002 (2011 article by Candiotti et al. describing the "use of opioids for the treatment of noncancer pain" as "particularly controversial"); PTX-3003 (2013 article by Dr. Buvanendran in which he stated that "[t]he use of opioids for the treatment of neuropathic pain remains controversial"); PTX-3004 (March 2016 Center for Disease Control and Prevention guidelines, which concluded: "No evidence shows a long-term benefit of opioids in pain and function versus no opioids for chronic pain" and "[e]xtensive evidence shows the possible harms of opioids."); PTX-1141 (Gilron stating that "available drugs to treat neuropathic pain have incomplete efficacy and dose-limiting adverse effects).]

In light of the conflicting evidence presented by the parties about the prior art teachings regarding opioid use to treat neuropathic pain, the Court finds that Defendants have not met their burden of demonstrating by clear and convincing evidence that a POSA would have had a reasonable expectation that tapentadol hydrochloride would be effective to treat polyneuropathic pain. Furthermore, even if Defendants had met their burden of demonstrating that a POSA would have expected efficacy (which they have not) Defendants have not rebutted Plaintiffs' evidence

that treatment of pain involves more than efficacy alone and a POSA would not have had an expectation of successfully *treating* polyneuropathic pain using tapentadol hydrochloride.

3. Prosecution history

In addition to their substantive arguments regarding obviousness, Plaintiffs contend that the arguments put forth by Defendants in this case were the same ones presented by the USPTO Examiner during the prosecution history of the '130 patent. [PFOF ¶¶ 500-501; PTX-1600 at GRT-NUC00043833-34, 43877-79.] Plaintiffs argue that despite having considered these arguments, the Examiner ultimately allowed the '130 patent claims and concluded that "the cited references do not teach []or provide adequate motivation to arrive at the instantly claimed methods" and that "the instant claims are seen to be novel and non-obvious over the teachings of the prior art." [PFOF ¶¶ 500-502; PTX-1600 at GRT-NUC00044296-97.]

Defendants contend that they are relying in this litigation on numerous prior art references that were not considered by the Examiner. [*See* DFOF ¶¶ 4029, 4032, 4035, 4040, 4042, 4044, 4046.] Moreover, Defendants contend that the prosecution history demonstrates that, even without considering the numerous references they rely on in this litigation, the Examiner first rejected the claims of the '130 patent as prima facie obvious over the '737 patent (which contains the same disclosure as the '593 patent at issue in the double-patenting inquiry). [*See* DFOF ¶¶ 4053-4055.] Defendants argue that Plaintiff did not contest the Examiner's determinations but rather rebutted the prima facie obviousness conclusion by submitting a declaration to the USPTO demonstrating unexpected results, which is a secondary consideration of nonobviousness. [*See* Defs. Br. at 55; DFOF ¶ 4053; PTX-1600 at GRT-NUC00043876-82, 43980-84, 44066-71, 44045-53.]

The Court notes that, while the Examiner's considerations and conclusions are instructive on the issue of invalidity, they must be viewed through the lens of the relevant standards of proof. It is well-settled that "[i]n civil litigation, a challenger who attacks the validity of patent claims

must overcome a presumption of validity with clear and convincing evidence that the patent is invalid." *In re Swanson*, 540 F.3d 1368, 1377 (Fed. Cir. 2008) (citing 35 U.S.C. § 282).

> In [US]PTO examinations . . . , the standard of proof—a preponderance of evidence—is substantially lower than in a civil case; there is no presumption of validity; and the examiner is not attacking the validity of the patent but is conducting a subjective examination of the claims in light of prior art.

Id. (internal citations and quotations omitted).

The Supreme Court has addressed the impact of the prosecution history on the standards and burdens of proving invalidity. *See generally Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91 (2011). In *i4i*, the Court affirmed that the "heavy burden of persuasion" borne by a patent challenger is unaltered by considerations of whether the patent examiner considered the evidence during prosecution. *Id.* at 102, 108-12.

Here, while the USPTO Examiner initially found the claims of the '130 patent prima facie obvious, that finding was based on a preponderance of the evidence standard rather than the relevant clear and convincing evidence standard applicable to this case. Furthermore, although Defendants have presented additional evidence not considered by the examiner about the meaning of "pain" and use of opioids to treat neuropathic pain, Plaintiffs have also put forth evidence counteracting these points.

In this litigation, the '130 patent claims are presumed valid and Defendants bear the burden of overcoming this presumption by presenting clear and convincing evidence of obviousness. In light of the conflicting evidence presented by the parties about the meaning of the term "pain" in the '593 patent as well as the prior art teachings regarding the controversy surrounding opioid use to treat neuropathic pain, Defendants have failed to meet their burden.

4. Secondary considerations of non-obviousness

Plaintiffs presented evidence of two secondary considerations of nonobviousness—unexpected results and long-felt need. [*See* PFOF ¶¶ 532-51.] Defendants contend that Plaintiffs' evidence was not legally probative. [*See* DFOF ¶¶ 4056-69.]

a. Unexpected results

Dr. Christoph testified about results that he considered unexpected when using tapentadol hydrochloride to treat polyneuropathic pain. First, Dr. Christoph discovered that tapentadol hydrochloride unexpectedly provided the benefit of treating mononeuropathic pain and polyneuropathic pain at a dose that did not inhibit normal nociceptive pain transmissions. [PFOF ¶¶ 533, 536; '130 patent at 16:62-66 ("In both pain models [tapentadol] produces a selective inhibition of the pathologically induced pain response, without at the same time influencing the normal pain response."); 3/14 a.m. Tr. (Christoph) at 40:15-41:8, 43:24-46:22; PTX-1600 at GRT-NUC44045-53.] This property was discovered using animal models redesigned or newly designed in Dr. Christoph's lab. [PFOF ¶ 534; 3/14 a.m. Tr. (Christoph) at 37:9-21.] Selective inhibition of neuropathic pain without affecting the nociceptive pathway beneficially allows for neuropathic pain treatment without impairing the normal protective mechanisms of nociceptive pain. [PFOF ¶ 535; 3/23 Tr. (Ossipov) at 117:21-118:23; 3/14 a.m. Tr. (Christoph) at 46:23-47:15.]

Second, Dr. Christoph discovered that tapentadol hydrochloride is more potent in the treatment of polyneuropathic pain than it is for mononeuropathic pain. [PFOF ¶ 540; 3/14 a.m. Tr. (Christoph) at 47:16-48:7; PTX-1600 at GRT-NUC44048-50.] By comparing the results from the redesigned animal models, Dr. Christoph discovered that the minimally effective dose of tapentadol hydrochloride was threefold less for polyneuropathic pain treatment as compared to mononeuropathic pain. [PFOF ¶ 540; 3/14 a.m. Tr. (Christoph) at 47:16-48:1.] Dr. Christoph also discovered that the maximally effective dose (*i.e.*, the dose needed to reach full antineuropathic

efficacy) of tapentadol hydrochloride was tenfold less for polyneuropathic pain as compared to mononeuropathic pain. [PFOF ¶ 540; 3/14 a.m. Tr. (Christoph) at 48:2-7.] This was surprising to Dr. Christoph because polyneuropathic pain is the more severe condition. [PFOF ¶ 540; 3/14 a.m. Tr. (Christoph) at 48:8-13.]

Third, Dr. Christoph discovered that in the STZ polyneuropathic pain model, tapentadol hydrochloride outperformed morphine. [PFOF ¶ 541; PTX-1600 at GRT-NUC44052.] Dr. Christoph found it "astonishing" that less tapentadol was required to achieve the same level of efficacy as morphine, especially because morphine is more potent than tapentadol in other pain models. [PFOF ¶ 541; 3/14 a.m. Tr. (Christoph) at 51:4-54:6.]

Fourth, Dr. Christoph also discovered that tapentadol hydrochloride possesses multiple layers of synergism, which allows lower dosages to be used to achieve desired effects and provides some explanation for the other unexpected properties tapentadol hydrochloride exhibits. [PFOF ¶ 542; 3/14 a.m. Tr. (Christoph) at 54:7-12, 62:23-63:21.] Dr. Christoph discovered an 'intrinsic' synergism between the multiple mechanisms of action of tapentadol hydrochloride in treating neuropathic pain, which he published in the Journal of Pharmacology and Experimental Therapeutics. [PFOF ¶ 543; 3/14 a.m. Tr. (Christoph) at 59:11-60:17; PTX-699.] He also discovered a 'site-site' synergy in the spinal and supraspinal levels (*i.e.*, administering tapentadol hydrochloride into these two locations results in a synergistic effect), a type of synergy which is relatively rare. [PFOF ¶ 543; 3/14 a.m. Tr. (Christoph) at 61:13-62:15.] Dr. Christoph also published these results. [PFOF ¶ 544; PTX-797; 3/14 a.m. Tr. (Christoph) at 60:18-61:12.]

Defendants mainly contend that Plaintiffs' evidence of unexpected results is not legally probative because Plaintiffs have not shown a comparison to tramadol, which Defendants contend is the closest prior art. [*See* DFOF ¶¶ 4056-4060.] *See In re Baxter Travenol Labs.*, 952 F.2d 388,

392 (Fed. Cir. 1991) ("[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art."). The Court does not agree. First, as much of Defendants' obviousness challenge was based on the prior art category of "opioids," the Court finds that Plaintiffs' evidence comparing tapentadol hydrochloride to other opioids (such as morphine) is legally probative. Second, Plaintiffs presented evidence suggesting that morphine, as the gold standard in opioid treatment, was a particularly good comparison [3/14 p.m. Tr. (Christoph) at 11:16-21; 3/23 Tr. (Brown) at 26:7-17] and that tramadol was not an appropriate reference point because the compounds were very different with different mechanisms of action and different potencies [PFOF ¶ 538; 3/14 a.m. Tr. (Christoph) at 86:8-87:1.]

Defendants further contend that Plaintiffs have not established what expectation a POSA would have had before attempting to use tapentadol hydrochloride to treat polyneuropathic pain. [*See* DFOF ¶ 4061.] However, for each category of unexpected result, Dr. Christoph testified about the nature of the result and why it was surprising. Ultimately, Plaintiffs' evidence demonstrated that tapentadol hydrochloride had unexpected properties that distinguished it from being "just another opioid." [PFOF ¶ 546; 3/23 Tr. (Brown) at 26:7-15.] Accordingly, the Court finds that Plaintiffs' evidence of unexpected results weighs in favor of a finding that the asserted claims of the '130 patent are nonobvious.

b. Long-felt need

Dr. Brown testified that before NUCYNTA® ER entered the market, there was a long-felt, unresolved need for a new opioid that could treat chronic pain with lower side effects, the most common of which are constipation, nausea, vomiting, sleepiness, and dizziness. [PFOF ¶ 548; 3/23 Tr. (Brown) at 26:22-27:5.] Plaintiffs' evidence demonstrated that lowering these side effects of traditional opioids could reduce the number of incidents of patients terminating their opioid treatment altogether. [PFOF ¶ 548; 3/23 Tr. (Brown) at 28:8-12; PTX-698.] Finally, Dr. Brown

testified, and Dr. Buvanendran has written in the past, that NUCYNTA® ER has been successful at lowering the side effects experienced by patients taking other extended release opioids. [PFOF ¶¶ 549-50; 3/23 Tr. (Brown) at 27:18-28:4; PTX-3005 at 61.] Thus, Plaintiffs have demonstrated that NUCYNTA® ER has satisfied a long-felt need in the market for an opioid with lower side effects.

5. The asserted claims of the '130 patent do not violate the doctrine of obviousness-type double patenting

Having reviewed the evidence presented, the Court finds that the asserted claims of the '130 patent are patentably distinct from claim 117 of the '593 patent and, thus, the asserted claims of the '130 patent do not violate the judicially-created doctrine of obviousness-type double patenting. Accordingly, Defendants have failed to meet their burden of proving by clear and convincing evidence that the asserted claims of the '130 patent are invalid.

F. DEPOMED WILL BE IRREPARABLY HARMED BY A GENERIC LAUNCH

i. Legal Principles

The Hatch-Waxman Act provides that for any act of infringement described in Section 271(e)(2) of the Patent Act:

> (A) the court shall order the effective date of any approval of the drug or veterinary biological product involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed,
> (B) injunctive relief may be granted against an infringer to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug, veterinary biological product, or biological product, [and]
> (C) damages or other monetary relief may be awarded against an infringer only if there has been commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug, veterinary biological product, or biological product[.]

35 U.S.C. § 271(e)(4).

In general, to obtain injunctive relief "[a] plaintiff must demonstrate: (1) that it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are inadequate to compensate for that injury; (3) that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; and (4) that the public interest would not be disserved by a permanent injunction." *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 391 (2006). To satisfy the irreparable harm factor, a patentee must establish that: "1) that absent an injunction, it will suffer irreparable harm, and 2) that a sufficiently strong causal nexus relates the alleged harm to the alleged infringement." *Apple Inc. v. Samsung Elecs. Co.*, 695 F.3d 1370, 1374 (Fed. Cir. 2012). Evidence of price erosion, loss of market share, loss of profits, loss of research opportunities, and possible layoffs may constitute irreparable harm. *See Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1362 (Fed. Cir. 2008); *Robert Bosch LLC v. Pylon Mfg. Corp.*, 659 F.3d 1142, 1154 (Fed. Cir. 2011) (showing of lost market share and sales supported a finding of irreparable harm); *Purdue Pharma L.P. v. Boehringer Ingelheim GmbH*, 237 F.3d 1359, 1368 (Fed. Cir. 2001) (evidence of likelihood of price erosion and loss of market position caused by generic's entry to market supported finding of irreparable harm). "The phenomenon of price erosion in the pharmaceutical industry is well-known." *Hoffmann La Roche Inc. v. Cobalt Pharms. Inc.*, No. 07-4539, 2010 U.S. Dist. LEXIS 119432, *35 (D.N.J. Nov. 10, 2010). "Price erosion is most likely to occur in cases . . . in which no generic competitors have yet entered the marketplace, placing the patentee in an exclusive position." *Id.* at *38. "Direct competition in the same market is certainly one factor suggesting strongly the potential for irreparable harm without enforcement of the right to exclude." *Presidio Components, Inc. v. Am. Technical Ceramics Corp.*, 702 F.3d 1351, 1363 (Fed. Cir. 2012); *see also Trebro Mfg., Inc. v. FireFly Equip., LLC*, 748 F.3d 1159,

1171 (Fed. Cir. 2014) ("Trebro and FireFly are direct competitors selling competing products in this market. Thus, the record strongly shows a probability for irreparable harm.").

ii. Plaintiffs Have Met Their Burden

1. Irreparable harm

On April 2, 2015, Depomed acquired the exclusive U.S. rights to the NUCYNTA® products from Janssen for a contingency-free $1.05 billion cash payment. [PFOF ¶ 718; 3/9 Tr. (Anders) at 197:14-18; PTX1563 at DM_0000020.] The acquisition, which significantly exceeded Depomed's shareholder equity, represented a significant investment for Depomed. [PFOF ¶ 718; 3/9 Tr. (Anders) at 197:22-198:1; PTX1563 at DM_0000059.] In order to raise the capital necessary to outbid the other companies also vying for the rights to the NUCYNTA® products, Depomed took on approximately $920 million in debt, $575 million of which carries a minimum interest rate of 10.75% and is secured by substantially all of Depomed's assets. [PFOF ¶ 718; 3/9 Tr. (Anders) at 197:22-199:23; PTX1568 at DM_0000406-07; PTX1563 at DM_0000118.] The NUCYNTA® products became the flagship asset in Depomed's portfolio of pain and central nervous system specialty pharmaceuticals, and the NUCYNTA® products now account for approximately 60% of Depomed's revenues. [PFOF ¶ 720; 3/9 Tr. (Anders) at 179:24-180:1, 180:21-182:14; PTX-1559.] In making the decision to purchase the NUCYNTA® brand products, the proprietary nature of those products and the length of the exclusivity period afforded by the patents-in-suit were significant factors. [PFOF ¶ 719; 3/9 Tr. (Anders) at 188:25-189:23; PTX-829 at JN_NUCYNTA_1634430.]

If Defendants proceed to market with their proposed infringing generic NUCYNTA® products before the expiration of the patents-in-suit, these products would directly compete with NUCYNTA® in the United States, where Depomed currently has the exclusive rights to market and sell NUCYNTA®. Once Defendants' products enter the market, prescription volume for

NUCYNTA® will decline [3/9 Tr. (Anders) at 201:14-16], which will result in lost market share, lost revenue, and Depomed's business suffering. [PFOF ¶ 721; 3/9 Tr. (Anders) 200:12-201:20; PTX-1568 at DM_0000438-39.] *See Robert Bosch*, 659 F.3d at 1154 (finding that lost market share and price erosion can be irreparable harm). Significantly, Depomed asserts that the drop in revenue for NUCYNTA® means that it will be unable to fulfill the significant debt obligations it took on in order acquire the NUCYNTA® brand products from Janssen. [PFOF ¶ 722; 3/9 Tr. (Anders) at 197:22-201:23; PTX1568 at DM_0000406-07; PTX1563 at DM_0000118.]

The Court finds that if Defendants enter the market by launching their tapentadol hydrochloride products, it would threaten Depomed's business and cause extreme hardship. Thus, Depomed will be irreparably harmed without an injunction to prevent Defendants from launching their products.

2. Inadequate remedy at law

For substantially the same reasons that Depomed will be irreparably harmed by Defendants' launch, Depomed will not have an adequate remedy at law for the losses it will sustain. Direct competition with a low-cost generic version of NUCYNTA® ER will cause extreme hardship to Depomed operating under strict debt obligations. [*See infra.*] Monetary compensation cannot be quantified for the loss that Depomed will sustain by losing significant market share and revenue on its flagship product. *Novartis Consumer Health, Inc. v. Johnson & Johnson-Merck Consumer Pharms. Co.*, 290 F.3d 578, 596 (3d Cir. 2002); *Lazzaroni USA Corp. v. Steiner Foods*, 2006 U.S. Dist. LEXIS 20962, at *21 (D.N.J. Apr. 10, 2006) ("[L]oss of market share is the kind of harm for which there may be no adequate remedy at law." (internal quotation marks omitted)). There is no reason to believe that Defendants will stop infringing, or that the irreparable harm resulting from their infringement will otherwise cease, absent an injunction.

3. Balance of hardships

Defendants have not yet launched their products and will therefore not be forced to incur the costs of withdrawing the products from the market. Defendants did not call any fact witnesses to testify during trial. Thus, they presented no evidence about harm they will suffer if they are enjoined from launching their tapentadol hydrochloride products until the expiration of Plaintiffs' patents. However, as discussed, the harm that Depomed will suffer due to a low-cost generic competing with its flagship product (in which it invested $1.05 billion) is substantial and outweighs any harm Defendants might suffer by delaying their launch. Furthermore, any harm that Defendants may suffer from being enjoined was foreseeable and avoidable, as they were aware of the patents-in-suit covering NUCYNTA®, but chose to develop their infringing products anyway. [PFOF ¶ 723; PTO ¶¶ 58, 63, 73, 78, 90, 94, 99, 103-110.]

4. Public interest

Courts have long recognized the importance of the patent system in encouraging innovation, which provides incentive to innovative drug companies to invest in costly research and development activities. Among other things, pharmaceutical research requires the realization of profits from successful drugs to make up for the losses from drugs that never make it to market or prove unsuccessful for other reasons. *Eli Lilly & Co. v. Premo Pharm. Labs., Inc.*, 630 F.2d 120, 137 (3d Cir. 1980) ("In enacting the patent laws, Congress recognized that it is necessary to grant temporary monopolies on inventions in order to induce those skilled in the 'useful arts' to expend the time and money necessary to research and develop new products and to induce them 'to bring forth new knowledge.' This justification for sacrificing short-term price competition in order to foster creativity and improvement of products in long-run is particularly applicable to the pharmaceutical industry." (internal citation omitted)); *Sanofi-Aventis Deutschland GmbH v. Glenmark Pharms. Inc., USA*, 821 F. Supp. 2d 681, 696 (D.N.J. 2011) ("[The plaintiff] invested

significant resources with the expectation that it would be able to recoup its investment, and the patent system is designed to provide incentives for innovative drug companies to continue costly development efforts."). Not enforcing patent rights through injunctions may destroy confidence in the system and discourage investment in pharmaceutical research and development. The interests of a large portion of the public—those who have or will eventually develop conditions not adequately served by existing therapies—are served by a legal regime that protects investment in research and development. *Sanofi*, 821 F. Supp. 2d at 695-96 ("Importantly, the patent system provides incentive to the innovative drug companies to continue costly development efforts, and therefore there is a significant public interest in encouraging investment in drug development and protecting the exclusionary rights conveyed in valid pharmaceutical patents." (internal quotation marks omitted)). Thus, the public interest weighs in favor of an injunction.

V. CONCLUSION

For the foregoing reasons, the Court finds that Defendants have not met their burden of proving by clear and convincing evidence that the '593 patent, the '364 patent, or the '130 patent is invalid. Plaintiffs have met their burden of proving by a preponderance of the evidence that Alkem will induce infringement of the '130 patent. Plaintiffs have not met their burden of proving that Actavis or Roxane will induce infringement of the '130 patent. Plaintiffs have not met their burden of proving that any of the Defendants will contribute to infringement of the '130 patent.

This Opinion will be filed under temporary seal. The Opinion will be unsealed on Friday October 21, 2016 unless an appropriate motion to seal same (pursuant to Local Civil Rule 5.3(c)) is filed by October 14, 2016. An appropriate order accompanies this Opinion.

Dated: September 30, 2016

CLAIRE C. CECCHI, U.S.D.J.

US006248737B1

(12) **United States Patent**
Buschmann et al.

(10) **Patent No.: US 6,248,737 B1**
(45) **Date of Patent: Jun. 19, 2001**

(54) **1-PHENYL-3-DIMETHYLAMINOPROPANE COMPOUNDS WITH A PHARMACOLOGICAL EFFECTS**

(75) Inventors: **Helmut Buschmann**, Aachen; **Wolfgang Strassburger**, Wuerselen; **Elmar Friderichs**, Stolberg, all of (DE)

(73) Assignee: **Gruenenthal GmbH**, Aachen (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/466,911**

(22) Filed: **Jun. 6, 1995**

(30) **Foreign Application Priority Data**

Jul. 23, 1994 (DE) 44 26 245

(51) **Int. Cl.**[7] **A61K 31/135**; C07C 217/62

(52) **U.S. Cl.** **514/231.8**; 514/114; 514/452; 514/456; 514/488; 514/534; 514/546; 514/653; 514/654; 544/86; 549/362; 549/398; 558/190; 558/273; 560/32; 560/37; 560/66; 560/250; 560/252

(58) **Field of Search** 564/355, 356, 564/374, 440, 442, 443; 514/653, 654, 114, 231.8, 512, 546, 452, 456, 488, 534; 544/86; 558/190, 273; 560/252, 32, 37, 66, 250; 549/362, 398

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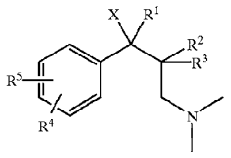
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Primary Examiner—Richard L. Raymond
(74) *Attorney, Agent, or Firm*—Crowell & Moring, L.L.P.

(57) **ABSTRACT**

1-phenyl-3 -dimethylaminopropane compounds corresponding to the formula I

I



a method of preparing them, and the use of these substances as analgesic active ingredients in pharmaceutical compositions.

8 Claims, No Drawings

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Spassov et al., "Stereochemistry of Disasteromeric 3 Dialkylaminopropanols and O Derivatives", *J. Prakt. Chem.*, 323, pp. 793–800 (1981).

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1-PHENYL-3-DIMETHYLAMINOPROPANE COMPOUNDS WITH A PHARMACOLOGICAL EFFECTS

BACKGROUND OF THE INVENTION

The present invention relates to 1-phenyl-3-dimethylaminopropane compounds, to a method of preparing them, and to the use of these substances as pharmaceutical active ingredients.

The treatment of chronic and non-chronic pain situations is of great importance in medicine. This is reflected in the large number of publications. Thus, for example, 1-naphthyl-3-aminopropane-1-ols with an analgesic-narcotic effect are known from EP 176 049. Secondary and tertiary alcohols with γ-amino groups are described in *J. Pharm. Sci.* 59, 1038 (1970) and in *J. Prakt. Chem.* 323, 793 (1981); phenyl-dimethylaminopropanols containing a para-substituted phenyl radical are described in *Chem. Abstr.* 54, 20963c (1960) and in *Chem. Abstr.* 63, 6912e (1965). These compounds also possess analgesic properties. In contrast, the 3-dimethylaminopropan-1-ols containing 2-phenyl radicals described in DE 32 42 922 have an antidepressant effect. The 1-phenyl-propan-1-ols described in *J. Pharm. Sci.* 57, 1487 (1968) have different pharmacological effects depending on the γ-aza ring.

Opioids have been used for many years as analgesics for the treatment of pain, although they give rise to a series of side effects, for example addiction and dependency, respiratory depression, gastrointestinal inhibition and obstipation. They can therefore only be given over an extended period of time or in higher doses subject to special precautionary measures such as special prescription regulations (Goodman, Gilman in "*The Pharmacological Basis of Therapeutics*", Pergamon Press, New York (1990)).

Tramadol hydrochloride—(1RS,2RS)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride—assumes a special position amongst centrally-acting analgesics, since this active ingredient gives rise to a pronounced inhibition of pain without the side effects which are known for opioids (*J. Pharmacol. Exptl. Ther.*4 267, 331 (1993)). Tramadol is a racemate and consists of identical amounts of (+) and (−) enantiomer. In vivo the active ingredient forms the metabolite O-desmethyl-tramadol, which is likewise present as a mixture of enantiomers. Investigations have shown that both the enantiomers of tramadol and the enantiomers of tramadol metabolites contribute to the analgesic effect (*J. Pharmacol. Exp. Ther.* 260, 275 (1992)).

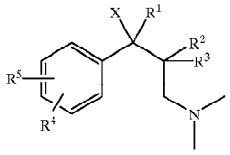
SUMMARY OF THE INVENTION

The underlying object of the present invention was to provide substances with an analgesic effect, which are suitable for the treatment of severe pain without giving rise to the side effects which are typical of opioids.

A further object was to provide analgesic substances which do not exhibit the side effects, for example nausea and vomiting, which occur during treatment with tramadol in some cases.

It has been found that these stringent requirements are fulfilled by certain 1-phenyl-3-dimethylaminopropane compounds. These substances are characterized by a pronounced analgesic effect which is significantly enhanced compared with that of tramadol.

The present invention accordingly relates to 1-phenyl-3-dimethylaminopropane compounds of formula I



in which

X represents OH, F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group;

R^1 is a C_{1-4}-alkyl group;

R^2 represents H or a C_{1-4}-alkyl group and R^3 represents H or a straight chain C_{1-4}-alkyl group, or R^2 and R^3 together constitute a C_{4-7} cycloalkyl radical, and

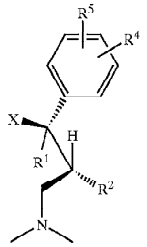
if R^5 is H, R^4 represents meta-O-Z, where Z is H, C_{1-4}-alkyl, $PO(OC_{1-4}\text{-alkyl})_2$, $CO(OC_{1-5}\text{-alkyl})$, $CONH—C_6H_4—(C_{1-3}\text{-alkyl})$ or $CO—C_6H_4—R^7$, wherein R^7 is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^8)_2$, where R^8 is C_{1-4}-alkyl or 4-morpholino, or R^4 represents meta-S-C_{1-3}-alkyl, meta-Cl, meta-F or meta-$CR^9R^{10}R^{11}$, ortho-OH, ortho-O-C_{2-3}-alkyl, para-F or para-$CR^9R^{10}R^{11}$, where R^9, R^{10} and R^{11} represent H or F, or

if R^5 represents Cl, F, OH or O—C_{1-3}-alkyl in the para-position, R^4 represents Cl, F, OH or O—C_{1-3}-alkyl in the meta-position, or

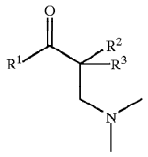
R^4 and R^5 together represent 3,4-OCH=CH— or 3,4-OCH=CHO—, as diastereoisomers or enantiomers in the form of free bases or salts of physiologically acceptable acids.

1-phenyl-3-dimethylaminopropane compounds of formula I are preferred in which X constitutes OH, F, Cl or H, R^1 represents a C_{1-4}-alkyl group; R^2 represents H or CH_3, and R^3 represents H or CH_3, and if R^5 is H, R^4 represents OC_{1-3}-alkyl, —OH, —S—C_{1-3}-alkyl, F, Cl, CH_3, $—CF_2H$ or $—CF_3$ in the meta-position, or para-CF_3, or if R5 is a para-Cl or para-F, R^4 represents meta-Cl or meta-F, or R^4 and R^5 together represent 3,4-OCH=CH—.

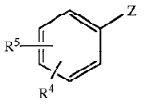
1-phenyl-3-dimethylaminopropane compounds of formula I are particularly preferred in which the R^2 and R^3 radicals have different meanings, in the form of their diastereoisomers of configuration Ia



The present invention also relates to a method of preparing 1-phenyl-3-dimethylaminopropane compounds of formula I, in which the variable X represents OH, which is characterized in that a β-dimethylaminoketone of formula II

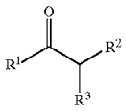


is reacted with an organometallic compound of formula III



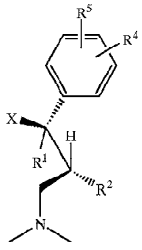
in which Z represents MgCl, MgBr, MgI or Li, to form a compound of formula I in which X represents OH.

The reaction of a β-dimethylaminoketone with a Grignard reagent of formula III, in which Z represents MgCl, MgBr or MgI, or with an organolithium compound of formula III, can be carried out in an a liphatic ether, for example diethyl ether and/or tetrahydrofuran, at temperatures between −70° C. and +60° C. Organolithium compounds of formula II can be obtained by the replacement of halogen by lithium, for example, by reacting a compound of formula III, in which Z represents Cl, Br or I, with a solution of n-butyllithium in n-hexane. β-dimethylaminoketones of formula II can be obtained from ketones of general formula IV



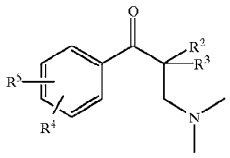
by reaction with dimethylamine hydrochloride and formaldehyde in glacial acetic acid or in a C_{1-4}-alkyl alcohol or by reaction with dimethylammonium ethylene chloride in acetonitrile using acetyl chloride as a catalyst (*Synthesis* 1973, 703).

Upon reaction of a β-dimethylaminoketone of formula II, in which the variables R^2 and R^3 have different meanings, with an organometallic compound of formula III, 1-phenyl-3-dimethylaminopropane compounds of formula I are obtained having the relative configuration of formula Ia

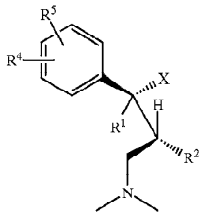


in which the X and the dimethylamino group are disposed threo in relation to each other. In contrast, if the reaction for the preparation of 1-phenyl-1-hydroxy-3-aminopropanes were carried out according to the method disclosed in DD 124 521, i.e. if β-aminoketones corresponding to the formula

V



were reacted with an alkyl Grignard reagent R^1MgHal, this would result in compounds with the relative configuration Ib



in which the OH group and the dimethylamino radical are disposed erythro in relation to each other.

1-phenyl-3-dimethylaminopropane compounds of formula I, in which R^4 and/or R^5 constitute the OH group, can be prepared from the corresponding 1-(4(5)-methoxyphenyl)-3-dimethylaminopropanol compounds by selective ether cleavage with diisobutylaluminium hydride in an aromatic hydrocarbon, for example toluene, at a temperature between 60 and 130° C. (*Synthesis* 1975, 617).

The present invention also relates to a method of preparing 1-phenyl-3-dimethylaminopropane compounds of formula I, in which X represents H, which is characterized in that a compound of formula I, in which X represents Cl, is reacted with zinc borohydride, zinc cyanoborohydride and/or tin cyanoborohydride.

The reaction is usually conducted in a solvent, for example diethyl ether and/or tetrahydrofuran, at a temperature between 0° C. and 30° C.

Compounds of formula I, in which X is H and R^4 and/or R^5 constitute the OH group, can be prepared from the corresponding methoxyphenyl compounds by heating them for several hours with concentrated hydrobromic acid (*Chem. Rev.* 54, 615 (1954); *J. Am. Chem. Soc.* 74, 1316 (1952)).

The present invention further relates to a method of preparing 1-phenyl-3-dimethylaminopropane compounds of formula I, where X represents F, which is characterized in that a compound of formula I, in which X represents OH, is reacted with dimethylaminosulfur trifluoride in a solvent.

Suitable solvents include dichloromethane, 1,1,2-trichloroethane and/or toluene. The reaction is usually conducted at a temperature between −50° C. and +30° C. (*Org. React.* 35, 513 (1988)). If a compound of formula I with X—OH is used in which R^4 and/or R^5 constitute OH groups, these OH groups must be protected before reaction with the fluorine compound, for example by reaction with benzoyl chloride.

The present invention also relates to a method of preparing 1-phenyl-3-dimethylaminopropane compounds of formula I, in which X represents Cl, which is characterized in that a compound of formula I, in which X represents OH, is reacted with thionyl chloride.

The reaction is usually conducted in the absence of solvent at a temperature between 0° C. and 20° C. Replacement of OH by Cl is effected while maintaining the configuration.

The present invention also relates to a method of preparing 1-phenyl-3-dimethylaminopropane compounds of formula I, in which X represents an $OCOR^6$ group where R^6 is a C_{1-3}-alkyl, which is characterized in that a compound of formula I, in which X represents OH, is reacted with an acid chloride Cl—$COOR^6$.

The reaction is preferably conducted in a solvent, for example dichloromethane, toluene and/or tetrahydrofuran, at a temperature between −10° C. and +30° C.

1-phenyl-3-dimethylaminopropane compounds of formula I, in which R^5 is H and R^4 is a meta-phosphate group, meta-carbonate group, meta-carbamate group or meta-carboxylate group, can be obtained by the reaction of the corresponding 1-(3-hydroxyphenyl)-3-dimethylaminopropane compounds of formula I in the form of their alkali salts with an alkali salt of a dialkyl chlorophosphate, with an alkyl chloroformate, with an aryl isocyanate or with a carboxylic acid chloride. These reactions are usually conducted in a solvent, for example toluene, dichloromethane, diethyl ether and/or tetrahydrofuran, at temperatures between −15° C. and +110° C. (*Drugs of the Future* 16, 443 (1991); *J. Med. Chem.* 30, 2008 (1987) and 32, 2503 (1989); *J. Org. Chem.* 43, 4797 (1978); *Tetrahedron Lett.* 1977, 1571; *J. Pharm. Sci.* 57, 774 (1968)).

The compounds of formula I can be converted in a known manner into their salts with physiologically acceptable acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid and/or aspartic acid. Salt formation is preferably effected in a solvent, for example diethyl ether, diisopropyl ether, alkyl acetates, acetone and/or 2-butanone. Moreover, trimethylchlorosilane in aqueous solution is suitable for the preparation of hydrochlorides.

1-phenyl-3-dimethylaminopropane compounds of formula I are toxicologically harmless, so that they are suitable as pharmaceutical active ingredients in drugs.

Accordingly, the present invention also relates to the use of a 1-phenyl-3-dimethylaminopropane compound of formula I as a pharmaceutical active ingredient. Compounds of formula I are preferably used for the treatment of pain.

In addition to at least one 1-phenyl-3-dimethylaminopropane compound of formula I, the analgesics according to the invention may contain carriers, fillers, solvents, diluents, colorants and/or binders. The selection of auxiliary substances and of the amounts of the same to be used depends on whether the drug is to be administered orally, intravenously, intraperitoneally, intradermally, intramuscularly, intranasally or locally, for example for infections of the skin, of the mucous membranes or of the eye. Preparations in the form of tablets, dragees, capsules, granules, drops, liquids and syrups are suitable for oral application. Solutions, suspensions, readily reconstitutable dry preparations, and sprays are suitable for parenteral, topical and inhalative applications. Compounds of formula I according to the invention in a deposit in dissolved form or in a patch, optionally with the addition of a skin penetration promoter, are suitable preparations for percutaneous application. Forms of preparations which can be administered orally or percutaneously may effect delayed release of the compounds of formula I according to the invention.

The amount of active ingredient to be administered to patients varies depending on the patient's weight, on the manner of administration, the indication and the degree of severity of the illness. 50 to 500 mg/kg of at least one 1-phenyl-3-dimethylaminopropane compound of formula I are usually administered.

EXAMPLES

The yields of the compounds prepared have not been optimised.

All temperatures are uncorrected.

Unless otherwise indicated, petroleum ether with a boiling point of 50–70° C. was used. The term "ether" denotes diethyl ether.

Silica gel 60 (0.040–0.063 mm) manufactured by E. Merck, Darmstadt, was used as the stationary phase for column chromatography.

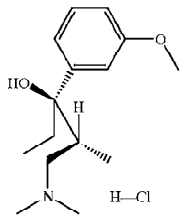
Thin layer chromatography investigations were conducted using prefabricated silica gel 60 F 254 HPTLC plates manufactured by E. Merck, Darmstadt.

Racemate separation was effected on a Chiracel OD column.

The mixture ratios of the mobile phases for all chromatographic investigations are expressed as volume/volume.

RT denotes room temperature; m.p. denotes melting point.

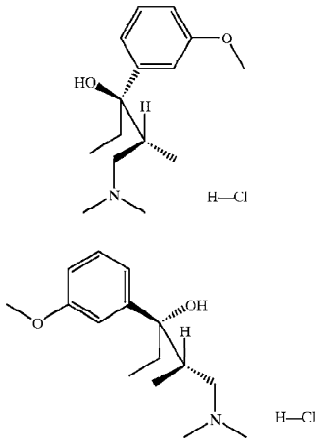
Example 1



(2RS,3RS)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol Hydrochloride(1)

207.63 g (1.11 mole) 3-bromoanisole dissolved in 400 ml dry tetrahydrofuran were added drop-wise to 26.99 g (1.11 mole) magnesium turnings in 150 ml dry tetrahydrofuran so that the reaction mixture boiled gently. After the addition of 3-bromoanisole was complete the mixture was heated under reflux for one hour and thereafter was cooled to 5–10° C. 128.30 g (0.89 mole) 1-dimethylamino-2-methylpentan-3-one dissolved in 400 ml tetrahydrofuran were added at this temperature. The reaction mixture was allowed to stand overnight and then cooled again to 5–10° C. The Grignard solution was decomposed by the addition of 300 ml of 20% ammonium chloride solution. The reaction mixture was diluted with 400 ml ether, the organic phase was separated off and the aqueous phase was extracted twice with 250 ml ether. The combined organic phases were dried over sodium sulphate. After removing the solvent by distillation, the residue (212 g) was taken up in 3200 ml 2-butanone and added to 120.60 g (1.11 mole) trimethylchlorosilane and 20 ml water. 121.5 g of hydrochloride (1) (38% theoretical) with a melting point of 198–199° C. crystallised out at 4–5° C.

Example 2



Enantiomers of (1):

(−)-(2S,3S)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol Hydrochloride(−1)

and

(+)-(2R,3R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol Hydrochloride(+1).

The base was released from (1) with dichloromethane/sodium hydroxide solution. After drying the solution dichloromethane was distilled off under vacuum. The racemate was then separated on the chiral HPLC column. The hydrochlorides, which had a melting point of 150–151° C., were prepared from the enantiomers obtained by reaction with trimethylchlorosilane/water in 2-butanone.

(−1):

yield: 42% theoretical

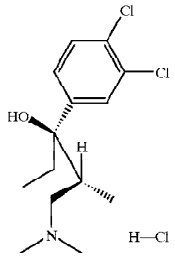
$[\alpha]_{D^{RT}}$=−31.8° (c=0.99; methanol)

(+1):

yield: 41% theoretical

$[\alpha]_{D^{RT}}$=+33.0° (c=0.96; methanol)

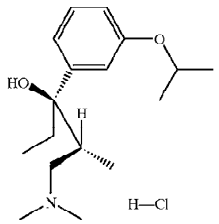
Example 3



(2RS,3RS)-3-(3,4-dichlorophenyl)-1-dimethylamino-2-methylpentan-3-ol Hydrochloride (2)

39 g of crude mixture were prepared analogously to Example 1 from 15 g (105 mmole) 1-dimethylamino-2-methylpentan-3-one, 35.5 g (157 mmole) 4-bromo-1,2-dichlorobenzene and 3.8 g (157 mmole) magnesium turnings. This mixture was introduced on to a 7×40 cm column packed with silica gel and eluted with 4:1 ethyl acetate/methanol. 14.9 g of base were obtained, from which 11.2 g of hydrochloride (2) (31% theoretical) with a melting point of 183–184° C. were obtained with trimethylchlorosilane/water in 2-butanone/diisopropyl ether.

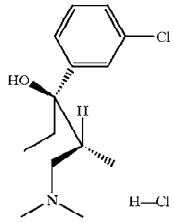
Example 4



(2RS,3RS)-3-(3-isopropoxyphenyl)-1-dimethylamino-2-methylpentan-3-ol Hydrochloride (3)

25 g of crude mixture were prepared analogously to Example 1 from 14.3 g (100 mmole) 1-dimethylamino-2-methylpentan-3-one, 20.0 g (157 mmole) 1-bromo-3-isopropoxybenzene and 2.79 g (115 mmole) magnesium turnings. This mixture was introduced on to a 7×40 cm column packed with silica gel and eluted with 15:1 ethyl acetate/methanol. 9.0 g of base were obtained, from which 8.3 g of hydrochloride (3) (26% theoretical) with a melting point of 133–134° C. were obtained with trimethylchlorosilane/water in 2-butanone.

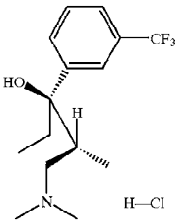
Example 5



(2RS,3RS)-3-(3-chlorophenyl)-1-dimethylamino-2-methylpentan-3-ol Hydrochloride (4)

63 g of crude mixture were obtained under the conditions cited for Example 1 from 38.0 g (270 mmole) 1-dimethylamino-2-methylpentan-3-one, 74.7 g (390 mmole) 1 -bromo-3-chlorobenzene and 9.50 g (390 mmole) magnesium turnings. This mixture was introduced on to a 7×45 cm column packed with silica gel and eluted with 7:1 diisopropyl ether/methanol. 12.8 g of base were obtained, from which 10.8 g of hydrochloride (4) (14% theoretical) with a melting point of 160–162° C. were obtained with trimethylchlorosilane/water in 2-butanone/ether.

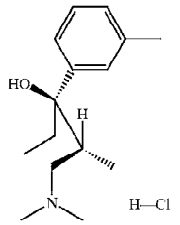
Example 6



(2RS,3RS)-1-dimethylamino-2-methyl-3-(3-trifluoromethylphenyl)-pentan-3-ol Hydrochloride(5)

21.2 g of crude mixture were obtained under the conditions cited for Example 1 from 14.3 g (100 mmole) 1-dimethylamino-2-methylpentan-3-one, 29.3 g (130 mmole) 1-bromo-3-trifluoromethylbenzene and 3.2 g (130 mmole) magnesium turnings. This mixture was introduced on to a 6×40 cm column packed with silica gel and eluted with 10:1 diisopropyl ether/methanol. 9.1 g of base were obtained, from which 7.8 g of hydrochloride (5) (18.5% theoretical) with a melting point of 189–190° C. was obtained with trimethylchlorosilane/water in 2-butanone.

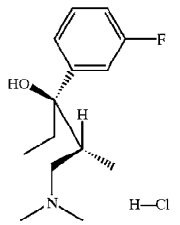
Example 7



(2RS,3RS)-1-dimethylamino-2-methyl-3-(3-m-tolyl)-pentan-3-ol Hydrochloride (6)

75 g of crude mixture were obtained as in Example 1 from 47.3 g (330 mmole) 1-dimethylamino-2-methylpentan-3-one, 64.6 g (400 mmole) 3-bromotoluene and 9.72 g (400 mmole) of magnesium turnings. This mixture was introduced on to a 7×50 cm column packed with silica gel and eluted with 7:1 diisopropyl ether/methanol. 24.3 g of base were obtained, from which 21.5 g of hydrochloride (6) (24% theoretical) with a melting point of 154–155° C. were obtained with trimethylchlorosilane/water in 2-butanone.

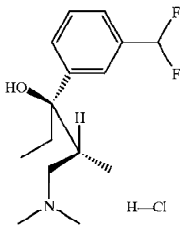
Example 8



(2RS, 3RS)-1-dimethylamino-3-(3-fluorophenyl)-2-methylpentan-3-ol Hydrochloride (7)

70 g of crude mixture were obtained under the conditions cited for Example 1 from 54.0 g (380 mmole) 1-dimethylamino-2-methylpentan-3-one, 82.5 g (470 mmole) 1-bromo-3-fluorobenzene and 9.23 g (470 mmole) magnesium turnings. This mixture was introduced on to a 7×50 cm column packed with silica gel and eluted with 1:1 ethyl acetate/methanol. 13.0 g of base were obtained, from which 11.2 g of hydrochloride (7) (11.5% theoretical) with a melting point of 145–146° C. was obtained with trimethylchlorosilane/water in 2-butanone.

Example 9

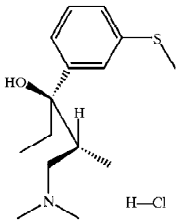


(2RS,3RS)-3-(3-difluoromethylphenyl)-1-dimethylamino-2-methylpentan-3-ol Hydrochloride(8)

7.0 g (34 mmole) 1-bromo-3-difluoromethylbenzene, prepared from 3-bromobenzaldehyde and diethylaminosulphur trifluoride in dichloromethane according to Org. React. 35, 513 (1988) were dissolved in 110 ml of dry tetrahydrofuran and cooled to −75° C. After the addition of 21.12 ml (34 mmole) of a 1.6 molar solution of n-butyllithium in hexane the mixture was stirred for one hour at −75° C. 4.8 g (34 mmole) 1-dimethylamino-2-methylpentan-3-one dissolved in 15 ml of dry tetrahydrofuran were then added dropwise. The reaction mixture was warmed to room temperature over 2.5 hours.

Work-up was effected by the drop-wise addition of 65 ml of 5% hydrochloric acid with cooling in an ice bath, so that the internal temperature did not exceed 15° C. After phase separation the organic phase was extracted with 40 ml of 5% hydrochloric acid. The combined aqueous phases were washed twice with 50 ml ether. In order to release the base, the mixture was added to concentrated sodium hydroxide solution and extracted with dichloromethane. 7.8 g of crude product were obtained in this manner and was introduced on to a 7×40 cm column packed with silica gel. Elution with 1:1 ethyl acetate/methanol gave 4.89 g of base, from which 4.6 g of hydrochloride (8) (44% theoretical) with a melting point of 194–195° C. was obtained with trimethylchlorosilane/water in 2-butanone.

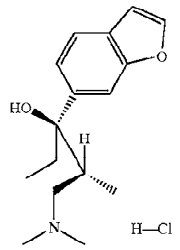
Example 10



(2RS,3RS)-1-dimethylamino-2-methyl-3-(3-methylsulphanylphenyl)-pentan-3-ol Hydrochloride(9)

38 g of crude mixture were obtained under the conditions cited for Example 1 from 17.6 g (123 mmole) 1-dimethylamino-2-methylpentan-3-one, 25.0 g (123 mmole) 1-bromo-3-methylsulphanylbenzene and 3.0 g (123 mmole) magnesium turnings. This mixture was introduced on to a 7×40 cm column packed with silica gel and eluted with 10:1 ethyl acetate/methanol. 8.35 g of base were obtained, from which 7.2 g of hydrochloride (9) (19% theoretical) with a melting point of 159–160° C. were obtained with trimethylchlorosilane/water in 2-butanone.

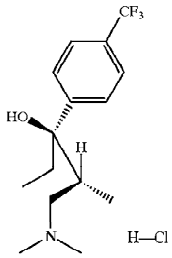
Example 11



(2RS,3RS)-3-benzofuran-6-yl-1-dimethylamino-2-methylpentan-3-ol Hydrochloride(10)

3.45 g (18 mmole) 6-bromobenzofurane (prepared according to EP 355 827) and 6 ml 1,2-dibromoethane, dissolved in 60 ml dry ether, were added drop-wise over 1.5 hours to 2.12 g (87 mmole) magnesium turnings in 30 ml dry ether; after the addition the mixture was heated under reflux for 30 minutes. Thereafter, 2.5 g (18 mmole) 1-dimethylamino-2-methylpentan-3-one dissolved in 7.5 ml ether was added drop-wise over 1.5 hours whilst cooling in an ice bath to maintain an internal temperature of 5–10° C. The reaction mixture was allowed to stand for 12 hours at room temperature, and was then cooled again to 5–10° C. and added to 35 ml of 20% aqueous ammonium chloride solution. After phase separation, the aqueous phase was extracted twice with 50 ml ether. The combined organic phases were dried over sodium sulphate. After removing the solvent by distillation the residue (3.9 g) was introduced on to a 5×16 cm column packed with silica gel. 0.95 g of base were obtained by elution with 7:1 diisopropyl ether/methanol, from which 0.82 g of hydrochloride (10) (15.5% theoretical) with a melting point of 162° C. were obtained with trimethylchlorosilane/water in ethyl acetate/2-butanone.

Example 12



(2RS,3RS)-1-dimethylamino-2-methyl-3-(4-trifluoromethylphenyl)-pentan-3-ol Hydrochloride (11)

44 g of crude mixture were obtained as in Example 1 from 20 g (140 mmole) 1-dimethylamino-2-methylpentan-3-one, 31.5 g (140 mmole) 1-bromo-4-trifluoromethylbenzene, 16.5 g (680 mmole) magnesium turnings and 47 ml 1,2-dibromoethane. This mixture was introduced on to a 7×50 cm column packed with silica gel and eluted with 5:1 ethyl acetate/methanol. 16.4 g of base were obtained, from which 12.3 g of hydrochloride (11) (27% theoretical) with a melting point of 170–171° C. were obtained with trimethylchlorosilane/water in 2-butanone.

Example 13

(3RS)-1-dimethylamino-3-(3-methoxyphenyl)-hexan-3-ol Hydrochloride (12)

18.5 g of crude mixture were obtained as in Example 1 from 10 g (70 mmole) 1-dimethylamino-hexan-3-one, 18.7 g (100 mmole) 1-bromo-3-methoxybenzene and 2.3 g (100 mmole) magnesium turnings. This mixture was introduced on to a 6×50 cm column packed with silica gel and eluted with 1:1 ethyl acetate/methanol. 6.84 g of base were obtained, from which 6.15 g of hydrochloride (12) (32% theoretical) with a melting point of 179–180° C. were obtained with trimethylchlorosilane/water in 2-butanone.

Example 14

(3RS)-1-dimethylamino-3-(3-methoxyphenyl)-heptan-3-ol Hydrochloride (13)

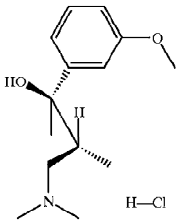
17.3 g of crude mixture were obtained as in Example 1 from 10 g (64 mmole) 1-dimethylamino-heptan-3-one, 15.9 g (157 mmole) 1-bromo-3-methoxybenzene and 2.06 g (85 mmole) magnesium turnings. This mixture was introduced on to a 6×40 cm column packed with silica gel and eluted with ethyl acetate. 5.4 g of base were obtained, from which 4.1 g of hydrochloride (13) (21% theoretical) with a melting point of 150° C. were obtained with trimethylchlorosilane/water in 2-butanone.

Example 15

(3RS)-1-dimethylamino-3-(3-methoxyphenyl)-4,4-dimethylpentan-3-ol Hydrochloride(14)

37 g of crude mixture were obtained as in Example 1 from 18.6 g (118 mmole) 1-dimethylamino-4,4-dimethylpentan-3-one, 28.4 g (152 mmole) 1-bromo-3-methoxybenzene and 3.7 g (152 mmole) magnesium turnings. This mixture was introduced on to a 7×40 cm column packed with silica gel and eluted with 5:1 ethyl acetate/methanol. 2.2 g of base were obtained, from which 1.8 g of hydrochloride (14) (5% theoretical) with a melting point of 213° C. were obtained with trimethylchlorosilane/water in 2-butanone.

Example 16

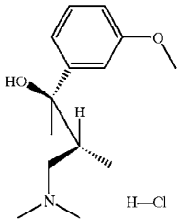


(2RS,3RS)-4-dimethylamino-2-(3-methoxyphenyl)-3-methylbutan-3-ol Hydrochloride(15)

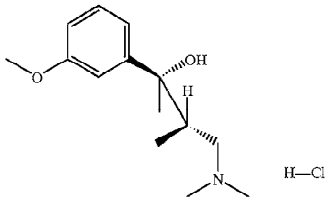
21 g of crude mixture were obtained as in Example 1 from 5.3 g (41 mmole) 4-dimethylamino-3-methylbutan-3-one, 23.0 g (123 mmole) 1-bromo-3-methoxybenzene and 3.0 g (123 mmole) magnesium turnings. This mixture was introduced on to a 4.5×27 cm column packed with silica gel and eluted with 4:1 ethyl acetate/methanol. 4.0 g of base were obtained, from which 3.6 g of hydrochloride (15) (32% theoretical) with a melting point of 124° C. were obtained with trimethylchlorosilane/water in 2-butanone.

Example 17

(+15)



(−15)



Enantiomers of (15):

(−)-(2S,3S)-4-dimethylamino-2-(3-methoxyphenyl)-3-methylbutan-3-ol Hydrochloride (−15)

and

(+)-(2R,3R)-4-dimethylamino-2-(3-methoxyphenyl)-3-methylbutan-3-ol Hydrochloride(+15).

The base was released from hydrochloride (15), which was prepared as in Example 16, with dichloromethane/sodium hydroxide solution. After drying and removal of dichloromethane by distillation, the racemate was then separated into the enantiomers on a chiral HPLC column. The hydrochlorides were obtained from the enantiomers with trimethylchlorosilane/water in 2-butanone.

(−15):

yield: 41% theoretical

m.p.: 117–118° C.

$[\alpha]_{D^{20}}$=−38.6° (c=1.05, methanol)

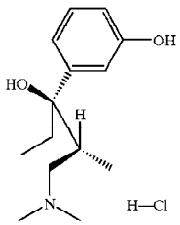
(+15):

yield: 41% theoretical

m.p.: 118–119° C.

$[\alpha]_{D^{20}}$=+41.0° (c=1.01; methanol)

Example 18

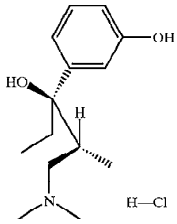


(2RS,3RS)-3-(3-dimethylamino-1-ethyl-1-hydroxy-2-methylpropyl)-phenol Hydrochloride(16).

The base was released from compound (1), which was prepared as in Example 1, with dichloromethane/sodium hydroxide solution. After drying the solution, dichloromethane was removed by distillation. 4.3 g (17 mmole) of base were dissolved in 25 ml dry toluene and slowly added drop-wise to 71 ml (85 mmole) of a 1.2 molar solution of diisobutylaluminium hydride in toluene. When the addition was complete, the mixture was heated for 8 hours under reflux and then cooled to room temperature. The reaction mixture was diluted with 25 ml toluene. 9.4 ml ethanol followed by 9.4 ml water were added drop-wise whilst cooling in an ice bath. After stirring for one hour whilst cooling in the ice bath the reaction mixture was freed from aluminium salts by filtration, and the residue was washed three times with 50 ml toluene in each case. Thereafter the combined organic phases were dried and toluene was removed by distillation. 3.95 g of hydrochloride (16) (85% theoretical) with a melting point of 213–214° C. were obtained from the base with aqueous hydrochloric acid solution in acetone.

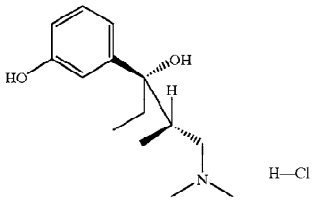
Example 19

(+16)



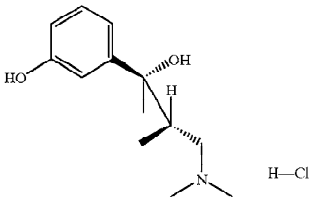
-continued

(-16)



-continued

(-17)



Enantiomers of (16):

(−) (2S, 3S)-3-(3-dimethylamino-1-ethyl-1-hydroxy-2-methylpropyl)-phenol Hydrochloride(−16)

and

(+)(2S,3S)-3-(3-dimethylamino-1-ethyl-1-hydroxy-2-methylpropyl)-phenol Hydrochloride(+16)

The enantiomers (−16) and (+16) were prepared under the conditions cited in Example 2.

(−16):

yield: 85% theoretical

m.p.: 208–209° C.

$[\alpha]_{D^{RT}}$=−34.6° (c=0.98; methanol)

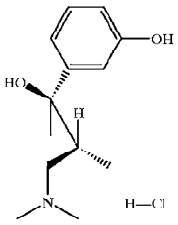
(+16):

yield: 85% theoretical

m.p.: 206–207° C.

$[\alpha]_{D^{RT}}$=+34.4° (c=1.06; methanol)

Example 20



(1RS,2RS)-3-(3dimethylamino-1-hydroxy-1,2-dimethylpropylphenol Hydrochloride(17)

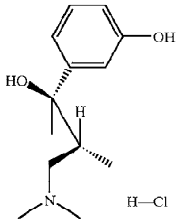
Compound (17) was prepared under the conditions cited in Example 18 starting from methoxy compound (15) which was obtained as in Example 16.

Yield: 85% theoretical

m.p.: 232° C.

Example 21

(+17)



Enantiomers of (17):

(−)-(1S,2S)-3-(3-dimethylamino-1-hydroxy-1,2-dimethylpropyl)-phenol Hydrochloride(−17)

and

(+)-(1R,2R)-3-(3-dimethylamino-1-hydroxy-1,2-dimethylpropyl)-phenolhydrochloride(+17)

The enantiomers (−17) and (+17) were prepared under the conditions cited in Example 2.

(−17):

yield: 82% theoretical

m.p.: 204–205° C.

$[\alpha]_{D^{RT}}$=−42.0° (c=0.94; methanol)

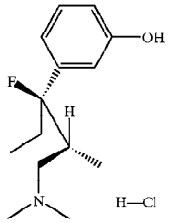
(+17):

yield: 83% theoretical

m.p.: 204–205° C.

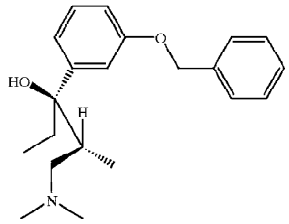
$[\alpha]_{D^{RT}}$=+41.2° (c=1.01; methanol)

Example 22



(+)-(1R,2R)-3-(3-dimethylamino-1-ethyl-1-fluoro-2-methylpropyl)-phenol Hydrochloride(+18)

1st Step

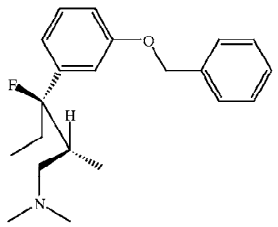


(+)-(1R,2R)-3-(3-benzyloxyphenyl)-1-dimethylamino-2-methylpentan-3-ol (+19)

The base was released with dichloromethane/sodium hydroxide solution from enantiomer (+16) obtained as in Example 19, and dichloromethane was removed by distillation after drying the solution. 5.3 g (22 mmole) of base were dissolved in 27 ml of dry dimethylformamide and added in several portions to 1.2 g of 50% sodium hydride.

After the addition of 2.8 ml (24 mmole) benzoyl chloride the mixture was heated for three hours at 70° C. The reaction mixture was then cooled to room temperature and poured on to an ice/water mixture. It was extracted three times with 70 ml ether in each case. After drying the combined organic phases over sodium sulphate, the solvent was distilled off and the residue was introduced on to a 4.5×30 cm column packed with silica gel. 6.8 g of base (+19) (92% theoretical) were obtained as a light yellow, highly viscous oil by elution with diisopropyl ether/methanol.

2nd Step



(+)-(2R,3R)-[3-(3-benzyloxyphenyl)-3-fluoro-2-methylpentyl]-dimethylamine(+20)

6.8 g (21 mmole) of (+19), dissolved in 80 ml dichloromethane, were added dropwise at −20° C. to a solution of 3.7 g (23 mmole) diethylaminosulphur trifluoride in 30 ml of dry dichloromethane. After the addition was complete, the mixture was stirred for 30 minutes at this temperature and then warmed to room temperature. After stirring for a further one hour at room temperature, the mixture was cooled to 0–5° C. and hydrolysed with 50 ml water. After phase separation, the aqueous phase was extracted twice with 50 ml dichloromethane. The combined organic phases were dried and freed from solvent by distillation under vacuum. The crude mixture obtained (8.04 g) was introduced on to a 6×50 cm column packed with silica gel and eluted with 1:1 ethyl acetate/methanol. 3.04 g of base (+20) (40% theoretical) were obtained as a light yellow, viscous oil.

3rd Step:

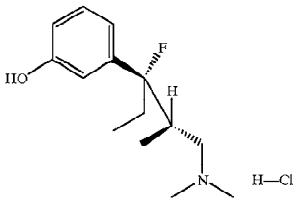
(+)-(1R,2R)-3-(3-dimethylamino-1-ethyl-1-fluoro-2-methylpropyl)-phenol Hydrochloride(+18)

3.0 g (91 mmole) of (+20) were dissolved in 15 ml of dry methanol and added to 0.44 g palladium on activated carbon (10% Pd) in a hydrogenation apparatus. 215 ml hydrogen was consumed after stirring for three hours at room temperature. The catalyst was removed by filtration, and the methanol was removed by distillation. 2.22 g of base were obtained, from which 2.0 g of hydrochloride (+18) (79% theoretical) were obtained with trimethylchlorosilane/water in 2-butanone.

m.p.: 174–176° C.

$[\alpha]_{D^{27}}$=+29.5° (c=1.08; methanol)

Example 23



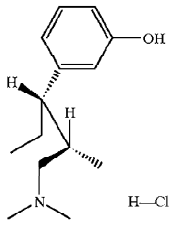
(−)-(1S,2S)-3-(3-dimethylamino-1-ethyl-1-fluoro-2-methylpropyl)-phenol Hydrochloride(−18)

Enantiomer (−18) was obtained in a yield of 29% theoretical from enantiomer (−16) obtained as in Example 19, under the conditions cited in Example 22.

m.p.: 170–172° C.

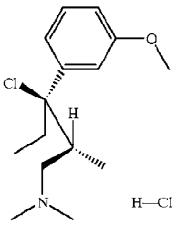
$[\alpha]_{D^{27}}$=−28.4° (c=1.03; methanol)

Example 24



(+)-(1S,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol Hydrochloride(+21)

1st Step:



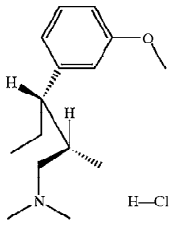
(+)-(2R,3R)-[3-chloro-3-(-3-methoxyphenyl)-2-methylpentyl]-dimethylamine Hydrochloride(+22)

10 g (35 mmole) of (+1), prepared as in Example 2, were added to 10 ml thionyl chloride at room temperature. Nitrogen was subsequently passed over the reaction mixture for two hours to remove excess thionyl chloride. After a fresh addition of 10 ml thionyl chloride the reaction mixture was allowed to stand for 12 hours before excess thionyl chloride was again removed over a period of 2.5 hours by means of a stream of nitrogen. After drying, the residue was dissolved in 10 ml of ice-cold 2-butanone and mixed with stirring with 200 ml ether and then with 140 ml diisopropyl ether. The supernatant solvent phase was decanted off and the remaining oil was again taken up in 10 ml 2-butanone. After the addition of seed crystals, 300 ml diisopropyl ether were added drop-wise with vigorous stirring over three hours, whereupon the hydrochloride crystallised out. 9.8 g of (22) (91% theoretical) were obtained.

m.p.: 120° C. (decomposition)

$[\alpha]_{D^{RT}}$=+24.7° (c=1.01; methanol)

2nd Step:



(+)-(2R,3S)-[3-(3-methoxyphenyl)-2-methylpentyl]-dimethylamine Hydrochloride(+23)

46 g of dried zinc chloride were dissolved in 580 ml of dry ether and subsequently added drop-wise to a slurry of 31 g sodium borohydride in 1800 ml ether. After stirring for 12 hours, 500 ml were removed by decantation from the zinc borohydride suspension obtained and added drop-wise to 9.8 g (32 mmole) of (+22) in 200 ml of dry ether. The reaction mixture was stirred for 72 hours at room temperature and then added drop-wise to 40 ml of a saturated ammonium chloride solution with cooling in an ice bath. After phase separation, the ether phase was washed twice with saturated brine; after drying over sodium sulphate the solvent was distilled off under vacuum. 7.3 g of an amine-borane complex were obtained, which were dissolved in 100 ml of dry methanol to isolate the free base. After the addition of 7.5 g triphenylphosphine the mixture was heated for 18 hours under reflux. After removing the solvent by distillation the residue was added to 100 ml of 5% hydrochloric acid, and the hydrochloric acid phase was subsequently washed twice with 50 ml ether. Thereafter the hydrochloric acid phase was made alkaline with concentrated sodium hydroxide solution whilst cooling in an ice bath, and was solvent-extracted twice with 50 ml dichloromethane. After drying the combined organic phases over sodium sulphate the solvent was distilled off under vacuum and the remaining residue (5.2 g) was taken up in 2-butanone. After the addition of trimethylchlorosilane/water, 4.3 g of hydrochloride (+23) (50% theoretical) crystallised out.

m.p.: 163–164° C.

$[\alpha]_{D^{RT}}$=+25.20 (c=0.95; methanol)

3rd Step:

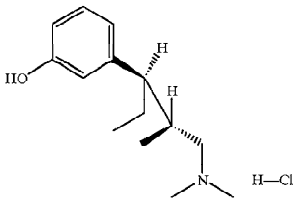
(+)-(1S,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol Hydrochloride(+21)

4.3 g (15 mmole) of (+23) from step 2 were added to 100 ml of concentrated hydrobromic acid. The mixture was then heated under reflux for two hours. After cooling to room temperature the reaction mixture was concentrated under the vacuum from a water pump. The residue was treated with concentrated sodium hydrogen carbonate solution until an alkaline reaction was obtained. After extracting twice with 50 ml dichloromethane in each case the combined organic phases were dried over sodium sulphate. Dichloromethane was then distilled off under vacuum and the residue (4 g) was taken up in 2-butanone. After the addition of trimethylchlorosilane/water, 3.8 g of hydrochloride (+21) (98% theoretical) crystallised out.

m.p.: 194–196° C.

$[\alpha]_{D^{RT}}$=+24.5° (c=1.10; methanol)

Example 25



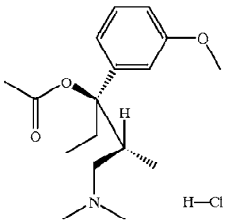
(−)-(1R,2S)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride(−21)

Enantiomer (−21) was obtained in 45% yield under the conditions cited in Example 24 from (−1), which was prepared as in Example 2.

m.p.: 168–170° C.

$[\alpha]_{D^{RT}}$=−27.5° (c=0.97; methanol)

Example 26



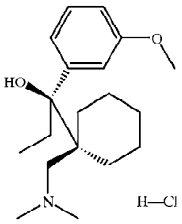
(+)-(1R,2R)-acetic acid-3-dimethylamino-1-ethyl-1-(3-methyoxyphenyl)-2-methylpropyl Ester Hydrochloride(+24)

The base was released from enantiomer (+1), which was prepared as in Example 2, with dichloromethane/sodium hydroxide solution. After drying the solution, dichloromethane was removed by distillation. 3.0 g (39 mmole) acetyl chloride were added drop-wise, whilst cooling in an ice bath, to 10 g (35 mmole) of the base obtained, which had been taken up in 150 ml of dry dichloromethane. After the addition of acetyl chloride was complete, the reaction mixture was warmed to room temperature, and after stirring for two hours was mixed with 100 ml of saturated sodium hydrogen carbonate solution. The organic phase was separated from the aqueous phase and the aqueous phase was extracted twice with 50 ml dichloromethane. The organic phases were combined and dried over sodium sulphate. After removing the solvent by distillation, 13.4 g crude mixture were obtained, from which 10.7 g, of hydrochloride (+24) (93% theoretical) was obtained with trimethylchlorosilane/water in 2-butanone/ethyl acetate.

m.p.: 153° C.

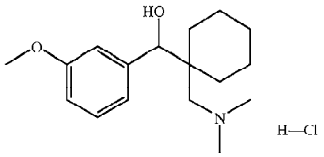
$[\alpha]_{D^{RT}}$=−17.3° (c=1.04; methanol)

Example 27



(1RS)-1-(1-dimethylaminomethyl-cyclohexyl)-1-(3-methoxyphenyl)-propan-1-ol Hydrochloride(25)

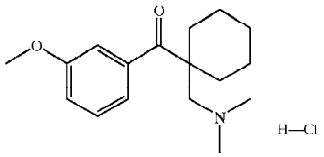
1st Step:



(1RS)-1-(1-dimethylaminomethyl-cyclohexyl)-(3-methoxyphenyl)-methanol Hydrochloride(26)

44 g crude mixture was obtained from 25 g (150 mmole) 1-dimethylaminomethyl-cyclohexane carbaldehyde, 32.9 g (180 mmole) 1-bromo-3-methoxybenzene and 4.3 g (180 mmole) magnesium turnings, under the conditions cited in Example 1. This mixture was introduced on to a 7×40 cm column packed with silica gel and eluted with 4 : 1 diisopropyl ether/methanol. 38 g of base were obtained, from which 40 g of hydrochloride (26) (85% theoretical) with a melting point of 235° C. were obtained with trimethylchlorosilane/water in 2-butanone.

2nd Step:



(1RS)-(1-dimethylaminomethyl-cyclohexyl)-(3-methoxyphenyl)-methanone IIydrochloride(27)

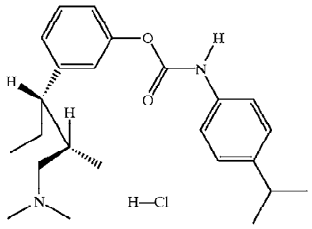
The base was released from (26) with dichloromethane/sodium hydroxide solution and after drying the solution dichloromethane was removed by distillation. 8.3 g (30 mmole) of base were dissolved in 30 ml n-hexane and added drop-wise to a suspension consisting of 95 g pyridinium chlorochromate (prepared according to Synthesis 1980, 223) absorbed on neutral alumina. After stirring for 72 hours at room temperature the reaction mixture was mixed with 120 ml dichloromethane, stirred for a further 2 hours and then filtered through 30 g alumina. The filter residue was washed three times by decantation with 50 ml dichloromethane and ether in each case. The organic phases were combined with the filtrate and freed from solvent by distillation. The residue obtained was taken up in 60 ml of 2 Normal sodium hydroxide solution and extracted four times with 20 mg ethyl acetate in each case. After drying the combined organic phases, the solvent was removed by distillation. 4.8 g crude mixture were obtained, which was introduced on to a 6×30 cm column packed with silica gel and eluted, firstly with ethyl acetate, then with 9:1 ethyl acetate/methanol and finally with 4:1 ethyl acetate/methanol. 3.8 g of base were obtained, from which 3.1 g of hydrochloride (27) (33% theoretical) with a melting point of 174° C. were obtained with trichlorosilane/water in 2-butanone.

3rd Step:

(1RS)-1-(1-dimethylaminomethyl-cyclohexyl)-1-(3-methoxyphenyl)-propan-1-ol Hydrochloride(25)

3.0 g crude mixture was obtained, under the conditions cited in Example 1, from 2.8 g (10 mmole) of (27) in the form of the base, 1.4 g (13 mmole) bromoethane and 0.32 g (13 mmole) magnesium turnings, using ether as the solvent. This mixture was introduced on to a 3×20 cm column packed with silica gel and eluted with 19:1 diisopropyl ether/methanol. 2.1 g of base were obtained, from which 1.9 g of hydrochloride (25) (55% theoretical) with a melting point of 230° C. were obtained with trichlorosilane/water in 2-butanone/ethyl acetate.

Example 28



(−)-(2R,3S)-{3[3-(p-isopropyl-phenyl-carbamoyl)-oxy-phenyl]-2-methylpentyl-dimethylamine Hydrochloride(−28)

The base was released from enantiomer (+21), which was prepared as in Example 24, with dichloromethane/sodium hydroxide solution, and after drying the solution dichloromethane was removed by distillation. 2.2 g (10 mmole) of the base obtained were dissolved in 20 ml of dry toluene and mixed with 1.8 g (11 mmole) 4-isopropylphenyl isocyanate. After stirring for 20 hours at room temperature the toluene was removed by distillation. The residue was reacted with trimethylchlorosilane/water in n-propyl acetate to form 3.2 g of hydrochloride (−28) (76% theoretical).

m.p.: 151−152° C.

$[\alpha]_D^{87}$=−5.2° (c=1.11; methanol)

Pharmacological Investigations

Writhing Test on Mice

The analgesic effectiveness of the compounds according to the invention was investigated in the phenylquinone-induced writhing test, modified according to I. C. Hendershot, J. Forsaith in *J. Pharmacol. Exptl. Ther.* 125, 237 (1959), on mice. Male NMRI mice with a weight between 25 and 30 g were used for this purpose. For each dose of substance, each 10 animals received, 30 minutes after the oral administration of a compound according to the invention, 0.3 ml per mouse of an 0.02% aqueous phenylquinone solution (phenylbenzoquinone manufactured by Sigma, Deisenhofen; solution prepared with the addition of 5% ethanol and kept on a water bath at 45° C.) administered intraperitoneally. Thereafter the animals were placed individually in observation cages. The number of pain-induced

stretching movements (writhing reaction=straightening of the body with stretching of the rear extremities) was counted with the aid of a push-button counter. The ED_{50} value (effective dose with 50% inhibition of writhing reaction) was calculated with a 95% confidence limit by means of regression analysis (evaluation program supplied by Martens EDV-Service, Eckental) from the dose-dependent decrease in the writhing reaction, by comparison with mice tested in parallel to which only phenylquinone had been administered. All the compounds according to the invention which were investigated exhibited a pronounced analgesic effect. The results are summarized in the following Table:

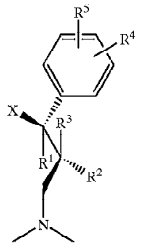
TABLE

		Writhing inhibition	
Example	Compound according to the invention	ED_{50} [mg/kg per os]	% Inhibition 25 mg/kg per os
1	(1)	5.8	
2	(−1)	22.3	
2	(+1)	1.1	
3	(2)	13.2	
4	(3)		−81.3
5	(4)	15.5	
6	(5)	8.3	
7	(6)	11.8	
8	(7)	27.3	
9	(8)	12.9	
10	(9)	12.8	
11	(10)	12.9	
13	(12)	19.9	
15	(14)	10.5	
16	(15)	3.8	
17	(+15)		−95.2
18	(16)		−100.0
19	(−16)	16.1	
19	(+16)	1.0	
20	(17)		−87.0
21	(−17)		−58.3
21	(+17)		−97.2
22	(+18)	15.7	
24	(+21)	1.9	

The foregoing description and examples have been set forth merely to illustrate the invention and are not intended to be limiting. Since modifications of the disclosed embodiments incorporating the spirit and substance of the invention may occur to persons skilled in the art, the invention should be construed to include all variations within the scope of the appended claims and equivalents thereof.

What is claimed is:

1. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer having a configuration corresponding to formula I



wherein

X represents OH, F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group;

R^1 is a C_{1-4}-alkyl group;

R^2 represents H or a C_{1-4}-alkyl group, and

R^3 is different from R^2 and represents H or a straight chain C_{1-4}-alkyl group, and

R^5 represents H, and R^4 represents meta-O—Z, where Z is H, C_{1-3}-alkyl, $PO(OC_{1-4}alkyl)_2$, $CO(OC_{1-5}$-alkyl), $CONH—C_6H_4—(C_{1-3}$-alkyl) or $CO—C_6H_4—R^7$, in which R^7 is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^8)_2$, where R^8 is C_{1-4}-alkyl or 4-morpholino,

or R^4 represents meta-S-C_{1-3}-alkyl, meta-Cl, meta-F, meta-$CR^9R^{10}R^{11}$, ortho-OH, ortho-O—C_{2-3}-alkyl, para-F or para-$CR^9R^{10}R^{11}$, where R^9, R^{10} and R^{11} independently represent H or F, or

R^5 represents para-Cl, para-F, para-OH or para-O—C_{1-3}-alkyl, and R^4 represents meta-Cl, meta-F, meta-OH or meta-O—C_{1-3}-alkyl, or

R^4 and R^5 together represent 3,4-OCH═CH— or 3,4-OCH═CHO—; or a salt thereof with a physiologically acceptable acid.

2. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 1, wherein

X represents OH, F, Cl or H;

R^1 represents a C_{1-4}-alkyl group;

R^2 represents H or CH_3;

R^3 is different from R^2 and represents H or CH_3, and

R^5 represents H, and R^4 represents meta-OC_{1-3}-alkyl, meta-OH, meta-S—C_{1-3}-alkyl, meta-F, meta-Cl, meta-CH_3, meta-CF_2H, meta-CF_3 or para-CF_3, or

R^5 represents para-Cl or para-F, and R^4 represents meta-Cl or meta-F, or

R^4 and R^5 together represent 3,4-OCH═CH—.

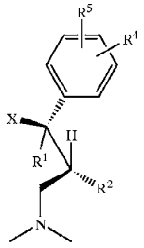
3. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 1, wherein X represents OH, F, Cl or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group.

4. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 1, wherein R^2 is C_{1-4}-alkyl.

5. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 1, wherein R^9, R^{10} and R^{11} represent F.

6. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer having a configuration corresponding to the formula Ia

Ia



wherein

X represents OH, F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group;

R^1 is a C_{1-4}-alkyl group;

R^2 represents a C_{1-4}-alkyl group, and

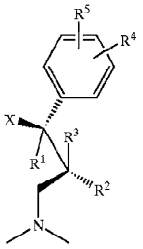
R^5 represents H, and R^4 represents meta-O—Z, where Z is H, C_{1-3}-alkyl, $PO(OC_{1-4}alkyl)_2$, $CO(OC_{1-5}$-alkyl), $CONH—C_6H_4—(C_{1-3}$-alkyl) or $CO—C_6H_4—R'$, in which R' is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^8)_2$, where R^8 is C_{1-4}-alkyl or 4-morpholino,

or R^4 represents meta-S—C_{1-3}-alkyl, meta-Cl, meta-F, meta-$CR^9R^{10}R^{11}$, ortho-OH, ortho-O—C_{2-3}-alkyl, para-F or para-$CR^9R^{10}R^{11}$, where R^9, R^{10} and R^{11} independently represent H or F, or

R^5 represents para-Cl, para-F, para-OH or para-O—C_{1-3}-alkyl, and R^4 represents meta-Cl, meta-F, meta-OH or meta-O—C_{1-3}-alkyl, or

R^4 and R^5 together represent 3,4-OCH═CH— or 3,4-OCH═CHO—; or a salt thereof with a physiologically acceptable acid.

7. An analgesic composition comprising at least one 1-phenyl-3-dimethylaminopropane diastereoisomer having a configuration corresponding to formula I



wherein

X represents OH, F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group;

R^1 is a C_{1-4}-alkyl group;

R^2 represents H or a C_{1-4}-alkyl group, and

R^3 is different from R^2 and represents H or a straight chain C_{1-4}-alkyl group, and

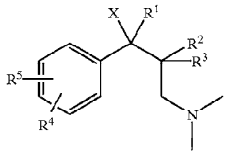
R^5 represents H, and R^4 represents meta-O—Z, where Z is H, C_{1-3}-alkyl, $PO(OC_{1-4}alkyl)_2$, $CO(OC_{1-5}$-alkyl), $CONH—C_6H_4—(C_{1-3}$-alkyl) or $CO—C_6H_4—R^7$, in which R^7 is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^8)_2$, where R^8 is C_{1-4}-alkyl or 4-morpholino,

or R^4represents meta-S—C_{2-3}-alkyl, meta-Cl, meta-F, meta-$CR^9R^{10}R^{11}$, ortho-OH, ortho-O—C_{2-3}-alkyl, para-F or para-$CR^9R^{10}R^{11}$, where R^9, R^{10} and R^{11} independently represent H or F, or

R^5 represents para-Cl, para-F, para-OH or para-O—C_{1-3}-alkyl, and R^4 represents meta-Cl, meta-F, meta-OH or meta-O—C_{1-3}-alkyl, or

R^4 and R^5 together represent 3,4-OCH═CH— or 3,4-OCH═CHO—; or a salt thereof with a physiologically acceptable acid, and at least one conventional pharmaceutical carrier or adjuvant.

8. A method of treating a mammal suffering from pain, said method comprising administering to said mammal an effective analgesic amount of a 1-phenyl-3-dimethylaminopropane compound corresponding to formula I



wherein

X represents OH, F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group;

R^1 is a C_{1-4}-alkyl group;

R^2 represents H or a C_{1-4}-alkyl group and R^3 represents H or a straight chain C_{1-4}-alkyl group, or R^2 and R^3 together form a C_{4-7} cycloalkyl radical, and

R^5 represents H, and R^4 represents meta-O—Z, where Z is H, C_{1-3}-alkyl, $PO(OC_{1-4}alkyl)_2$, $CO(OC_{1-5}$-alkyl), $CONH—C_6H_4—(C_{1-3}$-alkyl) or $CO—C_6H_4—R^7$, in which R^7 is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^8)_2$, where R^8 is C_{1-4}-alkyl or 4-morpholino,

or R^4 represents meta-S—C_{1-3}-alkyl, meta-Cl, meta-F, meta-$CR^9R^{10}R^{11}$, ortho-OH, ortho-O—C_{2-3}-alkyl, para-F or para-$CR^9R^{10}R^{11}$, where R^9, R^{10} and R^{11} independently represent H or F, or

R^5 represents para-Cl, para-F, para-OH or para-O—C_{1-3}-alkyl, and R^4 represents meta-Cl, meta-F, meta-OH or meta-O—C_{1-3}-alkyl, or

R^4 and R^5 together represent 3,4-OCH═CH— or 3,4-OCH═CHO—, or a salt thereof with a physiologically acceptable acid.

* * * * *

US007994364B2

(12) **United States Patent**
Fischer et al.

(10) **Patent No.: US 7,994,364 B2**
(45) **Date of Patent: Aug. 9, 2011**

(54) **CRYSTALLINE FORMS OF (−)-(1R,2R)-3-(3-DIMETHYLAMINO-1-ETHYL-2-METHYLPROPYL)-PHENOL HYDROCHLORIDE**

(75) Inventors: **Andreas Fischer**, Huertgenwald (DE); **Helmut Buschmann**, Esplugues de Llobregat (ES); **Michael Gruss**, Aachen (DE); **Dagmar Lischke**, Eschweiler (DE)

(73) Assignee: **Gruenenthal GmbH**, Aachen (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **12/634,777**

(22) Filed: **Dec. 10, 2009**

(65) **Prior Publication Data**

US 2010/0160447 A1 Jun. 24, 2010

Related U.S. Application Data

(63) Continuation of application No. 12/274,747, filed on Nov. 20, 2008, now abandoned, which is a continuation of application No. 11/646,232, filed on Dec. 28, 2006, now abandoned, which is a continuation of application No. PCT/EP2005/006884, filed on Jun. 27, 2005.

(30) **Foreign Application Priority Data**

Jun. 28, 2004 (EP) 04015091

(51) **Int. Cl.**
C07C 211/00 (2006.01)
A01N 33/02 (2006.01)
A61K 31/135 (2006.01)

(52) **U.S. Cl.** **564/336**; 514/649

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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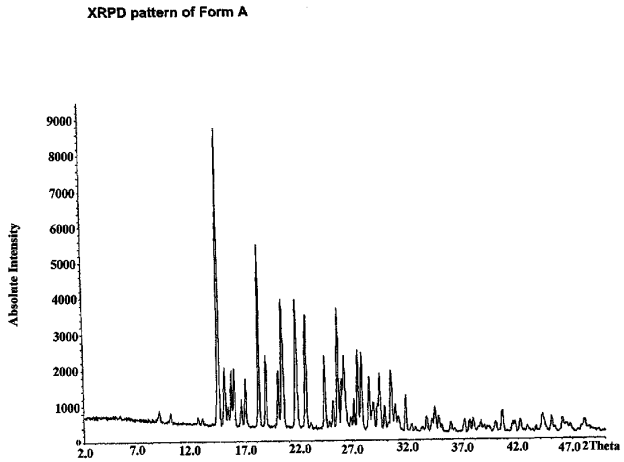
Remington: The Science and Practice of Pharmacy, Nineteenth Edition, vol. 1, pp. 156-168, 180, 1448-1460 (English counterpart of A.R. Gennaro, Remington Farmacia, 19th Ed. Medica Panamericana 1995, pp. 230-235, 245 and 2226-2234 cited against corresponding.

Primary Examiner — Daniel Sullivan
Assistant Examiner — Clinton Brooks
(74) *Attorney, Agent, or Firm* — Crowell & Moring LLP

(57) **ABSTRACT**

A hitherto unknown crystalline form of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride, pharmaceutical compositions containing the new crystalline form, methods of producing the new crystalline form, and a related method of use including treatment of, e.g., pain and/or urinary incontinence.

27 Claims, 8 Drawing Sheets



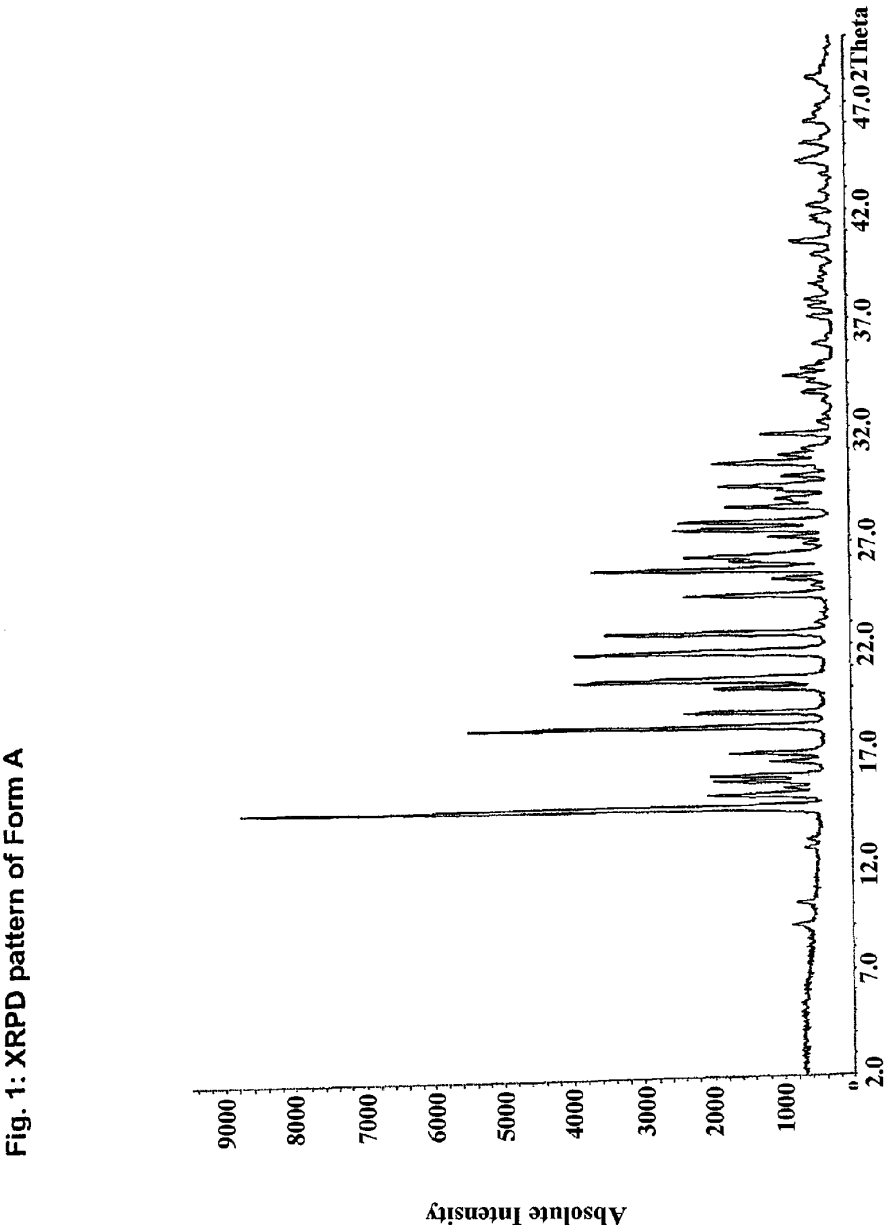


Fig. 1: XRPD pattern of Form A

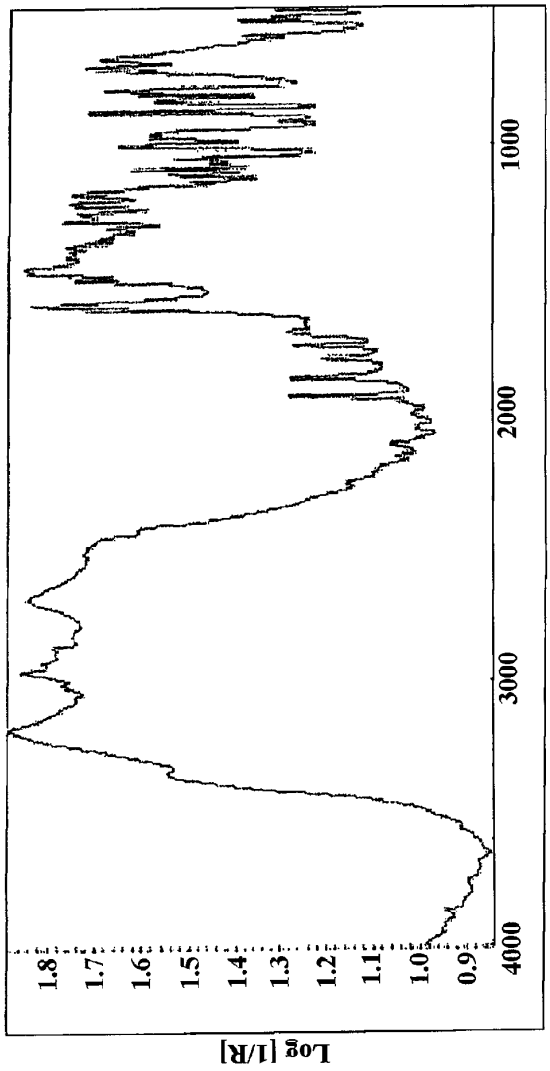


Fig.2: Infrared spectrum of Form A

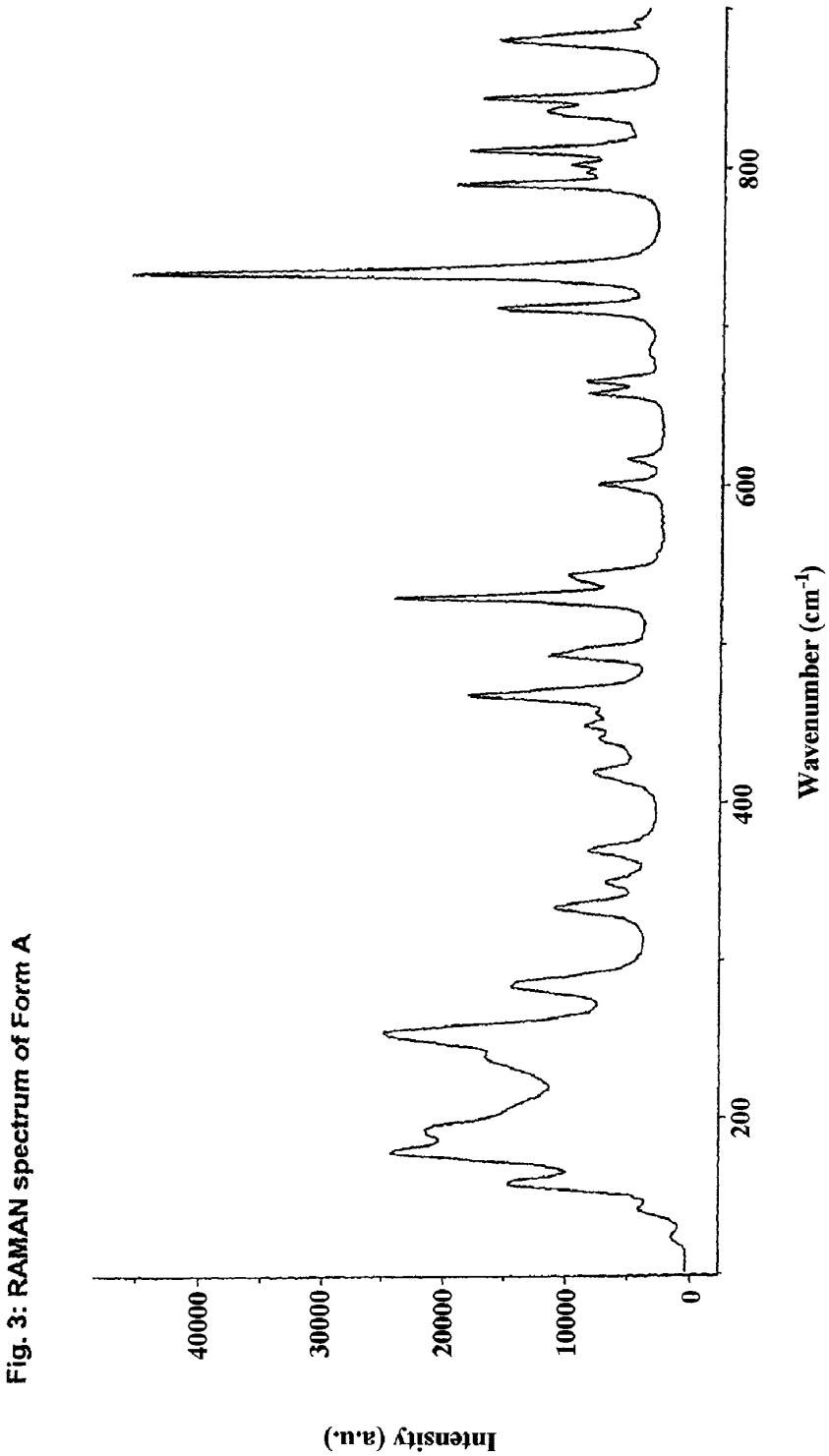


Fig. 3: RAMAN spectrum of Form A

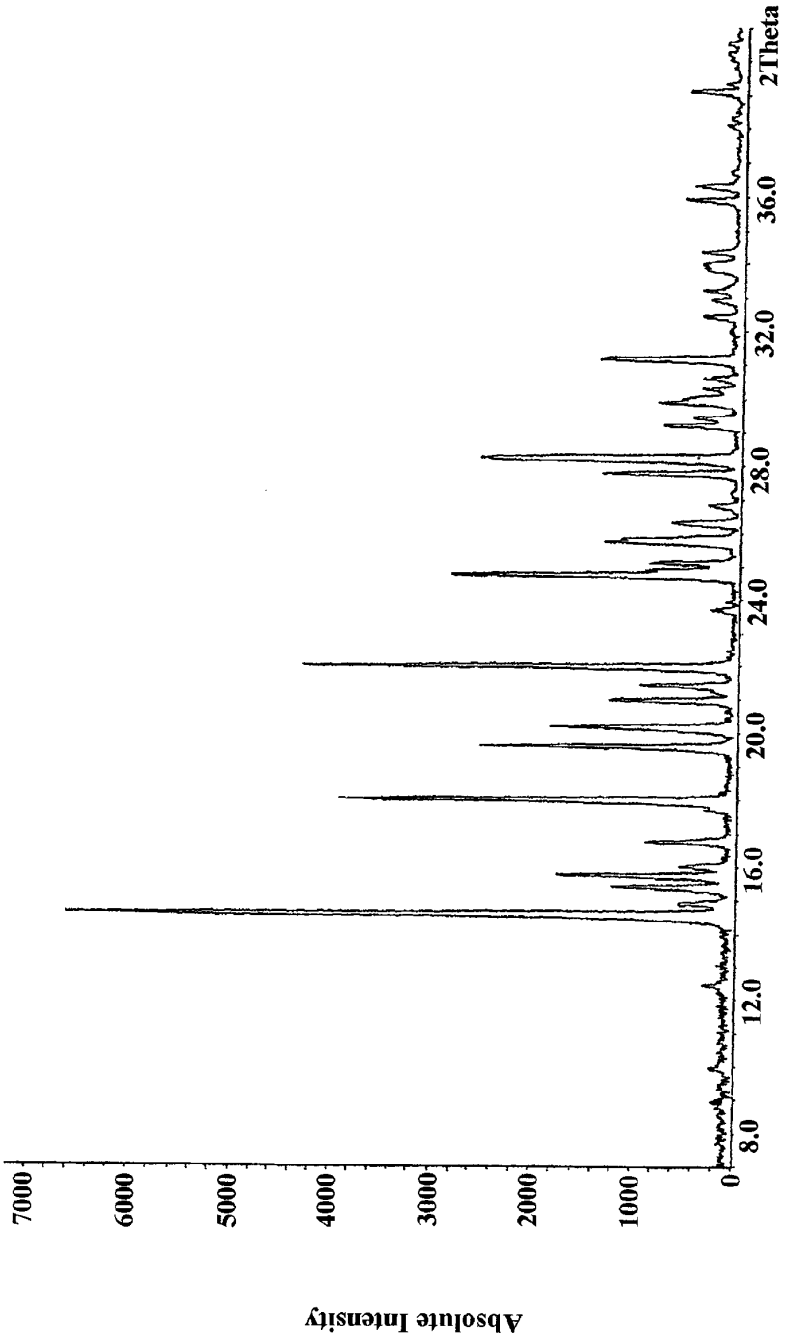


Fig. 4: XRPD pattern of Form B

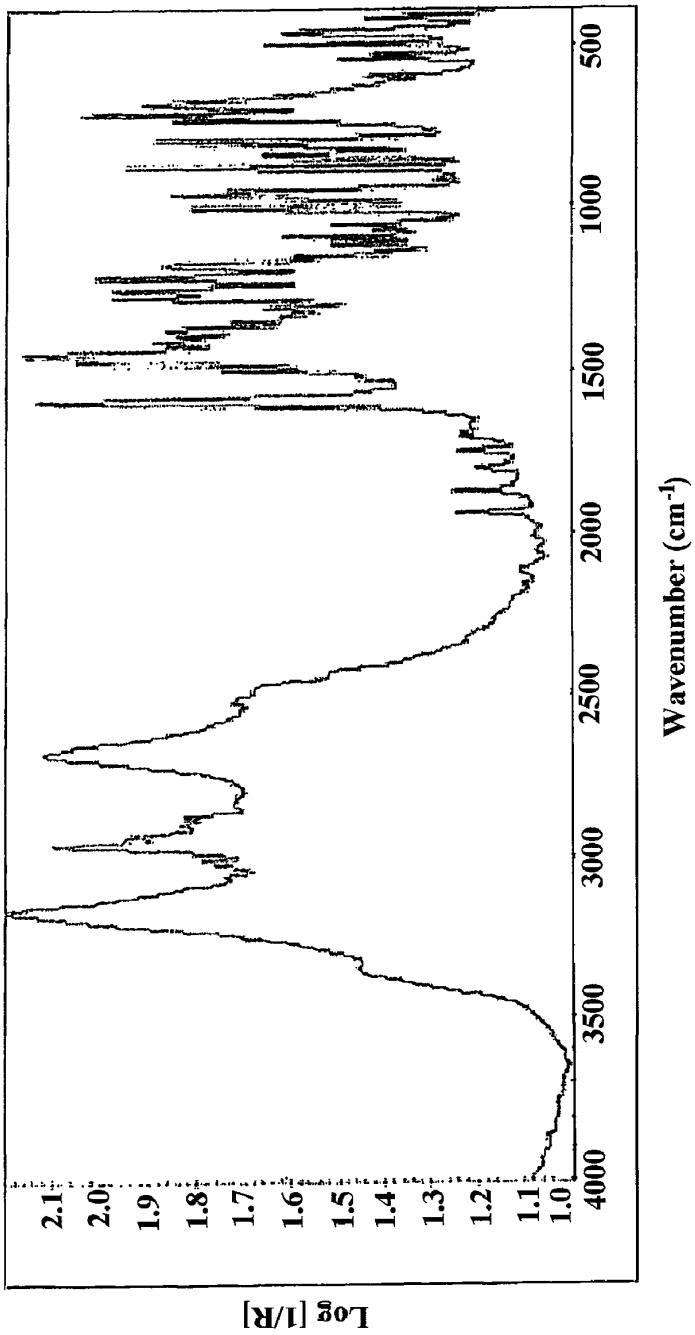


Fig. 5: Infrared spectrum of Form B

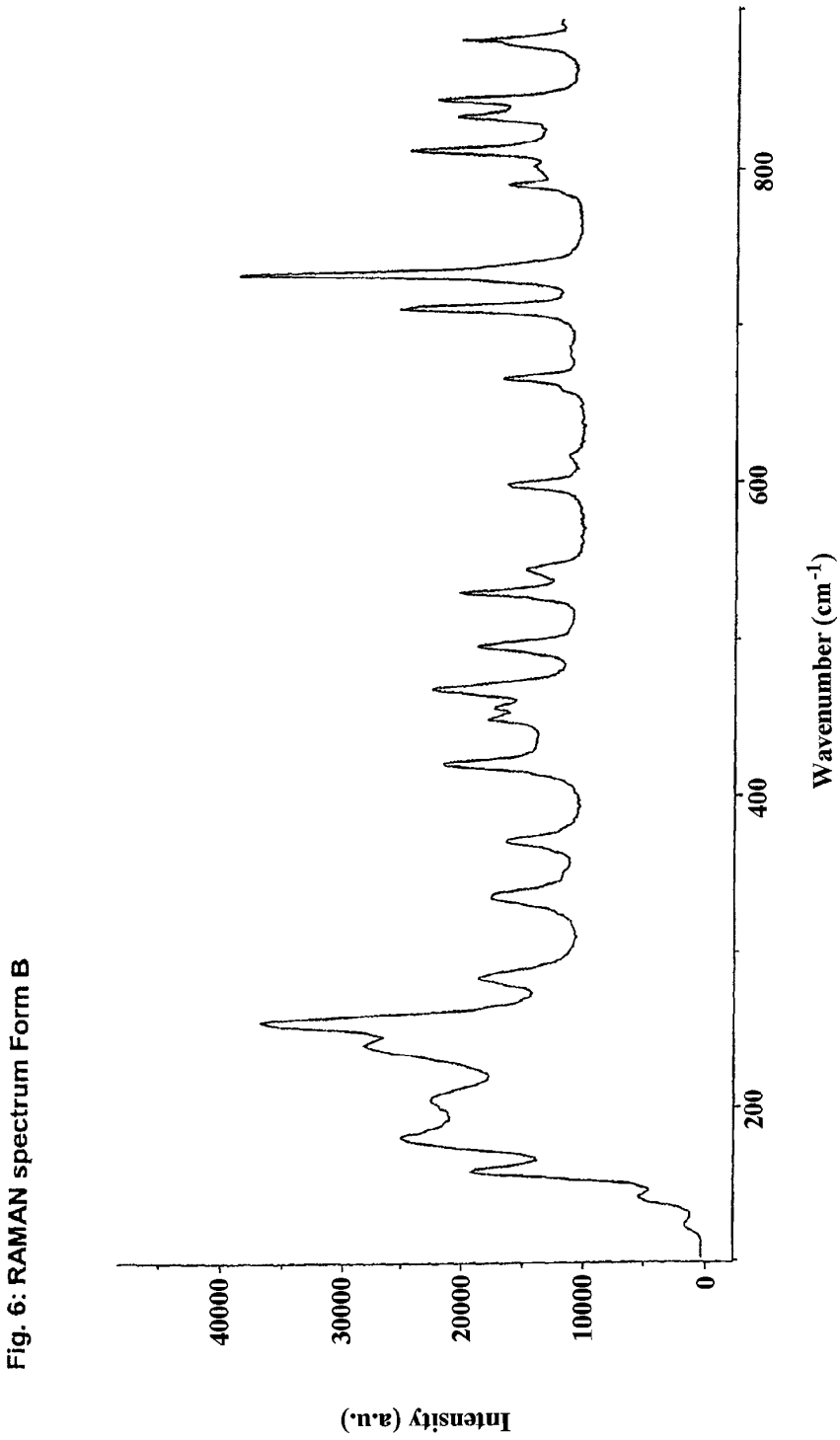


Fig. 6: RAMAN spectrum Form B

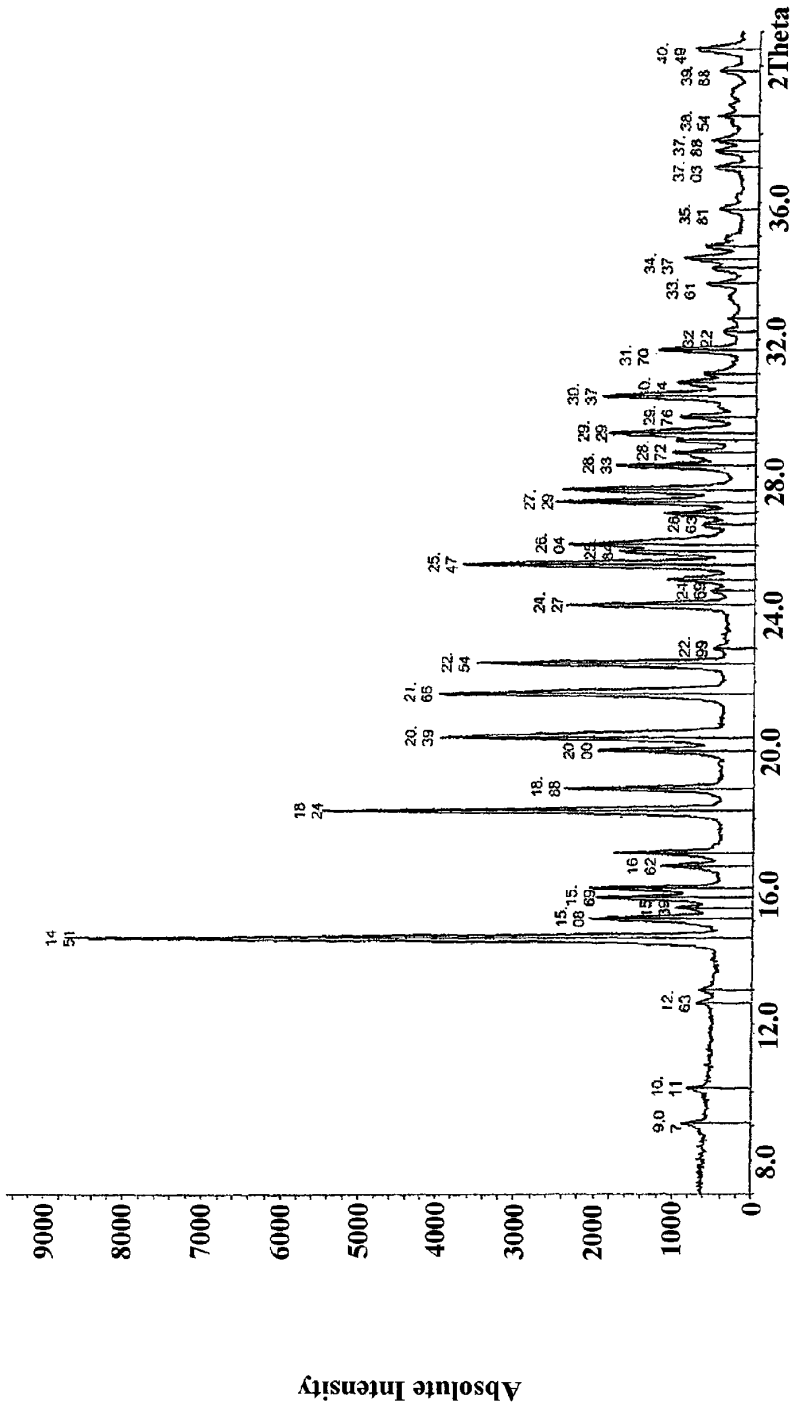


Fig. 7: labelled XRPD pattern of Form A

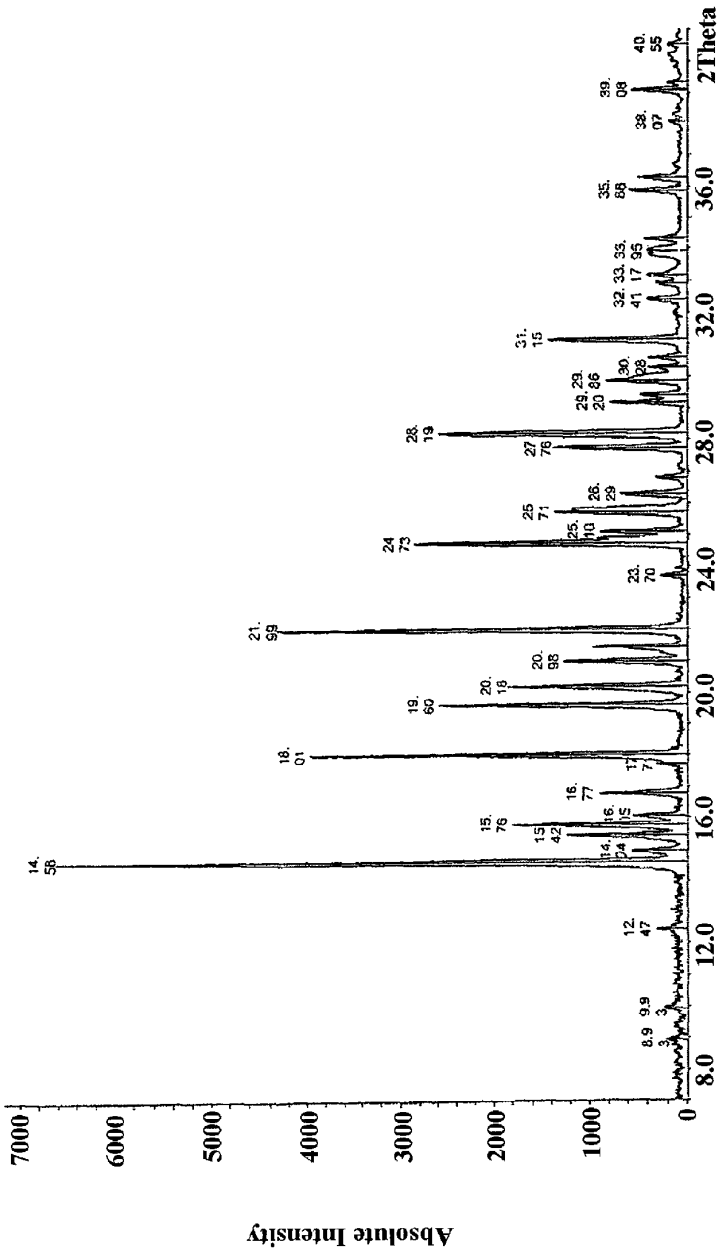


Fig. 8: labelled XRPD pattern of Form B

CRYSTALLINE FORMS OF (−)-(1R,2R)-3-(3-DIMETHYLAMINO-1-ETHYL-2-METHYLPROPYL)-PHENOL HYDROCHLORIDE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of co-pending application Ser. No. 12/274,747, filed Nov. 20, 2008, which in turn was a continuation of application Ser. No. 11/646,232, filed Dec. 28, 2006, now abandoned, which in turn was a continuation of International patent application no. PCT/EP2005/006884, filed Jun. 27, 2005, which claims benefit of European patent application Serial No. 04015091.4 filed Jun. 28, 2004, the entire disclosures of which are hereby incorporated in their entirety.

FIELD OF THE INVENTION

This invention relates to solid crystalline forms of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride compounds, methods of producing these compounds, and related treatments, including use as analgesics as well as pharmaceutical compositions containing these compounds.

BACKGROUND OF THE INVENTION

The treatment of pain conditions is of great importance in medicine. There is currently a world-wide need for additional pain therapy. The pressing requirement for a target-oriented treatment of pain conditions which is right for the patient, which is to be understood as the successful and satisfactory treatment of pain for the patients, is documented in the large number of scientific works which have recently and over the years appeared in the field of applied analgesics or on basic research on nociception.

BRIEF SUMMARY OF THE INVENTION

One object of the present invention is to provide new solid forms of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride useful in the treatment or inhibition of pain.

U.S. Pat. Nos. 6,248,737 and 6,344,558 as well as European Patent EP 693 475 B1 disclose the substance and the synthesis of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride in example 25. As proven by X-ray diffraction the 1R,2R configuration as shown in the drawing of the structure in example 25 is correct although the configuration is reported as (−)-(1R,2S) in U.S. Pat. No. 6,248,737 and (−)-(1S,2S) in U.S. Pat. No. 6,344,558 as well as in EP 693 475 B1.

It has now been surprisingly found that (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride can be produced in a reproducible manner in two different crystalline forms. The present invention provides a new form (Form A) of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride which is different from the form already known (Form B) obtained by the procedure described in example 25 of U.S. Pat. No. 6,248,737 and U.S. Pat. No. 6,344,558 as well as EP 693 475 B1. This new Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride is very stable at ambient conditions and therefore useful for producing a pharmaceutical composition.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows an X-ray diffraction pattern;
FIG. **2** shows an infrared spectrum;
FIG. **3** shows a RAMAN spectrum;
FIG. **4** shows an X-ray diffraction pattern;
FIG. **5** shows an infrared spectrum;
FIG. **6** shows a RAMAN spectrum;
FIG. **7** shows an X-ray diffraction pattern;
FIG. **8** shows an X-ray diffraction pattern

SUMMARY OF THE INVENTION

The new crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride can be identified by X-ray powder diffraction. The X-ray diffraction ("XRPD") pattern is shown in FIG. **1** with the peak listing shown as Table 1.

The most important X-ray lines (2-theta values) in terms of intensity characterizing Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride showing one or a combination of the following in a powder diffraction measurement when measured using Cu K_α radiation at ambient temperature are 14.5±0.2, 18.2±0.2, 20.4±0.2, 21.7±0.2 and 25.5±0.2.

To discriminate crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride from Form B it is more advantageous to look at the unique peaks in the X-ray diffraction diagram, i.e. e.g. the lines with sufficient intensity at 2-theta values, where Form B does not show lines with significant intensity. Such characteristic X-ray lines (2-theta values) for Form A in a powder diffraction pattern when measured using CuK_α radiation at ambient temperature are: 15.1±0.2, 16.0±0.2, 18.9±0.2, 20.4±0.2, 22.5±0.2, 27.3±0.2, 29.3±0.2 and 30.4±0.2.

Another method to identify crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride is IR-spectroscopy. The IR-Spectrum of Form A is shown as FIG. **2** with the peak listing shown in comparison to Form B as Table 2.

In the IR-spectrum it is characteristic for crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride to show a combination of the following IR bands: 3180±4 cm^{-1}, 2970±4 cm^{-1}, 2695±4 cm^{-1}, 2115±4 cm^{-1}, 1698±4 cm^{-1}, 1462±4 cm^{-1}, 1032±4 cm^{-1} and/or 972±4 cm^{-1}.

RAMAN technique can also be used to identify of the crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride. Especially the range between 800 cm^{-1} and 200 cm^{-1}, which is shown in FIG. **3**, is advantageously used also by way of RAMAN microscopy.

Crystal structure analysis of Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride showed monoclinic crystals with the following parameters of the elemental cell (length of side and angle):

a: 7.11 Å
b: 11.62 Å
c: 17.43 Å
β: 95.0°.

The elemental cell of the crystal of crystalline Form A has a volume of 1434±5 $Å^3$ and a calculated density of 1.20±0.01 g/cm^3.

The invention further relates to processes for the preparation of crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride.

The process starts from crystalline Form B of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride prepared according to U.S. Pat. No. 6,248,737 or 6,344,558 or European Patent EP 693 475 B1 incorporated herein by reference.

In one embodiment of the process (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form A is produced by dissolving the (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form B in acetone, acetonitrile or isopropanol, optionally followed by filtering, leaving the solution to crystallize and isolating the crystals of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form A preferably by filtering again.

If acetone or acetonitrile is used it is preferred that during this process the temperature is kept below +40° C., more preferably below +25° C., especially after filtering. It is further preferred that in this process between 5 mg and 1 mg, more preferably between 2.5 mg and 1.4 mg, especially between 2.0 mg and 1.4 mg (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride is dissolved per ml solvent.

The use of isopropanol is preferred, if seed crystals of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form A are available. The isopropanol used preferably contains about 0.5% per volume of water. The dissolution of the (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form B in isopropanol is performed at temperatures above room temperature, preferably above 65° C. but not exceeding 80° C. After complete dissolution the heat is turned of and the seed crystals are added during a first cooling phase. Thereafter the resulting mixture is cooled down to ≦15° C., preferably ≦10° C. and especially ≦5° C.

Optionally it is possible to reduce the solvent by evaporation, preferably in an evaporator under reduced pressure. Preferably the remaining volume of the solution after evaporation should not be less than 20% of the volume at the beginning of the process. Optionally it is also possible to add active carbon to the solution originally prepared.

In a preferred embodiment of the invention the (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form A obtained by the process described above is redesolved in acetone acetonitrile or isopropanol, preferably in the solvent already used in the first step, optionally is filtered to remove any insoluble residue and, optionally after reducing the amount of solvent by evaporation, is left to crystallize.

It is preferred that in the last crystallization step the temperature is maintained at ≦15° C., more preferably ≦10° C. and especially ≦5° C.

In a further embodiment of the process according to the invention (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form A is produced in the solid state by cooling (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form B between 24 h and 168 h to a temperature between −4° C. and −80° C. It is preferred that in this process the cooling temperature is between −10° C. and −60° C., preferably between −15° C. and −50° C., especially between −25° C. and −40° C. and the cooling is carried out for a time between 24 h and 120 h, preferably between 24 h and 72 h, especially between 24 h and 48 h.

This invention further relates to a new Crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride obtainable by dissolving (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form B in acetonitrile together with active carbon, heating the solution to the boiling point, removing the active carbon by filtering, stirring the solution at a temperature below 40° C., removing insoluble residue by filtering and removing part of the solvent leaving (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form A to crystallize, redissolving the crystals so obtained in acetonitrile, removing insoluble residue by filtering and removing part of the solvent leaving (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form A to crystallize.

Crystalline Form A according to the invention has the same pharmacological activity as Form B but is more stable under ambient conditions. It can be advantageously used as active ingredient in pharmaceutical compositions.

Therefore the invention further relates to a pharmaceutical composition containing as active ingredient (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form A according to the invention and at least one suitable additive and/or auxiliary substance.

Such pharmaceutical composition according to the invention contains, in addition to crystalline Form A (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride, one or more suitable additive and/or auxiliary substance such as for example carrier materials, fillers, solvents, diluents, coloring agents and/or binders, and may be administered as liquid medicament preparations in the form of injectable solutions, drops or juices, as semi-solid medicament preparations in the form of granules, tablets, pellets, patches, capsules, plasters or aerosols. The choice of the auxiliary substances, etc., as well as the amounts thereof to be used depend on whether the medicament is to be administered orally, per orally, parenterally, intravenously, intraperitoneally, intradermally, intramuscularly, intranasally, buccally, rectally or topically, for example to the skin, the mucous membranes or the eyes. For oral application suitable preparations are in the form of tablets, sugar-coated pills, capsules, granules, droplets, juices and syrups, while for parenteral, topical and inhalative application suitable forms are solutions, suspensions, readily reconstitutable dry preparations, as well as sprays. Form A in a depot form, in dissolved form or in a plaster, optionally with the addition of agents promoting skin penetration, are suitable percutaneous application preparations. Preparation forms that can be administered orally or percutaneously can provide for the delayed release of crystalline Form A according to the invention. In principle further active constituents known to the person skilled in the art may be added to the medicaments according to the invention.

Preferred formulations for crystalline Form A (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride according to the invention are presented in the PCT-application WO 03/035054 incorporated herein by reference.

The amount of active constituent to be administered to the patient varies depending on the patient's weight, on the type of application, medical indication and severity of the condition. Normally 0.005 to 1000 mg/kg, preferably 0.05 to 5 mg/kg of crystalline Form A according to the invention are administered.

Preferably, the crystalline Form A according to the invention is used for the treatment of pain or the treatment of urinary incontinence. Accordingly the invention also relates to the use of crystalline Form A according to the invention for the treatment of pain or the treatment of urinary incontinence.

Additionally the invention relates to a method of treatment using a sufficient amount of crystalline Form A according to the invention for the treatment of a disease, especially pain or urinary incontinence.

Certain embodiments of the present invention may be further understood by reference to the following specific examples. These examples and the terminology used herein are for the purpose of describing particular embodiments only and are not intended to be limiting.

Example 1

Master Recipe for Preparation of Form A

The master recipe is valid for a 50 ml scale.

Provide 1.9 g (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride prepared according to example 25 of European Patent EP 693 475 B1 in a 50 ml glass round bottom vessel with a 3-blade overhead stirrer with baffles.

Add 25 ml isopropanol and 0.5% (v/v) water

Stir at 800 rpm

Heat to 80° C.

Hold temperature while stirring for 10 minutes

Cool to 65° C.

Add 0.056 g seeds (Mean Sq. Wt. CL=58 μm^2, Median No Wt. CL=22 μm)

Cool to 0° C. over 1 hour

Filter slurry through PTFE filter column (5 μm pore size)

Dry solid material under slight vacuum until constant weight (approx. 24 hours)

Repeat the same procedure with the dry solid material obtained

Example 2

Preparation of Form A (1)

(−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was prepared according to example 25 of European Patent EP 693 475 B1. 32.2 mg of the thus synthesized (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was—by slight heating up to 40° C. and/or agitating on an orbital shaker for 30 min—dissolved in 20 ml acetone. Following that the solution was filtered through a nylon syringe filter having a mesh of 0.20 μm and the solution was left to crystallize by slow evaporation of the solvent. Crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was generated as proven by X-ray powder diffraction and by RAMAN microscopic analysis.

Example 3

Preparation of Form A (2)

(−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was prepared according to example 25 of European Patent EP 693 475 B1. 32.2 mg of the thus synthesized (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was—if necessary by agitating for e.g. 30 min—dissolved in 20 ml acetone. Following that the solution was filtered with a nylon syringe filter having a mesh of 0.20 μm and the solution was left to crystallize by slow evaporation of the solvent. In no step after and including the dissolving the temperature was allowed to rise above +25° C. Crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was generated as proven by X-ray powder diffraction experiment and by RAMAN microscopic analysis.

Example 4

Preparation of Form A (3)

(−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was prepared according to example 25 of European Patent EP 693 475 B1. 350 mg of the thus synthesized (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride were dissolved in 50 ml acetonitrile in a 250 ml flask. The mixture was stirred for 1.5 h on a water bath heated to 37° C.±1° C. Any insoluble residue was removed by filtering. Of the clear solution 35 ml was removed on a rotation evaporator at 70-80 mbar and a temperature of the water bath of 30° C.±1° C. The precipitated solid compound was filtered by vacuum. Crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was generated as proven by X-ray powder diffraction and by RAMAN microscopic analysis.

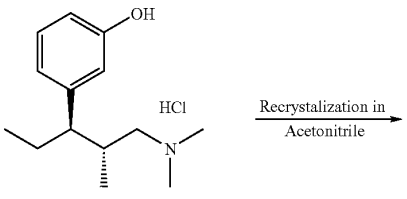
Example 5

Preparation of Form A (4)

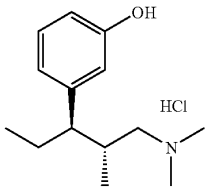
(−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was prepared according to example 25 of European Patent EP 693 475 B1. The thus synthesized (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was stored for 72 h at −40° C. Crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was generated as proven by X-ray powder diffraction and by RAMAN microscopic analysis.

Example 6

Preparation of Form A (5)



$C_{14}H_{24}ClNO$
Mol. Wt.: 257,80



$C_{14}H_{24}ClNO$
Mol. Wt.: 257,80

(−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was prepared according to example 25 of European Patent EP 693 475 B1. 370 mg of the thus synthesized (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride were added to 40 ml acetonitrile and 100 mg active carbon in a 100 ml flask and heated to the boiling point. The active carbon was filtered off from the hot solution by means of a paper filter and the filtrate concentrated to a volume of approx. 10 ml in a rotation evaporator at 150±10 mbar and 50° C. The solution was slowly rotated for 30 minutes at room temperature. Following that the solution was allowed to stand for 30 minutes at room temperature and than for 1 hour at 4° C. The Crystals are filtered by vacuum through a glass filter (276 mg yield).

266 mg of these Crystals were dissolved at room temperature in 45 ml acetonitrile, insoluble residues were removed by filtration and the solution was rotated for 1.5 h at 35-40° C. at atmospheric pressure in a rotation evaporator. Than the solution was concentrated at 50° C. and 150±10 mbar to a volume of approx. 10 ml and then slowly rotated for 30 minutes at room temperature. Following that the flask was allowed to stand for 12 h at 4° C.

The precipitated solid is filtered by vacuum through a glass filter and dried in the air.

Yield:

151 mg (40.8% of the theory in relation to used educt), white microcrystalline solid form

Example 7

Preparation of Form B (1)

(−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was prepared according to example 25 of European Patent EP 693 475 B1. Crystalline Form B of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was generated as proven by X-ray powder diffraction and by RAMAN microscopic analysis.

Example 8

Preparation of Form B (2)

(−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride prepared according to one of the examples 1 to 5 was milled for at least 20 min. Then it was kept at 130° C. in an oven for 80 min. Crystalline Form B of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was generated as proven by X-ray powder diffraction and by RAMAN microscopic analysis.

Example 9

Preparation of Form B (3)

(−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride prepared according to one of the examples 1 to 5 was cryogrinded for at least 15 min. Then it was kept at 125° C. in a TGA for 30 min. Crystalline Form B of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was generated as proven by X-ray powder diffraction and by RAMAN microscopic analysis.

Example 10

X-Ray Powder Diffraction Patterns of Forms A (1) and B (1)

Powder Data Collection was performed with a STOE Stadi P Transmission Powder Diffractometer equipped with a curved germanium monochromator and a linear position sensitive detector. The very carefully ground powders were prepared as flat samples. As source of the beam a copper X-ray tube with monochromatized Cu $K_{\alpha 1}$ (λ=1.54051 Å) radiation generated at 50 kV and 30 mA was used. The 2θ area for the measurement was 5°-40°. The used step width was 0.02 degrees in 2 theta. The data were collected at a temperature of 23±1°.

The X-ray pattern for Form A is shown in FIG. **1**, the X-ray pattern for Form B in FIG. **4**.

The data are shown in Table 1.

TABLE 1

Peak and Relative Intensity Listing (°2θ, peaks with I/I1 value of 10 and over)

Peak No.	A	I/I1	B	I/I1
1	9.07	10	14.58	100
2	10.11	9	14.94	9
3	14.51	100	15.42	19
4	15.08	24	15.76	27
5	15.39	11	16.05	8
6	15.69	22	16.77	14
7	15.96	24	18.01	60
8	16.62	13	19.60	39
9	17.00	20	20.18	27
10	18.24	63	20.98	19
11	18.88	28	21.43	14
12	20.00	23	21.99	65
13	20.39	47	23.71	4
14	21.66	47	24.73	43
15	22.54	41	25.10	14
16	24.27	28	25.71	21
17	25.03	13	26.29	10
18	25.47	43	26.81	5
19	25.84	20	27.76	20
20	26.04	27	28.19	39
21	26.94	13	29.20	12
22	27.29	29	29.86	13
23	27.63	28	30.28	5
24	28.33	20	30.58	6
25	28.72	12	31.15	22
26	29.09	12	32.41	6
27	29.29	21	32.91	5
28	29.76	11	33.17	6
29	30.37	23	34.34	6
30	30.74	11	35.88	9
31	31.70	14	36.29	7
32	34.37	11	39.08	9

Example 11

IR Spectrum of Forms A and B

The mid IR spectra were acquired on a Nicolet model 860 Fourier transform IR spectrophotometer equipped with a globar source, Ge/KBr beamsplitter, and deterated triglycine sulfate (DTGS) detector. A Spectra-Tech, Inc. diffuse reflectance accessory was utilized for sampling. Each spectrum represents 256 co-added scans at a spectral resolution of 4 cm^{-1}. A background data set was then acquired with an alignment mirror in place. A single beam sample data set was then acquired. Subsequently, a Log 1/R (R=Reflectance) spectrum was acquired by rationing the two data sets against each other.

The spectrophotometer was calibrated (wavelength) with polystyrene at the time of use.

The spectrum for Form A is shown in FIG. **2**. The spectrum for Form B is shown in FIG. **5**.

The data are shown in the following Table 2.

TABLE 2

IR Peak Listing

Form A		Form B	
Peak Pos. (cm^{-1})	Intensity (log 1/R)	Peak Pos. (cm^{-1})	Intensity (log 1/R)
3180.4	1.878	3170.2	2.196
2970	1.856	3013.1	1.791
1462.1	1.848	2962.5	2.098
2695.2	1.841	2933.4	1.945
1600.9	1.838	2682	2.116
1281.6	1.771	1940.5	1.242
1378.3	1.763	1870.7	1.246
1219.9	1.754	1801.7	1.201
1181.2	1.748	1749.5	1.236
1503.6	1.743	1598.1	2.138
1256.5	1.734	1503.2	1.755
712.6	1.725	1451.5	2.164
879.8	1.713	1417.2	1.89
684.7	1.692	1396.3	1.843
798.7	1.681	1377.1	1.864
1313.6	1.673	1353.2	1.726
1005.1	1.655	1313.2	1.661
731.2	1.63	1280.7	1.977
1090.9	1.626	1254.8	1.973
810.2	1.622	1217.6	2.015
971.5	1.588	1177.5	1.868
842.6	1.576	1154.6	1.597
831.7	1.574	1136.4	1.431
1111.5	1.55	1111.3	1.512
1049.8	1.534	1090.3	1.625
1136.5	1.498	1065.9	1.425
461.3	1.476	1049.9	1.52
1065.8	1.457	1004.6	1.813
495.1	1.438	958.7	1.855
542.1	1.408	946.6	1.735
595.8	1.384	912.5	1.292
527.9	1.327	877.8	1.951
912.4	1.304	842.7	1.657
1032.4	1.3	831.4	1.664
416.9	1.287	810.7	1.715
1698.3	1.282	795.2	1.892
1940.5	1.279	730.6	1.855
1870.6	1.277	711.7	2.04
1749.4	1.268	683.4	1.917
1801.6	1.208	595.6	1.439
2115.5	1.061	542.1	1.497
		527.7	1.425
		495.1	1.663
		464.4	1.622
		416.7	1.439

Example 12

Single Crystal Structure Analysis of Form A

A colorless crystal of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride prepared according to one of the examples 2 to 6 having approximate dimensions of 0.6×0.60×0.50 mm was mounted on a glass fiber in random orientation. Preliminary examination and data collection were performed with Cu K_α radiation (1.54184 Å) on a Enraf-Nonius CAD4 computer controlled kappa axis diffractometer equipped with a graphite crystal, incident beam monochromator.

Cell constants and an orientation matrix for data collection were obtained from least-squares refinement using the setting angles of 25 reflections in the range 16°<θ<24°, measured by the computer controlled diagonal slit method of centering. The monoclinic cell parameters and calculated volume are:

a=7.110(3), b=11.615(4), c=17.425(6) Å, β=95.00(3), V=1433.5(10) $Å^3$. For Z=4 and formula weight of 257.79 the calculated density is 1.20 $g \cdot cm^{-3}$. The space group was determined to be $P2_1$ (No. 19).

The data were collected at a temperature of −103±5° C. using ω-θ scan technique. The scan rate varied from 4 to 20°/min (in ω). The variable scan rate allows rapid data collection for intense reflections where a fast scan rate is used and assures good counting statistics for weak reflections where a slow scan rate is used. Data were collected to a maximum of 20 of 75.11°. The scan range)(in ° was determined as a function of θ to correct for the separation of the Kα doublet. The scan width was calculated as follows:

$$\theta \text{ scan width} = 0.8 + 0.140 \tan \theta$$

Moving-crystal moving-counter background counts were made by scanning an additional 25% above and below this range. Thus the ratio of peak counting time to background counting time was 2:1. The counter aperture was also adjusted as a function of θ. The horizontal aperture width ranged from 2.4 to 2.5 mm; the vertical aperture was set at 4.0 mm.

The data for Form A as collected in a commonly known ".cif"-document for complete reference of distances within the molecule are shown in Table 3.

TABLE 3

Table 3a.
Crystal data and structure refinement for Form_A.

Identification code	FormA	
Empirical formula	C14H24ClNO	
Formula weight	257.79	
Temperature	170(2) K	
Wavelength	1.54184 Å	
Crystal system	monoclinic	
Space group	P 21	
Unit cell dimensions	a = 7.110(3) Å	alpha = 90 deg.
	b = 11.615(4) Å	beta = 95.00(3) deg.
	c = 17.425(6) Å	gamma = 90 deg.
Volume	1433.5(10) $Å^3$	
Z	4	
Density (calculated)	1.195 Mg/m^3	
Absorption coefficient	2.230 mm^{-1}	
F(000)	560	
Theta range for data collection	4.58 to 75.11 deg.	
Index ranges	0 <= h <= 8, −14 <= k <= 14, −21 <= l <= 21	
Reflections collected	4531	
Independent reflections	4531 [R(int) = 0.0000]	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	4531/1/323	
Goodness-of-fit on F^2	1.035	
Final R indices [I > 2sigma(I)]	R1 = 0.0588, wR2 = 0.1629	
R indices (all data)	R1 = 0.0643, wR2 = 0.1673	
Absolute structure parameter	.027(19)	
Largest diff. peak and hole	0.686 and −0.696 e · $Å^{-3}$	

Table 3b.
Atomic coordinates (×10^4) and equivalent isotropic displacement parameters ($Å^2$ × 10^3) for Form_A. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Cl(1)	2148(1)	3541(1)	9878(1)	29(1)
Cl(2)	7279(1)	2551(1)	5089(1)	28(1)
O(1)	−588(5)	5289(3)	9077(2)	36(1)
N(1)	822(4)	3979(3)	4964(2)	22(1)
O(2)	4799(4)	769(3)	5795(2)	36(1)
N(2)	5722(5)	2083(3)	10053(2)	27(1)
C(1)	2263(6)	3215(4)	4667(2)	33(1)

TABLE 3-continued

C(2)	−85(6)	4736(4)	4336(2)	31(1)
C(3)	1580(5)	4713(3)	5628(2)	22(1)
C(4)	2627(5)	4056(3)	6291(2)	21(1)
C(5)	1401(6)	3130(4)	6613(2)	29(1)
C(6)	3437(5)	4902(3)	6925(2)	22(1)
C(7)	4927(5)	5729(4)	6656(2)	27(1)
C(8)	6603(6)	5138(4)	6351(3)	38(1)
C(9)	1930(5)	5552(3)	7326(2)	21(1)
C(10)	1188(6)	6603(3)	7050(2)	25(1)
C(11)	−137(6)	7175(3)	7448(2)	28(1)
C(12)	−739(6)	6733(4)	8117(2)	28(1)
C(13)	−19(6)	5686(4)	8404(2)	26(1)
C(14)	1313(5)	5102(3)	8001(2)	23(1)
C(20)	7093(7)	2841(5)	10502(3)	41(1)
C(21)	4877(7)	1235(5)	10570(3)	41(1)
C(22)	6542(6)	1458(3)	9408(2)	25(1)
C(23)	7484(5)	2230(3)	8856(2)	22(1)
C(24)	6086(6)	3070(4)	8447(2)	29(1)
C(25)	8541(5)	1512(3)	8274(2)	20(1)
C(26)	10222(6)	857(4)	8681(2)	28(1)
C(27)	11528(6)	374(4)	8118(3)	36(1)
C(28)	7250(5)	740(3)	7756(2)	22(1)
C(29)	6682(5)	−349(3)	7991(2)	24(1)
C(30)	5507(5)	−1019(3)	7501(2)	26(1)
C(31)	4871(6)	−654(3)	6769(2)	26(1)
C(32)	5427(6)	430(4)	6529(2)	26(1)
C(33)	6604(5)	1116(4)	7018(2)	24(1)

Table 3c.
Bond lengths [A] and angles [deg] for Form_A.

O(1)—C(13)	1.355(5)
O(1)—H(1)	.86(11)
N(1)—C(1)	1.482(5)
N(1)—C(3)	1.499(5)
N(1)—C(2)	1.504(5)
N(1)—H(1A)	.9100
O(2)—C(32)	1.374(5)
O(2)—H(2)	.90(9)
N(2)—C(20)	1.485(6)
N(2)—C(21)	1.495(6)
N(2)—C(22)	1.497(5)
N(2)—H(2A)	.9100
C(1)—H(1A)	.9801
C(1)—H(1B)	.9801
C(1)—H(1C)	.9801
C(2)—H(2A)	.9801
C(2)—H(2B)	.9801
C(2)—H(2C)	.9801
C(3)—C(4)	1.524(5)
C(3)—H(3A)	.9800
C(3)—H(3B)	.9800
C(4)—C(5)	1.522(5)
C(4)—C(6)	1.553(5)
C(4)—H(4)	.9800
C(5)—H(5A)	.9801
C(5)—H(5B)	.9801
C(5)—H(5C)	.9801
C(6)—C(9)	1.528(5)
C(6)—C(7)	1.533(6)
C(6)—H(6)	.9800
C(7)—C(8)	1.511(6)
C(7)—H(7A)	.9800
C(7)—H(7B)	.9800
C(8)—H(8A)	.9801
C(8)—H(8B)	.9801
C(8)—H(8C)	.9801
C(9)—C(14)	1.392(5)
C(9)—C(10)	1.398(5)
C(10)—C(11)	1.386(6)
C(10)—H(10)	.9800
C(11)—C(12)	1.376(6)
C(11)—H(11)	.9800
C(12)—C(13)	1.395(6)
C(12)—H(12)	.9800
C(13)—C(14)	1.402(5)
C(14)—H(14)	.9800
C(20)—H(20A)	.9801
C(20)—H(20B)	.9801
C(20)—H(20C)	.9801
C(21)—H(21A)	.9801
C(21)—H(21B)	.9801
C(21)—H(21C)	.9801
C(22)—C(23)	1.513(5)
C(22)—H(22A)	.9800
C(22)—H(22B)	.9800
C(23)—C(24)	1.525(5)
C(23)—C(25)	1.556(5)
C(23)—H(23)	.9800
C(24)—H(24A)	.9801
C(24)—H(24B)	.9801
C(24)—H(24C)	.9801
C(25)—C(28)	1.523(5)
C(25)—C(26)	1.537(5)
C(25)—H(25)	.9800
C(26)—C(27)	1.517(5)
C(26)—H(26A)	.9800
C(26)—H(26B)	.9800
C(27)—H(27A)	.9801
C(27)—H(27B)	.9801
C(27)—H(27C)	.9801
C(28)—C(33)	1.397(5)
C(28)—C(29)	1.400(6)
C(29)—C(30)	1.382(6)
C(29)—H(29)	.9800
C(30)—C(31)	1.381(6)
C(30)—H(30)	.9800
C(31)—C(32)	1.395(6)
C(31)—H(31)	.9800
C(32)—C(33)	1.392(6)
C(33)—H(33)	.9800
C(13)—O(1)—H(1)	116(6)
C(1)—N(1)—C(3)	113.4(3)
C(1)—N(1)—C(2)	111.2(3)
C(3)—N(1)—C(2)	109.4(3)
C(1)—N(1)—H(1A)	107.5
C(3)—N(1)—H(1A)	107.5
C(2)—N(1)—H(1A)	107.5
C(32)—O(2)—H(2)	127(6)
C(20)—N(2)—C(21)	110.7(4)
C(20)—N(2)—C(22)	113.7(3)
C(21)—N(2)—C(22)	109.6(3)
C(20)—N(2)—H(2A)	107.5
C(21)—N(2)—H(2A)	107.5
C(22)—N(2)—H(2A)	107.5
N(1)—C(1)—H(1A)	109.5
N(1)—C(1)—H(1B)	109.5
H(1A)—C(1)—H(1B)	109.5
N(1)—C(1)—H(1C)	109.5
H(1A)—C(1)—H(1C)	109.5
H(1B)—C(1)—H(1C)	109.5
N(1)—C(2)—H(2A)	109.5
N(1)—C(2)—H(2B)	109.5
H(2A)—C(2)—H(2B)	109.5
N(1)—C(2)—H(2C)	109.5
H(2A)—C(2)—H(2C)	109.5
H(2B)—C(2)—H(2C)	109.5
N(1)—C(3)—C(4)	114.8(3)
N(1)—C(3)—H(3A)	108.6
C(4)—C(3)—H(3A)	108.6
N(1)—C(3)—H(3B)	108.6
C(4)—C(3)—H(3B)	108.6
H(3A)—C(3)—H(3B)	107.6
C(5)—C(4)—C(3)	112.1(3)
C(5)—C(4)—C(6)	111.9(3)
C(3)—C(4)—C(6)	110.4(3)
C(5)—C(4)—H(4)	107.4
C(3)—C(4)—H(4)	107.4
C(6)—C(4)—H(4)	107.4
C(4)—C(5)—H(5A)	109.5
C(4)—C(5)—H(5B)	109.5
H(5A)—C(5)—H(5B)	109.5
C(4)—C(5)—H(5C)	109.5
H(5A)—C(5)—H(5C)	109.5
H(5B)—C(5)—H(5C)	109.5
C(9)—C(6)—C(7)	111.2(3)
C(9)—C(6)—C(4)	114.0(3)
C(7)—C(6)—C(4)	113.7(3)
C(9)—C(6)—H(6)	105.7
C(7)—C(6)—H(6)	105.7

TABLE 3-continued

C(4)—C(6)—H(6)	105.7
C(8)—C(7)—C(6)	114.2(4)
C(8)—C(7)—H(7A)	108.7
C(6)—C(7)—H(7A)	108.7
C(8)—C(7)—H(7B)	108.7
C(6)—C(7)—H(7B)	108.7
H(7A)—C(7)—H(7B)	107.6
C(7)—C(8)—H(8A)	109.5
C(7)—C(8)—H(8B)	109.5
H(8A)—C(8)—H(8B)	109.5
C(7)—C(8)—H(8C)	109.5
H(8A)—C(8)—H(8C)	109.5
H(8B)—C(8)—H(8C)	109.5
C(14)—C(9)—C(10)	118.7(3)
C(14)—C(9)—C(6)	119.0(3)
C(10)—C(9)—C(6)	122.2(3)
C(11)—C(10)—C(9)	119.9(4)
C(11)—C(10)—H(10)	120.0
C(9)—C(10)—H(10)	120.0
C(12)—C(11)—C(10)	121.3(4)
C(12)—C(11)—H(11)	119.3
C(10)—C(11)—H(11)	119.3
C(11)—C(12)—C(13)	119.8(4)
C(11)—C(12)—H(12)	120.1
C(13)—C(12)—H(12)	120.1
O(1)—C(13)—C(12)	118.6(4)
O(1)—C(13)—C(14)	122.3(4)
C(12)—C(13)—C(14)	119.0(4)
C(9)—C(14)—C(13)	121.2(3)
C(9)—C(14)—H(14)	119.4
C(13)—C(14)—H(14)	119.4
N(2)—C(20)—H(20A)	109.5
N(2)—C(20)—H(20B)	109.5
H(20A)—C(20)—H(20B)	109.5
N(2)—C(20)—H(20C)	109.5
H(20A)—C(20)—H(20C)	109.5
H(20B)—C(20)—H(20C)	109.5
N(2)—C(21)—H(21A)	109.5
N(2)—C(21)—H(21B)	109.5
H(21A)—C(21)—H(21B)	109.5
N(2)—C(21)—H(21C)	109.5
H(21A)—C(21)—H(21C)	109.5
H(21B)—C(21)—H(21C)	109.5
N(2)—C(22)—C(23)	114.4(3)
N(2)—C(22)—H(22A)	108.7
C(23)—C(22)—H(22A)	108.7
N(2)—C(22)—H(22B)	108.7
C(23)—C(22)—H(22B)	108.7
H(22A)—C(22)—H(22B)	107.6
C(22)—C(23)—C(24)	111.7(3)
C(22)—C(23)—C(25)	111.3(3)
C(24)—C(23)—C(25)	111.8(3)
C(22)—C(23)—H(23)	107.3
C(24)—C(23)—H(23)	107.3
C(25)—C(23)—H(23)	107.3
C(23)—C(24)—H(24A)	109.5
C(23)—C(24)—H(24B)	109.5
H(24A)—C(24)—H(24B)	109.5
C(23)—C(24)—H(24C)	109.5
H(24A)—C(24)—H(24C)	109.5
H(24B)—C(24)—H(24C)	109.5
C(28)—C(25)—C(26)	112.8(3)
C(28)—C(25)—C(23)	113.7(3)
C(26)—C(25)—C(23)	111.4(3)
C(28)—C(25)—H(25)	106.1
C(26)—C(25)—H(25)	106.1
C(23)—C(25)—H(25)	106.1
C(27)—C(26)—C(25)	112.3(3)
C(27)—C(26)—H(26A)	109.1
C(25)—C(26)—H(26A)	109.1
C(27)—C(26)—H(26B)	109.1
C(25)—C(26)—H(26B)	109.1
H(26A)—C(26)—H(26B)	107.9
C(26)—C(27)—H(27A)	109.5
C(26)—C(27)—H(27B)	109.5
H(27A)—C(27)—H(27B)	109.5
C(26)—C(27)—H(27C)	109.5
H(27A)—C(27)—H(27C)	109.5
H(27B)—C(27)—H(27C)	109.5
C(33)—C(28)—C(29)	118.2(4)
C(33)—C(28)—C(25)	119.6(3)
C(29)—C(28)—C(25)	122.2(3)
C(30)—C(29)—C(28)	120.1(4)
C(30)—C(29)—H(29)	120.0
C(28)—C(29)—H(29)	120.0
C(31)—C(30)—C(29)	122.0(4)
C(31)—C(30)—H(30)	119.0
C(29)—C(30)—H(30)	119.0
C(30)—C(31)—C(32)	118.4(4)
C(30)—C(31)—H(31)	120.8
C(32)—C(31)—H(31)	120.8
O(2)—C(32)—C(31)	117.4(4)
O(2)—C(32)—C(33)	122.3(4)
C(31)—C(32)—C(33)	120.3(4)
C(28)—C(33)—C(32)	121.1(4)
C(28)—C(33)—H(33)	119.5
C(32)—C(33)—H(33)	119.5

Symmetry transformations used to generate equivalent atoms:

Table 3d.

Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for Form_A.

	x	y	z	U(eq)
H(1)	−380(15)	4570(10)	9180(5)	110(3)
H(1A)	−96	3523	5133	26
H(2)	5310(14)	1310(9)	5510(5)	100(3)
H(2A)	4770	2536	9841	32
H(1A)	1737	2848	4189	43
H(1B)	2630	2622	5051	43
H(1C)	3374	3671	4564	43
H(2A)	838	5299	4182	41
H(2B)	−1162	5141	4525	41
H(2C)	−523	4261	3891	41
H(3A)	525	5130	5827	29
H(3B)	2438	5287	5439	29
H(4)	3700	3668	6086	27
H(5A)	2110	2747	7048	38
H(5B)	1040	2563	6210	38
H(5C)	262	3484	6788	38
H(6)	4100	4422	7324	28
H(7A)	4328	6227	6252	35
H(7B)	5381	6223	7090	35
H(8A)	7580	5710	6270	49
H(8B)	6204	4761	5860	49
H(8C)	7111	4561	6723	49
H(10)	1604	6936	6577	32
H(11)	−656	7908	7248	36
H(12)	−1670	7153	8392	36
H(14)	1819	4364	8198	30
H(20A)	6484	3193	10927	54
H(20B)	7521	3445	10166	54
H(20C)	8179	2384	10710	54
H(21A)	4403	1642	11006	53
H(21B)	5842	677	10760	53
H(21C)	3833	830	10281	53
H(22A)	5532	1026	9118	32
H(22B)	7472	900	9629	32
H(23)	8433	2688	9162	29
H(24A)	5114	2639	8133	38
H(24B)	6755	3580	8115	38
H(24C)	5491	3530	8830	38
H(25)	9081	2070	7933	26
H(26A)	10938	1379	9040	37
H(26B)	9748	224	8982	37
H(27A)	10856	−210	7794	46
H(27B)	12632	24	8403	46
H(27C)	11941	997	7792	46
H(29)	7118	−637	8505	31
H(30)	5114	−1776	7677	34
H(31)	4048	−1144	6428	34
H(33)	6986	1876	6842	31

TABLE 3-continued

Table 3e.
Anisotropic displacement parameters ($Å^2 \times 10^3$) for Form_A.
The anisotropic displacement factor exponent takes the form:
$-2\ pi^2\ [h^2\ a^{*2}\ U11 + \ldots + 2\ h\ k\ a^*\ b^*\ U12]$

	U11	U22	U33	U23	U13	U12
Cl(1)	23(1)	27(1)	36(1)	−3(1)	−1(1)	4(1)
Cl(2)	23(1)	25(1)	35(1)	−2(1)	−2(1)	−5(1)
O(1)	35(2)	41(2)	33(2)	7(1)	8(1)	13(1)
N(1)	19(2)	28(2)	18(1)	1(1)	−4(1)	−5(1)
O(2)	33(2)	52(2)	21(1)	5(1)	−11(1)	−12(2)
N(2)	22(2)	31(2)	27(2)	2(1)	2(1)	8(1)
C(1)	29(2)	44(2)	26(2)	−6(2)	1(2)	6(2)
C(2)	25(2)	41(2)	26(2)	11(2)	−8(2)	−4(2)
C(3)	20(2)	20(2)	26(2)	2(1)	−4(1)	−4(1)
C(4)	19(2)	23(2)	20(2)	−1(1)	−2(1)	3(1)
C(5)	33(2)	25(2)	28(2)	2(2)	−3(2)	−4(2)
C(6)	17(2)	26(2)	20(2)	−2(1)	−6(1)	6(1)
C(7)	18(2)	30(2)	32(2)	−10(2)	−6(1)	0(2)
C(8)	20(2)	40(2)	54(3)	−11(2)	5(2)	−3(2)
C(9)	18(2)	26(2)	19(2)	−6(1)	−7(1)	1(1)
C(10)	23(2)	24(2)	26(2)	0(2)	−4(1)	1(1)
C(11)	23(2)	28(2)	32(2)	0(2)	−9(2)	5(2)
C(12)	20(2)	31(2)	32(2)	−5(2)	−1(2)	5(2)
C(13)	22(2)	33(2)	24(2)	0(2)	−2(1)	3(2)
C(14)	20(2)	24(2)	25(2)	0(2)	−5(1)	5(1)
C(20)	40(3)	51(3)	32(2)	−12(2)	−3(2)	−1(2)
C(21)	39(3)	49(3)	37(2)	10(2)	16(2)	10(2)
C(22)	27(2)	23(2)	25(2)	−1(2)	2(2)	2(2)
C(23)	21(2)	22(2)	22(2)	−2(1)	−3(1)	2(1)
C(24)	32(2)	27(2)	27(2)	2(2)	−1(2)	8(2)
C(25)	15(2)	24(2)	20(2)	1(1)	−3(1)	1(1)
C(26)	21(2)	33(2)	30(2)	−2(2)	−4(2)	6(2)
C(27)	25(2)	39(2)	43(2)	1(2)	4(2)	7(2)
C(28)	18(2)	27(2)	21(2)	−1(2)	1(1)	5(1)
C(29)	22(2)	25(2)	25(2)	−1(2)	1(1)	3(1)
C(30)	24(2)	22(2)	33(2)	−4(2)	6(2)	−1(2)
C(31)	19(2)	31(2)	28(2)	−10(2)	1(1)	−2(2)
C(32)	21(2)	35(2)	21(2)	−2(2)	2(1)	−2(2)
C(33)	17(2)	30(2)	25(2)	1(2)	1(1)	−4(1)

Example 13

Single Crystal Structure Analysis of Form B

A colorless chunk of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride prepared according to one of the examples 7 to 9 having approximate dimensions of 0.44×0.40×0.35 mm was mounted on a glass fiber in random orientation. Preliminary examination and data collection were performed with Mo K_α radiation (λ=0.71073 Å) on a Nonius KappaCCD diffractometer.

Cell constants and an orientation matrix for data collection were obtained from least-squares refinement using the setting angles of 6172 reflections in the range 5<θ<27°. The orthorhombic cell parameters and calculated volume are: a=7.0882(3), b=11.8444(6), c=17.6708(11) Å, V=1483.6(2) $Å^3$. For Z=4 and formula weight of 257.79 the calculated density is 1.15 $g \cdot cm^{-3}$. The refined mosaicity from DENZO/SCALEPACK was 0.68° (<1 mod, <2 poor) indicating moderate crystal quality. The space group was determined by the program ABSEN. From the systematic presence of:

h00 h=2n

0k0 k=2n

00l l=2n

and from subsequent least-squares refinement, the space group was determined to be $P2_12_12_1$ (number 19).

The data were collected to a maximum 2θ value of 55.0°, at a temperature of 343±1 K.

The data from examples 12 and 13 are compared in Table 3f:

TABLE 3f

	Form A (monoklin)	Form B (orthorhombic)
Formula	C14 H24 Cl N O	C14 H24 Cl N O
M.W./g/mol	257.79	257.79
Space group	No. 4, $P2_1$	No. 19, $P2_12_12_1$
Z (No. of Units)	4	4
a/Å	7.110(3)	7.0882(3)
b/Å	11.615(4)	11.8444(6)
c/Å	17.425(6)	17.6708(11)
α/°	90	90
β/°	95.00(3)	90
γ/°	90	90
Volume of elementary cell/$Å^3$	1434	1484
Density (calc.)/g/cm^3	1.20	1.15

The data for Form B as collected in a commonly known ".cif"-document for complete reference of distances within the molecule are shown below Table 4:

TABLE 4

Table 4a.
Crystal data and structure refinement for Form_B.

Identification code	FormB	
Empirical formula	C14H2H22ClNO	
Formula weight	257.79	
Temperature	343 K	
Wavelength	.71073 Å	
Crystal system	orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.0882(3) Å	alpha = 90 deg.
	b = 11.8444(6) Å	beta = 90 deg.
	c = 17.6708(11) Å	gamma = 90 deg.
Volume	1483.56(13) $Å^3$	
Z	4	
Density (calculated)	1.154 Mg/m^3	
Absorption coefficient	0.244 mm^{-1}	
F(000)	560	
Theta range for data collection	5.04 to 27.49 deg.	
Index ranges	−9 <= h <= 9, −15 <= k <= 15, −22 <= l <= 22	
Reflections collected	3207	
Independent reflections	3207 [R(int) = 0.0000]	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	3207/0/167	
Quality-of-fit on F^2	1.012	
Final R indices [I > 2sigma(I)]	R1 = 0.0440, wR2 = 0.1137	
R indices (all data)	R1 = 0.0598, wR2 = 0.1246	
Absolute structure parameter	−.03(8)	
Extinction coefficient	.033(7)	
Largest diff. peak and hole	0.265 and −0.202 e · $Å^{-3}$	

Table 4b.
Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for Form_B. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Cl	7978(1)	−1959(1)	7646(1)	74(1)
O(33)	4870(3)	85(2)	3443(1)	94(1)
N(6)	5522(3)	1571(2)	7545(1)	64(1)
C(1)	11558(4)	−160(3)	5596(2)	98(1)
C(2)	10168(3)	333(2)	6149(2)	75(1)
C(3)	8514(3)	925(2)	5758(1)	58(1)
C(4)	7395(3)	1654(2)	6327(1)	58(1)
C(5)	6394(3)	922(2)	6909(1)	64(1)
C(6)	4611(5)	782(3)	8089(2)	96(1)
C(7)	6834(5)	2342(3)	7943(2)	95(1)
C(31)	7273(3)	131(2)	5286(1)	57(1)
C(32)	6643(3)	472(2)	4583(1)	61(1)
C(33)	5509(3)	−219(2)	4138(1)	68(1)

TABLE 4-continued

C(34)	5050(3)	−1291(2)	4395(2)	74(1)
C(35)	5679(4)	−1637(2)	5098(2)	75(1)
C(36)	6782(3)	−946(2)	5542(1)	66(1)
C(41)	6029(4)	2461(2)	5931(2)	80(1)

Table 4c.
Bond lengths [A] and angles [deg] for Form_B.

O(33)—H(33)	.76(3)
O(33)—C(33)	1.358(3)
N(6)—H(6)	.82(2)
N(6)—C(7)	1.481(4)
N(6)—C(6)	1.488(3)
N(6)—C(5)	1.496(3)
C(1)—C(2)	1.505(4)
C(2)—C(3)	1.531(3)
C(3)—C(31)	1.534(3)
C(3)—C(4)	1.546(3)
C(4)—C(5)	1.520(3)
C(4)—C(41)	1.530(3)
C(31)—C(32)	1.381(3)
C(31)—C(36)	1.396(3)
C(32)—C(33)	1.391(3)
C(33)—C(34)	1.387(4)
C(34)—C(35)	1.382(4)
C(35)—C(36)	1.377(4)
H(33)—O(33)—C(33)	118(3)
H(6)—N(6)—C(7)	104.9(15)
H(6)—N(6)—C(6)	108.8(16)
C(7)—N(6)—C(6)	110.7(2)
H(6)—N(6)—C(5)	107.8(16)
C(7)—N(6)—C(5)	114.5(2)
C(6)—N(6)—C(5)	110.0(2)
C(1)—C(2)—C(3)	112.7(3)
C(2)—C(3)—C(31)	113.8(2)
C(2)—C(3)—C(4)	110.8(2)
C(31)—C(3)—C(4)	113.71(16)
C(5)—C(4)—C(41)	111.75(18)
C(5)—C(4)—C(3)	111.13(17)
C(41)—C(4)—C(3)	112.08(19)
N(6)—C(5)—C(4)	114.03(18)
C(32)—C(31)—C(36)	118.5(2)
C(32)—C(31)—C(3)	119.66(19)
C(36)—C(31)—C(3)	121.8(2)
C(31)—C(32)—C(33)	121.6(2)
O(33)—C(33)—C(34)	117.5(2)
O(33)—C(33)—C(32)	123.2(2)
C(34)—C(33)—C(32)	119.3(2)
C(35)—C(34)—C(33)	119.3(2)
C(36)—C(35)—C(34)	121.2(2)
C(35)—C(36)—C(31)	120.0(2)

Symmetry transformations used to generate equivalent atoms:

Table 4d.
Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for Form_B.

	x	y	z	U(eq)
H(33)	5160(4)	660(2)	3290(2)	80(10)
H(6)	4710(3)	1983(17)	7365(13)	54(6)
H(1A)	10962	−753	5313	148
H(1B)	12620	−460	5867	148
H(1C)	11980	419	5256	148
H(2A)	10815	871	6472	90
H(2B)	9682	−266	6469	90
H(3)	9079	1455	5398	70
H(4)	8312	2119	6602	70
H(5A)	5415	492	6655	76
H(5B)	7293	388	7117	76
H(6A)	3594	393	7842	144
H(6B)	4128	1200	8512	144
H(6C)	5524	243	8264	144
H(7A)	7907	1923	8120	143
H(7B)	6200	2680	8366	143
H(7C)	7246	2922	7601	143
H(32)	6984	1181	4403	74
H(34)	4325	−1772	4097	88
H(35)	5352	−2351	5274	90
H(36)	7200	−1195	6012	79

TABLE 4-continued

H(41A)	5030	2036	5700	120
H(41B)	6693	2879	5549	120
H(41C)	5506	2975	6295	120

Table 4e.
Anisotropic displacement parameters ($Å^2 \times 10^3$) for Form_B.
The anisotropic displacement factor exponent takes the form:
$-2\ pi^2\ [h^2\ a^{*2}\ U11 + \ldots + 2\ h\ k\ a^*\ b^*\ U12]$

	U11	U22	U33	U23	U13	U12
Cl	71(1)	66(1)	86(1)	5(1)	−1(1)	−13(1)
O(33)	102(1)	107(2)	74(1)	12(1)	−17(1)	−43(1)
N(6)	63(1)	68(1)	59(1)	6(1)	3(1)	15(1)
C(1)	68(1)	106(2)	122(3)	−12(2)	14(2)	17(2)
C(2)	52(1)	86(2)	85(2)	−1(1)	−1(1)	12(1)
C(3)	52(1)	64(1)	60(1)	5(1)	4(1)	−2(1)
C(4)	62(1)	54(1)	59(1)	4(1)	−1(1)	1(1)
C(5)	68(1)	58(1)	65(1)	5(1)	9(1)	9(1)
C(6)	102(2)	100(2)	87(2)	23(2)	33(2)	14(2)
C(7)	95(2)	118(2)	73(2)	−21(2)	−12(2)	0(2)
C(31)	53(1)	58(1)	59(1)	2(1)	12(1)	4(1)
C(32)	60(1)	63(1)	61(1)	0(1)	8(1)	−8(1)
C(33)	64(1)	81(2)	58(1)	−3(1)	7(1)	−14(1)
C(34)	69(1)	71(1)	81(2)	−11(1)	15(1)	−16(1)
C(35)	87(2)	58(1)	80(2)	1(1)	24(1)	−3(1)
C(36)	72(1)	58(1)	67(1)	4(1)	13(1)	6(1)
C(41)	96(2)	71(1)	73(2)	14(1)	5(1)	24(1)

Example 14

RAMAN Spectrum of Forms A and B

Form A and B were investigated using RAMAN spectroscopy. The RAMAN spectrometer used was a Bruker Raman FT 100. The RAMAN Microscope was a Renishaw 1000 System, 20× Obj. Long working distance, diode laser 785 nm. Raman spectroscopy was able to distinguish clearly between Forms A and B. Differences between the spectra of the two forms appear in the whole spectral range (3200-50 cm^{-1}), but the difference in the range between 800-200 cm-1 were most significant.

The results for Form A are shown in FIG. **3**, the results for Form B in FIG. **6**.

Furthermore the samples were investigated by RAMAN microscopy. The spectra of both forms were also distinguishable. Here, spectra were taken in the wavenumber range of 2000-100 cm^{-1}.

Example 16

Variable Temperature X-Ray Powder Diffraction Experiment

A variable temperature X-ray powder diffraction experiment was run thereby producing Form B from Form A. Form A converted to Form B from 40-50° C. during the experiment. The result is reversible with Form B changing over into Form A at lower temperature.

The foregoing description and examples have been set forth merely to illustrate the invention and are not intended to be limiting. Since modifications of the described embodiments incorporating the spirit and substance of the invention may occur to persons skilled in the art, the invention should be construed broadly to include all variations within the scope of the appended claims and equivalents thereof.

The invention claimed is:

1. A crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride

exhibiting at least X-ray lines (2-theta values) in a powder diffraction pattern when measured using Cu K_α radiation at 15.1±0.2, 16.0±0.2, 18.9±0.2, 20.4±0.2, 22.5±0.2, 27.3±0.2, 29.3±0.2 and 30.4±0.2.

2. The crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride according to claim **1** exhibiting at least X-ray lines (2-theta values) in a powder diffraction when measured using Cu K_α radiation at 14.5±0.2, 18.2±0.2, 20.4±0.2, 21.7±0.2 and 25.5±0.2.

3. The crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride according to claim **1** exhibiting an X-ray pattern (2-theta values) in a powder diffraction when measured using Cu K_α radiation essentially the same as that provided in FIG. **1**.

4. The crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride according to claim **1** wherein the crystal has a monoclinic form.

5. A process for producing a (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form A, said process comprising:

dissolving a (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form B in acetone, acetonitrile or isopropanol to form a solution:

leaving the solution to crystallize and

isolating crystals of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form A;

wherein during the process the temperature is kept below +40° C.

6. The process for producing a (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form A according to claim **5** wherein during the process the temperature is kept below +25° C.

7. The process of claim **5** wherein said (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form B is dissolved in acetonitrile, and further comprising the steps of:

stirring the solution;

removing insoluble residue by filtering and

evaporating the acetonitrile leaving (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form A to crystallize.

8. The process according to claim **5** wherein said (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form B is dissolved in isopropanol at temperatures above room temperature, and after complete dissolution no further heat is provided and further comprising:

adding seed crystals of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form A and then cooling the mixture down to ≦15° C.

9. The process of claim **8**, wherein said (−)-(1R,2R)-3-(3-dimethyl-amino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form B is dissolved in isopropanol at a temperature above 65° C. but not exceeding 80° C.

10. The process of claim **8**, wherein said mixture is cooled down to ≦10° C.

11. The process of claim **8**, wherein said mixture is cooled down to ≦5° C.

12. The process according to claim **5** further comprising redissolving the (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form A in a solvent selected from acetone, acetonitrile and isopropanol, then optionally filtering the solution to remove any insoluble residue and optionally reducing the amount of solvent by evaporation, then allowing the solution to crystallize.

13. The process of claim **12**, wherein said solvent is the same as that used to form the (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form A before the step of redissovling.

14. The process of claim **12**, wherein during the step of allowing the solution to crystallize, the temperature is maintained at ≦15° C.

15. The process of claim **12**, wherein during the step of allowing the solution to crystallize, the temperature is maintained at ≦10° C.

16. The process of claim **12**, wherein during the step of allowing the solution to crystallize, the temperature is maintained at ≦5° C.

17. A process for producing crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride comprising the step of cooling (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-hydrochloride phenol of Form B for a time between 24 hours and 168 hours at a temperature of between −4° C. and −80° C.

18. The process of claim **17** wherein the cooling temperature is between −10° C. and −60° C.

19. The process of claim **17**, wherein the cooling temperature is between −15° C. and −50° C.

20. The process of claim **17**, wherein the cooling temperature is between −25° C. and −40° C.

21. The process of claim **17**, wherein the cooling is carried out for a time between 24 hours and 120 hours.

22. The process of claim **17**, wherein the cooling is carried out for a time between 24 hours and 72 hours.

23. The process of claim **17**, wherein the cooling is carried out for a time between 24 hours and 48 hours.

24. A crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride according to claim **1**, produced by the process of:

dissolving (−) (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form B in acetonitrile together with active carbon,

heating the solution to the boiling point,

removing the active carbon by filtering,

stirring the solution at a temperature below 40° C.,

removing insoluble residue by filtering and removing part of the solvent,

leaving (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form A to crystallize,

redissolving the resulting crystals in acetonitrile,

removing insoluble residue by filtering and removing part of the solvent, and

leaving (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form A to crystallize.

25. A solid pharmaceutical composition comprising, as an active ingredient, a crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride exhibiting at least X-ray lines (2-theta values) in a powder diffraction pattern when measured using Cu K_α radiation at 15.1±0.2, 16.0±0.2, 18.9±0.2, 20.4±0.2, 22.5±0.2, 27.3±0.2, 29.3±0.2 and 30.4±0.2, and at least one suitable additive or auxiliary substance.

26. A solid pharmaceutical composition comprising, as an active ingredient, a crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride according to claim **25**, produced by the process of:

dissolving (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form B in acetonitrile together with active carbon,

heating the solution to the boiling point,

removing the active carbon by filtering,

stirring the solution at a temperature below 40° C.,

removing insoluble residue by filtering and removing part of the solvent,

leaving (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form A to crystallize, and

redissolving the resulting crystals in acetonitrile,

removing insoluble residue by filtering and removing part of the solvent, and

leaving (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form A to crystallize, and

at least one suitable additive or auxiliary substance.

27. A method of treating or inhibiting pain or urinary incontinence, said method comprising the step of administering a pharmaceutically effective amount of a crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride exhibiting at least X-ray lines (2-theta values) in a powder diffraction pattern when measured using Cu K_α radiation at 15.1±0.2, 16.0±0.2, 18.9±0.2, 20.4±0.2, 22.5±0.2, 27.3±0.2, 29.3±0.2 and 30.4±0.2 to a subject in need thereof.

* * * * *

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(54) **ABUSE-PROOFED DOSAGE FORM**

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(57) **ABSTRACT**

An abuse-proofed, thermoformed dosage form containing, in addition to one or more active ingredients with abuse potential optionally together with physiologically acceptable auxiliary substances, at least one synthetic or natural polymer with a breaking strength of at least 500 N and to a process for the production thereof.

34 Claims, No Drawings

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ABUSE-PROOFED DOSAGE FORM

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a division of U.S. patent application Ser. No. 10/718,112, filed Nov. 20, 2003, now U.S. Pat. No. 8,114,383, which claims priority of German Patent Application No. 103 36 400.5, filed Aug. 6, 2003, the entire contents of both of which applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to an abuse-proofed, thermoformed dosage form containing, in addition to one or more active ingredients with abuse potential (A) optionally together with physiologically acceptable auxiliary substances (B), at least one synthetic or natural polymer (C) and optionally at least one wax (D), wherein component (C) exhibits a breaking strength of at least 500 N, and to a process for the production of the dosage form according to the invention.

2. Description of Related Art

Many pharmaceutical active ingredients, in addition to having excellent activity in their appropriate application, also have abuse potential, i.e. they can be used by an abuser to bring about effects other than those intended. Opiates, for example, which are highly active in combating severe to very severe pain, are frequently used by abusers to induce a state of narcosis or euphoria.

In order to make abuse possible, the corresponding dosage forms, such as tablets or capsules are comminuted, for example ground in a mortar, by the abuser, the active ingredient is extracted from the resultant powder using a preferably aqueous liquid and the resultant solution, optionally after being filtered through cotton wool or cellulose wadding, is administered parenterally, in particular intravenously. An additional phenomenon of this kind of administration, in comparison with abusive oral administration, is a further accelerated increase in active ingredient levels giving the abuser the desired effect, namely the "kick" or "rush". This kick is also obtained if the powdered dosage form is administered nasally, i.e. is sniffed. Since controlled-release dosage forms containing active ingredients with abuse potential do not give rise to the kick desired by the abuser when taken orally even in abusively high quantities, such dosage forms are also comminuted and extracted in order to be abused.

U.S. Pat. No. 4,070,494 proposed adding a swellable agent to the dosage form in order to prevent abuse. When water is added to extract the active ingredient, this agent swells and ensures that the filtrate separated from the gel contains only a small quantity of active ingredient.

The multilayer tablet disclosed in WO 95/20947 is based on a similar approach to preventing parenteral abuse, said tablet containing the active ingredient with abuse potential and at least one gel former, each in different layers.

WO 03/015531 A2 discloses another approach to preventing parenteral abuse. A dosage form containing an analgesic opioid and a dye as an aversive agent is described therein. The colour released by tampering with the dosage form is intended to discourage the abuser from using the dosage form which has been tampered with.

Another known option for complicating abuse involves adding antagonists to the active ingredients to the dosage form, for example naloxone or naltexone in the case of opiates, or compounds which cause a physiological defence response, such as for example Radix ipecacuanha=ipecac root.

However, since in most cases of abuse it is still necessary to pulverise the dosage form comprising an active ingredient suitable for abuse, it was the object of the present invention to complicate or prevent the pulverisation preceding abuse of the dosage form comprising the agents conventionally available for potential abuse and accordingly to provide a dosage form for active ingredients with abuse potential which ensures the desired therapeutic effect when correctly administered, but from which the active ingredients cannot be converted into a form suitable for abuse simply by pulverisation.

SUMMARY OF THE INVENTION

Said object has been achieved by the provision of the abuse-proofed, thermoformed dosage form according to the invention which contains, in addition to one or more active ingredients with abuse potential (A), at least one synthetic or natural polymer (C) and optionally at least one wax (D), wherein component (C) exhibits a breaking strength of at least 500 N.

DETAILED DESCRIPTION OF THE INVENTION

The use of polymers having the stated minimum breaking strength, preferably in quantities such that the dosage form also exhibits such a minimum breaking strength, means that pulverisation of the dosage form is considerably more difficult using conventional means, so considerably complicating or preventing the subsequent abuse.

If comminution is inadequate, parenteral, in particular intravenous, administration cannot be performed safely or extraction of the active ingredient therefrom takes too long for the abuser or there is no "kick" when taken orally, as release is not spontaneous.

According to the invention, comminution is taken to mean pulverisation of the dosage form with conventional means which are available to an abuser, such as for example a mortar and pestle, a hammer, a mallet or other usual means for pulverisation by application of force.

The dosage form according to the invention is thus suitable for preventing parenteral, nasal and/or oral abuse of pharmaceutical active ingredients with abuse potential.

Pharmaceutical active ingredients with abuse potential are known to the person skilled in the art, as are the quantities thereof to be used and processes for the production thereof, and may be present in the dosage form according to the invention as such, in the form of the corresponding derivatives thereof, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof, as racemates or stereoisomers. The dosage form according to the invention is also suitable for the administration of several active ingredients. It is preferably used to administer a specific active ingredient.

The dosage form according to the invention is in particular suitable for preventing abuse of a pharmaceutical active ingredient selected from the group consisting of opiates, opioids, tranquillisers, preferably benzodiazepines, barbiturates, stimulants and other narcotics.

The dosage form according to the invention is very particularly suitable for preventing abuse of an opiate, opioid, tranquilliser or another narcotic selected from the group consisting of N-{1-[2-(4-ethyl-5-oxo-2-tetrazolin-1-yl)ethyl]-4-methoxymethyl-4-piperidyl}propionanilide (alfentanil), 5,5-

diallylbarbituric acid (allobarbital), allylprodine, alphaprodine, 8-chloro-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]-benzodiazepine (alprazolam), 2-diethylaminopropiophenone (amfepramone), (±)-α-methyl-phenethylamine (amphetamine), 2-(α-methylphenethylamino)-2-phenylacetonitrile (amphetaminil), 5-ethyl-5-isopentylbarbituric acid (amobarbital), anileridine, apocodeine, 5,5-diethylbarbituric acid (barbital), benzylmorphine, bezitramide, 7-bromo-5-(2-pyridyl)-1H-1,4-benzodiazepine-2(3H)-one (bromazepam), 2-bromo-4-(2-chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo-[4,3-a][1,4]diazepine (brotizolam), 17-cyclopropylmethyl-4,5α-epoxy-7α[(S)-1-hydroxy-1,2,2-trimethyl-propyl]-6-methoxy-6,14-endo-ethanomorphinane-3-ol (buprenorphine), 5-butyl-5-ethylbarbituric acid (butobarbital), butorphanol, (7-chloro-1,3-dihydro-1-methyl-2-oxo-5-phenyl-2H-1,4-benzodiazepine-3-yl)-dimethylcarbamate (camazepam), (1S,2S)-2-amino-1-phenyl-1-propanol (cathine/D-norpseudoephedrine), 7-chloro-N-methyl-5-phenyl-3H-1,4-benzodiazepine-2-ylamine-4-oxide (chlorodiazepoxide), 7-chloro-1-methyl-5-phenyl-1H-1,5-benzodiazepine-2,4(3H,5H)-dione (clobazam), 5-(2-chlorophenyl)-7-nitro-1H-1,4-benzodiazepine-2(3H)-one (clonazepam), clonitazene, 7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepine-3-carboxylic acid (clorazepate), 5-(2-chlorophenyl)-7-ethyl-1-methyl-1H-thieno[2,3-e][1,4]diazepine-2(3H)-one (clotiazepam), 10-chloro-11b-(2-chlorophenyl)-2,3,7,11b-tetrahydrooxazolo[3,2-d][1,4]benzodiazepine-6(5H)-one (cloxazolam), (−)-methyl-[3β-benzoyloxy-2β(1αH,5αH)-tropancarboxylate] (cocaine), 4,5α-epoxy-3-methoxy-17-methyl-7-morphinene-6α-ol (codeine), 5-(1-cyclohexenyl)-5-ethylbarbituric acid (cyclobarbital), cyclorphan, cyprenorphine, 7-chloro-5-(2-chlorophenyl)-1H-1,4-benzodiazepine-2(3H)-one (delorazepam), desomorphine, dextromoramide, (+)-(1-benzyl-3-dimethylamino-2-methyl-1-phenylpropyl)propionate (dextropropoxyphen), dezocine, diampromide, diamorphone, 7-chloro-1-methyl-5-phenyl-1H-1,4-benzodiazepine-2(3H)-one (diazepam), 4,5α-epoxy-3-methoxy-17-methyl-6α-morphinanol (dihydrocodeine), 4,5α-epoxy-17-methyl-3,6a-morphinandiol (dihydromorphine), dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, (6aR,10aR)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromene-1-ol (dronabinol), eptazocine, 8-chloro-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine (estazolam), ethoheptazine, ethylmethylthiambutene, ethyl [7-chloro-5-(2-fluorophenyl)-2,3-dihydro-2-oxo-1H-1,4-benzodiazepine-3-carboxylate] (ethyl loflazepate), 4,5α-epoxy-3-ethoxy-17-methyl-7-morphinene-6α-ol (ethylmorphine), etonitazene, 4,5α-epoxy-7α-(1-hydroxy-1-methylbutyl)-6-methoxy-17-methyl-6,14-endo-etheno-morphinan-3-ol (etorphine), N-ethyl-3-phenyl-8,9,10-trinorbornan-2-ylamine (fencamfamine), 7-[2-(α-methyl-phenethylamino)ethyl]-theophylline) (fenethylline), 3-(α-methylphenethylamino)propionitrile (fenproporex), N-(1-phenethyl-4-piperidyl) propionanilide (fentanyl), 7-chloro-5-(2-fluorophenyl)-1-methyl-1H-1,4-benzodiazepine-2(3H)-one (fludiazepam), 5-(2-fluorophenyl)-1-methyl-7-nitro-1H-1,4-benzodiazepine-2(3H)-one (flunitrazepam), 7-chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1H-1,4-benzodiazepine-2(3H)-one (flurazepam), 7-chloro-5-phenyl-1-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2(3H)-one (halazepam), 10-bromo-11b-(2-fluorophenyl)-2,3,7,11b-tetrahydro[1,3]oxazolyl[3,2-d][1,4]benzodiazepine-6(5H)-one (haloxazolam), heroin, 4,5α-epoxy-3-methoxy-17-methyl-6-morphinanone (hydrocodone), 4,5α-epoxy-3-hydroxy-17-methyl-6-morphinanone (hydromorphone), hydroxypethidine, isomethadone, hydroxymethyl morphinane, 11-chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4H-[1,3]oxazino [3,2-d][1,4]benzodiazepine-4,7(6H)-dione (ketazolam), 1-[4-(3-hydroxyphenyl)-1-methyl-4-piperidyl]-1-propanone (ketobemidone), (3S,6S)-6-dimethylamino-4,4-diphenyl-heptan-3-yl acetate (levacetylmethadol (LAAM)), (−)-6-dimethylamino-4,4-diphenol-3-heptanone (levomethadone), (−)-17-methyl-3-morphinanol (levorphanol), levophenacylmorphane, lofentanil, 6-(2-chlorophenyl)-2-(4-methyl-1-piperazinylmethylene)-8-nitro-2H-imidazo[1,2-a][1,4]-benzodiazepine-1(4H)-one (loprazolam), 7-chloro-5-(2-chlorophenyl)-3-hydroxy-1H-1,4-benzodiazepine-2(3H)-one (lorazepam), 7-chloro-5-(2-chlorophenyl)-3-hydroxy-1-methyl-1H-1,4-benzodiazepine-2(3H)-one (lormetazepam), 5-(4-chlorophenyl)-2,5-dihydro-3H-imidazo[2,1-a]isoindol-5-ol (mazindol), 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepine (medazepam), N-(3-chloropropyl)-α-methylphenethylamine (mefenorex), meperidine, 2-methyl-2-propyltrimethylene dicarbamate (meprobamate), meptazinol, metazocine, methylmorphine, N,α-dimethylphenethylamine (methamphetamine), (±)-6-dimethylamino-4,4-diphenyl-3-heptanone (methadone), 2-methyl-3-o-tolyl-4(3H)-quinazolinone (methaqualone), methyl [2-phenyl-2-(2-piperidyl)acetate] (methylphenidate), 5-ethyl-1-methyl-5-phenylbarbituric acid (methylphenobarbital), 3,3-diethyl-5-methyl-2,4-piperidinedione (methyprylon), metopon, 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine (midazolam), 2-(benzhydrylsulfinyl)-acetamide (modafinil), 4,5α-epoxy-17-methyl-7-morphinan-3,6α-diol (morphine), myrophine, (±)-trans-3-(1,1-dimethylheptyl)-7,8,10,10α-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyrane-9(6αH)-one (nabilone), nalbuphine, nalorphine, narceine, nicomorphine, 1-methyl-7-nitro-5-phenyl-1H-1,4-benzodiazepine-2(3H)-one (nimetazepam), 7-nitro-5-phenyl-1H-1,4-benzodiazepine-2(3H)-one (nitrazepam), 7-chloro-5-phenyl-1H-1,4-benzodiazepine-2(3H)-one (nordazepam), norlevorphanol, 6-dimethylamino-4,4-diphenyl-3-hexanone (normethadone), normorphine, norpipanone, the exudation of plants belonging to the species *Papaver somniferum* (opium), 7-chloro-3-hydroxy-5-phenyl-1H-1,4-benzodiazepine-2(3H)-one (oxazepam), (cis-trans)-10-chloro-2,3,7,11b-tetrahydro-2-methyl-11b-phenyloxazolo[3,2-d][1,4]benzodiazepine-6-(5H)-one (oxazolam), 4,5α-epoxy-14-hydroxy-3-methoxy-17-methyl-6-morphinanone (oxycodone), oxymorphone, plants and parts of plants belonging to the species *Papaver somniferum* (including the subspecies *setigerum*), papavereturn, 2-imino-5-phenyl-4-oxazolidinone (pernoline), 1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol (pentazocine), 5-ethyl-5-(1-methylbutyl)-barbituric acid (pentobarbital), ethyl-(1-methyl-4-phenyl-4-piperidine carboxylate) (pethidine), phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, pholcodine, 3-methyl-2-phenylmorpholine (phenmetrazine), 5-ethyl-5-phenylbarbituric acid (phenobarbital), α,α-dimethylphenethylamine (phentermine), 7-chloro-5-phenyl-1-(2-propynyl)-1H-1,4-benzodiazepine-2(3H)-one (pinazepam), α-(2-piperidyl)benzhydryl alcohol (pipradrol), 1'-(3-cyano-3,3-diphenylpropyl)[1,4'-bipiperidine]-4'-carboxamide (piritramide), 7-chloro-1-(cyclopropylmethyl)-5-phenyl-1H-1,4-benzodiazepine-2(3H)-one (prazepam), profadol, proheptazine, promedol, properidine, propoxyphene, N-(1-methyl-2-piperidinoethyl)-N-(2-pyridyl)propionamide, methyl {3-[4-methoxycarbonyl-4-(N-phenylpropanamido)piperidino]propanoate} (remifentanil), 5-sec-butyl-5-ethylbarbituric acid (secbutabarbital), 5-allyl-

5-(1-methylbutyl)-barbituric acid (secobarbital), N-{4-methoxymethyl-1-[2-(2-thienyl)ethyl]-4-piperidyl}-propionanilide (sufentanil), 7-chloro-2-hydroxy-methyl-5-phenyl-1H-1,4-benzodiazepin-2(3H)-one (temazepam), 7-chloro-5-(1-cyclohexenyl)-1-methyl-1H-1,4-benzodiazepine-2(3H)-one (tetrazepam), ethyl (2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate) (tilidine (cis and trans)), tramadol, 8-chloro-6-(2-chlorophenyl)-1-methyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine (triazolam), 5-(1-methylbutyl)-5-vinylbarbituric acid (vinylbital), (1R*,2R*)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol, (1R,2R,4S)-2-(dimethylamino)methyl-4-(p-fluoro-benzyloxy)-1-(m-methoxyphenyl)cyclohexanol, (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)phenol, (1S,2S)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol, (2R,3R)-1-dimethylamino-3(3-methoxyphenyl)-2-methyl-pentan-3-ol, (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexane-1,3-diol, 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)phenyl 2-(4-isobutoxy-phenyl)-propionate, 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl) phenyl 2-(6-methoxy-naphthalen-2-yl)-propionate, 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(4-isobutyl-phenyl)-propionate, 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(6-methoxy-naphthalen-2-yl)-propionate, (RR-SS)-2-acetoxy-4-trifluoromethyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-4-trifluoromethyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-4-chloro-2-hydroxy-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-4-methyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-4-methoxy-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-5-nitro-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2',4'-difluoro-3-hydroxy-biphenyl-4-carboxylic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester and for corresponding stereoisomeric compounds, the corresponding derivatives thereof in each case, in particular esters or ethers, and the physiologically acceptable compounds thereof in each case, in particular the salts and solvates thereof.

The compounds (1R*,2R*)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol, (1R,2R,4S)-2-(dimethylamino) methyl-4-(p-fluorobenzyloxy)-1-(m-methoxyphenyl)cyclohexanol or the stereoisomeric compounds thereof or the physiologically acceptable compounds thereof, in particular the hydrochlorides thereof, the derivatives thereof, such as esters or ethers, and processes for the production thereof are known, for example, from EP-A-693475 or EP-A-780369. The corresponding descriptions are hereby introduced as a reference and are deemed to be part of the disclosure.

In order to achieve the necessary breaking strength of the dosage form according to the invention, at least one synthetic or natural polymer (C) is used which has a breaking strength, measured using the method disclosed in the present application, of at least 500 N. At least one polymer selected from the group consisting of polymethylene oxide, polyethylene oxide, polypropylene oxide, polyethylene, polypropylene, polyvinyl chloride, polycarbonate, polystyrene, polyacrylate, copolymers thereof, and mixtures of at least two of the stated polymers is preferably used for this purpose. The polymers are distinguished by a molecular weight of at least 0.5 million, determined by rheological measurements. Thermoplastic polyalkylene oxides, such as polyethylene oxides, with a molecular weight of at least 0.5 million, preferably of up to 15 million, determined by rheological measurements, are very particularly preferred. These polymers have a viscosity at 25° C. of 4500 to 17600 cP, measured on a 5 wt. % aqueous solution using a model RVF Brookfield viscosimeter (spindle no. 2/rotational speed 2 rpm), of 400 to 4000 cP, measured on a 2 wt. % aqueous solution using the stated viscosimeter (spindle no. 1 or 3/rotational speed 10 rpm) or of 1650 to 10000 cP, measured on a 1 wt. % aqueous solution using the stated viscosimeter (spindle no. 2/rotational speed 2 rpm).

The polymers are used in powder form.

In order to achieve the necessary breaking strength of the dosage form according to the invention, it is furthermore possible additionally to use at least one natural or synthetic wax (D) with a breaking strength, measured using the method disclosed in the present application, of at least 500 N. Waxes with a softening point of at least 60° C. are preferred. Carnauba wax and beeswax are particularly preferred. Carnauba wax is very particularly preferred. Carnauba wax is a natural wax which is obtained from the leaves of the carnauba palm and has a softening point of ≧80° C. When the wax component is additionally used, it is used together with at least one polymer (C) in quantities such that the dosage form has a breaking strength of at least 500 N.

The dosage forms according to the invention are distinguished in that, due their hardness, they cannot be pulverised, for example by grinding in a mortar. This virtually rules out oral or parenteral, in particular intravenous or nasal abuse. However, in order to prevent any possible abuse in the event of comminution and/or pulverisation of the dosage form according to the invention which has nevertheless been achieved by application of extreme force, the dosage forms according to the invention may, in a preferred embodiment, contain further agents which complicate or prevent abuse as auxiliary substances (B).

The abuse-proofed dosage form according to the invention, which comprises, apart from one or more active ingredients with abuse potential, at least one hardening polymer (C) and optionally at least one wax (D), may accordingly also comprise at least one of the following components (a)-(f) as auxiliary substances (B):

(a) at least one substance which irritates the nasal passages and/or pharynx,

(b) at least one viscosity-increasing agent, which, with the assistance of a necessary minimum quantity of an aqueous liquid, forms a gel with the extract obtained from the dosage form, which gel preferably remains visually distinguishable when introduced into a further quantity of an aqueous liquid,

(c) at least one antagonist for each of the active ingredients with abuse potential,

(d) at least one emetic,

(e) at least one dye as an aversive agent,

(f) at least one bitter substance.

Components (a) to (f) are additionally each individually suitable for abuse-proofing the dosage form according to the invention. Accordingly, component (a) is preferably suitable for proofing the dosage form against nasal, oral and/or parenteral, preferably intravenous, abuse, component (b) is preferably suitable for proofing against parenteral, particularly preferably intravenous and/or nasal abuse, component (c) is preferably suitable for proofing against nasal and/or parenteral, particularly preferably intravenous, abuse, component (d) is preferably suitable for proofing against parenteral, particularly preferably intravenous, and/or oral and/or nasal abuse, component (e) is suitable as a visual deterrent against oral or parenteral abuse and component (f) is suitable for proofing against oral or nasal abuse. Combined

use according to the invention of at least one of the above-stated components makes it possible still more effectively to prevent abuse of dosage forms according to the invention.

In one embodiment, the dosage form according to the invention may also comprise two or more of components (a)-(f) in a combination, preferably (a), (b) and optionally (c) and/or (f) and/or (e) or (a), (b) and optionally (d) and/or (f) and/or (e).

In another embodiment, the dosage form according to the invention may comprise all of components (a)-(f).

If the dosage form according to the invention comprises component (a) to counter abuse, substances which irritate the nasal passages and/or pharynx which may be considered according to the invention are any substances which, when administered via the nasal passages and/or pharynx, bring about a physical reaction which is either so unpleasant for the abuser that he/she does not wish to or cannot continue administration, for example burning, or physiologically counteracts taking of the corresponding active ingredient, for example due to increased nasal secretion or sneezing. These substances which conventionally irritate the nasal passages and/or pharynx may also bring about a very unpleasant sensation or even unbearable pain when administered parenterally, in particular intravenously, such that the abuser does not wish to or cannot continue taking the substance.

Particularly suitable substances which irritate the nasal passages and/or pharynx are those which cause burning, itching, an urge to sneeze, increased formation of secretions or a combination of at least two of these stimuli. Appropriate substances and the quantities thereof which are conventionally to be used are known per se to the skilled person or may be identified by simple preliminary testing.

The substance which irritates the nasal passages and/or pharynx of component (a) is preferably based on one or more constituents or one or more plant parts of at least one hot substance drug.

Corresponding hot substance drugs are known per se to the person skilled in the art and are described, for example, in "Pharmazeutische Biologie—Drogen and ihre Inhaltsstoffe" by Prof. Dr. Hildebert Wagner, 2nd., revised edition, Gustav Fischer Verlag, Stuttgart-N.Y., 1982, pages 82 et seq. The corresponding description is hereby introduced as a reference and is deemed to be part of the disclosure.

The dosage form according to the invention may preferably contain the plant parts of the corresponding hot substance drugs in a quantity of 0.01 to 30 wt. %, particularly preferably of 0.1 to 0.5 wt. %, in each case relative to the total weight dosage unit.

If one or more constituents of corresponding hot substance drugs are used, the quantity thereof in a dosage unit according to the invention preferably amounts to 0.001 to 0.005 wt. %, relative to the total weight of the dosage unit.

A dosage unit is taken to mean a separate or separable administration unit, such as for example a tablet or a capsule.

One or more constituents of at least one hot substance drug selected from the group consisting of Allii sativi bulbus (garlic), Asari rhizoma cum herba (Asarum root and leaves), Calami rhizoma (calamus root), Capsici fructus (capsicum), Capsici fructus *acer* (cayenne pepper), Curcumae longae rhizoma (turmeric root), Curcumae xanthorrhizae rhizoma (Javanese turmeric root), Galangae rhizoma (galangal root), Myristicae semen (nutmeg), Piperis nigri fructus (pepper), Sinapis albae semen (white mustard seed), Sinapis nigri semen (black mustard seed), Zedoariae rhizoma (zedoary root) and Zingiberis rhizoma (ginger root), particularly preferably from the group consisting of Capsici fructus (capsicum), Capsici fructus *acer* (cayenne pepper) and Piperis nigri fructus (pepper) may preferably be added as component (a) to the dosage form according to the invention.

The constituents of the hot substance drugs preferably comprise o-methoxy(methyl)phenol compounds, acid amide compounds, mustard oils or sulfide compounds or compounds derived therefrom.

Particularly preferably, at least one constituent of the hot substance drugs is selected from the group consisting of myristicin, elemicin, isoeugenol, β-asarone, safrole, gingerols, xanthorrhizol, capsaicinoids, preferably capsaicin, capsaicin derivatives, such as N-vanillyl-9E-octadecenamide, dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin, norcapsaicin and nomorcapsaicin, piperine, preferably trans-piperine, glucosinolates, preferably based on non-volatile mustard oils, particularly preferably based on p-hydroxybenzyl mustard oil, methylmercapto mustard oil or methylsulfonyl mustard oil, and compounds derived from these constituents.

Another option for preventing abuse of the dosage form according to the invention consists in adding at least one viscosity-increasing agent as a further abuse-preventing component (b) to the dosage form, which, with the assistance of a necessary minimum quantity of an aqueous liquid, forms a gel with the extract obtained from the dosage form, which gel is virtually impossible to administer safely and preferably remains visually distinguishable when introduced into a further quantity of an aqueous liquid.

For the purposes of the present invention visually distinguishable means that the active ingredient-containing gel formed with the assistance of a necessary minimum quantity of aqueous liquid, when introduced, preferably with the assistance of a hypodermic needle, into a further quantity of aqueous liquid at 37° C., remains substantially insoluble and cohesive and cannot straightforwardly be dispersed in such a manner that it can safely be administered parenterally, in particular intravenously. The material preferably remains visually distinguishable for at least one minute, preferably for at least 10 minutes.

The increased viscosity of the extract makes it more difficult or even impossible for it to be passed through a needle or injected. If the gel remains visually distinguishable, this means that the gel obtained on introduction into a further quantity of aqueous liquid, for example by injection into blood, initially remains in the form of a largely cohesive thread, which, while it may indeed be broken up into smaller fragments, cannot be dispersed or even dissolved in such a manner that it can safely be administered parenterally, in particular intravenously. In combination with at least one optionally present component (a) to (e), this additionally leads to unpleasant burning, vomiting, bad flavour and/or visual deterrence.

Intravenous administration of such a gel would most probably result in obstruction of blood vessels, associated with serious embolism or even death of the abuser.

In order to verify whether a viscosity-increasing agent is suitable as component (b) for use in the dosage form according to the invention, the active ingredient is mixed with the viscosity-increasing agent and suspended in 10 ml of water at a temperature of 25° C. If this results in the formation of a gel which fulfils the above-stated conditions, the corresponding viscosity-increasing agent is suitable for preventing or averting abuse of the dosage forms according to the invention.

If component (b) is added to the dosage form according to the invention, one or more viscosity-increasing agents are used which are selected from the group consisting of microcrystalline cellulose with 11 wt. % carboxymethylcellulose sodium (Avicel® RC 591), carboxymethylcellulose sodium

(Blanose®, CMC-Na C300P®, Frimulsion BLC-5®, Tylose C300 P®), polyacrylic acid (Carbopol® 980 NF, Carbopol® 981), locust bean flour (Cesagum® LA-200, Cesagum® LID/150, Cesagum® LN-1), pectins such as citrus pectin (Cesapectin® HM Medium Rapid Set), apple pectin, pectin from lemon peel, waxy maize starch (C*Gel 04201®), sodium alginate (Frimulsion ALG (E401)®), guar flour (Frimulsion BM®, Polygum 26/1-75®), iota carrageen (Frimulsion D021®), karaya gum, gellan gum (Kelcogel F®, Kelcogel LT100®), galactomannan (Meyprogat 150®), tara bean flour (Polygum 43/10), propylene glycol alginate (Protanal-Ester SD-LB®), sodium hyaluronate, tragacanth, tara gum (Vidogum SP 200®), fermented polysaccharide welan gum (K1A96), xanthan gum (Xantural 180®). Xanthans are particularly preferred. The names stated in brackets are the trade names by which the materials are known commercially. In general, a quantity of 0.1 to 5 wt. % of the viscosity-increasing agent(s) is sufficient to fulfil the above-stated conditions.

The component (b) viscosity-increasing agents, where provided, are preferably present in the dosage form according to the invention in quantities of ≧5 mg per dosage unit, i.e. per administration unit.

In a particularly preferred embodiment of the present invention, the viscosity-increasing agents used as component (b) are those which, on extraction from the dosage form with the necessary minimum quantity of aqueous liquid, form a gel which encloses air bubbles. The resultant gels are distinguished by a turbid appearance, which provides the potential abuser with an additional optical warning and discourages him/her from administering the gel parenterally.

It is also possible to formulate the viscosity-increasing agent and the other constituents in the dosage form according to the invention in a mutually spatially separated arrangement.

In order to discourage and prevent abuse, the dosage form according to the invention may furthermore comprise component (c), namely one or more antagonists for the active ingredient or active ingredients with abuse potential, wherein the antagonists are preferably spatially separated from the remaining constituents of the invention dosage according to the form and, when correctly used, do not exert any effect.

Suitable antagonists for preventing abuse of the active ingredients are known per se to the person skilled in the art and may be present in the dosage form according to the invention as such or in the form of corresponding derivatives, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof.

If the active ingredient present in the dosage form is an opiate or an opioid, the antagonist used is preferably an antagonist selected from the group consisting of naloxone, naltrexone, nalmefene, nalid, nalmexone, nalorphine or naluphine, in each case optionally in the form of a corresponding physiologically acceptable compound, in particular in the form of a base, a salt or solvate. The corresponding antagonists, where component (c) is provided, are preferably used in a quantity of ≧10 mg, particularly preferably in a quantity of 10 to 100 mg, very particularly preferably in a quantity of 10 to 50 mg per dosage form, i.e. per administration unit.

If the dosage form according to the invention comprises a stimulant as active ingredient, the antagonist is preferably a neuroleptic, preferably at least one compound selected from the group consisting of haloperidol, promethazine, fluphenazine, perphenazine, levomepromazine, thioridazine, perazine, chlorpromazine, chlorprothixine, zuclopentixol, flupentixol, prothipendyl, zotepine, benperidol, pipamperone, melperone and bromperidol.

The dosage form according to the invention preferably comprises these antagonists in a conventional therapeutic dose known to the person skilled in the art, particularly preferably in a quantity of twice to four times the conventional dose per administration unit.

If the combination to discourage and prevent abuse of the dosage form according to the invention comprises component (d), it may comprise at least one emetic, which is preferably present in a spatially separated arrangement from the other components of the dosage form according to the invention and, when correctly used, is intended not to exert its effect in the body.

Suitable emetics for preventing abuse of an active ingredient are known per se to the person skilled in the art and may be present in the dosage form according to the invention as such or in the form of corresponding derivatives, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof.

An emetic based on one or more constituents of radix ipecacuanha (ipecac root), preferably based on the constituent emetine may preferably be considered in the dosage form according to the invention, as are, for example, described in "Pharmazeutische Biologie—Drogen and ihre Inhaltsstoffe" by Prof. Dr. Hildebert Wagner, 2nd, revised edition, Gustav Fischer Verlag, Stuttgart, N.Y., 1982. The corresponding literature description is hereby introduced as a reference and is deemed to be part of the disclosure.

The dosage form according to the invention may preferably comprise the emetic emetine as component (d), preferably in a quantity of ≧10 mg, particularly preferably of ≧20 mg and very particularly preferably in a quantity of ≧40 mg per dosage form, i.e. administration unit.

Apomorphine may likewise preferably be used as an emetic in the abuse-proofing according to the invention, preferably in a quantity of preferably ≧3 mg, particularly preferably of ≧5 mg and very particularly preferably of ≧7 mg per administration unit.

If the dosage form according to the invention contains component (e) as a further abuse-preventing auxiliary substance, the use of a such a dye brings about an intense coloration of a corresponding aqueous solution, in particular when the attempt is made to extract the active ingredient for parenteral, preferably intravenous administration, which coloration may act as a deterrent to the potential abuser. Oral abuse, which conventionally begins by means of aqueous extraction of the active ingredient, may also be prevented by this coloration. Suitable dyes and the quantities required for the necessary deterrence may be found in WO 03/015531, wherein the corresponding disclosure should be deemed to be part of the present disclosure and is hereby introduced as a reference.

If the dosage form according to the invention contains component (f) as a further abuse-preventing auxiliary substance, this addition of at least one bitter substance and the consequent impairment of the flavour of the dosage form additionally prevents oral and/or nasal abuse.

Suitable bitter substances and the quantities effective for use may be found in US-2003/0064099 A1, the corresponding disclosure of which should be deemed to be the disclosure of the present application and is hereby introduced as a reference. Suitable bitter substances are preferably aromatic oils, preferably peppermint oil, eucalyptus oil, bitter almond oil, menthol, fruit aroma substances, preferably aroma substances from lemons, oranges, limes, grapefruit or mixtures thereof, and/or denatonium benzoate.

The solid dosage form according to the invention is suitable to be taken orally or rectally, preferably orally.

The orally administrable dosage form according to the invention may assume multiparticulate form, preferably in the form of microtablets, microcapsules, micropellets, granules, spheroids, beads or pellets, optionally packaged in capsules or pressed into tablets. The multiparticulate forms preferably have a size or size distribution in the range from 0.1 to 3 mm, particularly preferably in the range from 0.5 to 2 mm. Depending on the desired dosage form, conventional auxiliary substances (B) are optionally also used for the formulation of the dosage form.

The solid, abuse-proofed dosage form according to the invention is preferably produced by mixing the components (A), (B), (C) and/optionally (D) and at least one of the optionally present further abuse-preventing components (a)-(f) and, optionally after granulation, press-forming the resultant mixture to yield the dosage form with preceding, simultaneous, or subsequent exposure to heat.

Mixing of components (A), (B), (C) and optionally (D) and of the optionally present further components (a)-(f) proceeds in a mixer known to the person skilled in the art. The mixer may, for example, be a roll mixer, shaking mixer, shear mixer or compulsory mixer.

The resultant mixture is preferably formed directly by application of pressure to yield the dosage form according to the invention with preceding, simultaneous or subsequent exposure to heat. The mixture may, for example, be formed into tablets by direct tabletting. In direct tabletting with simultaneous exposure to heat, the tabletting tool, i.e. bottom punch, top punch and die are briefly heated at least to the softening temperature of the polymer (C) and pressed together. In direct tabletting with subsequent exposure to heat, the formed tablets are briefly heated at least to the softening temperature (glass transition temperature, melting temperature; sintering temperature) of component (C) and cooled again. In direct tabletting with preceding exposure to heat, the material to be pressed is heated immediately prior to tabletting at least to the softening temperature of component (C) and then pressed.

The resultant mixture of components (A), (B), (C) and optionally (D) and the optionally present components (a) to (f) may also first be granulated and then be formed with preceding, simultaneous, or subsequent exposure to heat to yield the dosage form according to the invention.

In a further preferred embodiment, the dosage form according to the invention assumes the form of a tablet, a capsule or is in the form of an oral osmotic therapeutic system (OROS), preferably if at least one further abuse-preventing component (a)-(f) is also present.

If components (c) and/or (d) and/or (f) are present in the dosage form according to the invention, care must be taken to ensure that they are formulated in such a manner or are present in such a low dose that, when correctly administered, the dosage form is able to bring about virtually no effect which impairs the patient or the efficacy of the active ingredient.

If the dosage form according to the invention contains component (d) and/or (f), the dosage must be selected such that, when correctly orally administered, no negative effect is caused. If, however, the intended dosage of the dosage form is exceeded inadvertently, in particular by children, or in the event of abuse, nausea or an inclination to vomit or a bad flavour are produced. The particular quantity of component (d) and/or (f) which can still be tolerated by the patient in the event of correct oral administration may be determined by the person skilled in the art by simple preliminary testing.

If, however, irrespective of the fact that the dosage form according to the invention is virtually impossible to pulverise, the dosage form containing the components (c) and/or (d) and/or (f) is provided with protection, these components should preferably be used at a dosage which is sufficiently high that, when abusively administered, they bring about an intense negative effect on the abuser. This is preferably achieved by spatial separation of at least the active ingredient or active ingredients from components (c) and/or (d) and/or (f), wherein the active ingredient or active ingredients is/are present in at least one subunit (X) and components (c) and/or (d) and/or (f) is/are present in at least one subunit (Y), and wherein, when the dosage form is correctly administered, components (c), (d) and (f) do not exert their effect on taking and/or in the body and the remaining components of the formulation, in particular component (C), are identical.

If the dosage form according to the invention comprises at least 2 of components (c) and (d) or (f), these may each be present in the same or different subunits (Y). Preferably, when present, all the components (c) and (d) and (f) are present in one and the same subunit (Y).

For the purposes of the present invention, subunits are solid formulations, which in each case, apart from conventional auxiliary substances known to the person skilled in the art, contain the active ingredient(s), at least one polymer (C) and optionally at least one of the optionally present components (a) and/or (b) and/or (e) or in each case at least one polymer (C) and the antagonist(s) and/or emetic(s) and/or component (e) and/or component (f) and optionally at least one of the optionally present components (a) and/or (b). Care must here be taken to ensure that each of the subunits is formulated in accordance with the above-stated process.

One substantial advantage of the separated formulation of active ingredients from components (c) or (d) or (f) in subunits (X) and (Y) of the dosage form according to the invention is that, when correctly administered, components (c) and/or (d) and/or (f) are hardly released on taking and/or in the body or are released in such small quantities that they exert no effect which impairs the patient or therapeutic success or, on passing through the patient's body, they are only liberated in locations where they cannot be sufficiently absorbed to be effective. When the dosage form is correctly administered, hardly any of components (c) and/or (d) and/or (f) is released into the patient's body or they go unnoticed by the patient.

The person skilled in the art will understand that the above-stated conditions may vary as a function of the particular components (c), (d) and/or (f) used and of the formulation of the subunits or the dosage form. The optimum formulation for the particular dosage form may be determined by simple preliminary testing. What is vital is that each subunit contains the polymer (C) and has been formulated in the stated manner.

Should, contrary to expectations, the abuser succeed in comminuting such a dosage form according to the invention, which comprises components (c) and/or (e) and/or (d) and/or (f) in subunits (Y), for the purpose of abusing the active ingredient and obtain a powder which is extracted with a suitable extracting agent, not only the active ingredient but also the particular component (c) and/or (e) and/or (f) and/or (d) will be obtained in a form in which it cannot readily be separated from the active ingredient, such that when the dosage form which has been tampered with is administered, in particular by oral and/or parenteral administration, it will exert its effect on taking and/or in the body combined with an additional negative effect on the abuser corresponding to component (c) and/or (d) and/or (f) or, when the attempt is

made to extract the active ingredient, the coloration will act as a deterrent and so prevent abuse of the dosage form.

A dosage form according to the invention, in which the active ingredient or active ingredients is/are spatially separated from components (c), (d) and/or (e), preferably by formulation in different subunits, may be formulated in many different ways, wherein the corresponding subunits may each be present in the dosage form according to the invention in any desired spatial arrangement relative to one another, provided that the above-stated conditions for the release of components (c) and/or (d) are fulfilled.

The person skilled in the art will understand that component(s) (a) and/or (b) which are optionally also present may preferably be formulated in the dosage form according to the invention both in the particular subunits (X) and (Y) and in the form of independent subunits corresponding to subunits (X) and (Y), provided that neither the abuse-proofing nor the active ingredient release in the event of correct administration is impaired by the nature of the formulation and the polymer (C) is included in the formulation and formulation is carried out in accordance with the above-stated process.

In a preferred embodiment of the dosage form according to the invention, subunits (X) and (Y) are present in multiparticulate form, wherein microtablets, microcapsules, micropellets, granules, spheroids, beads or pellets are preferred and the same form, i.e. shape, is selected for both subunit (X) and subunit (Y), such that it is not possible to separate subunits (X) from (Y) by mechanical selection. The multiparticulate forms are preferably of a size in the range from 0.1 to 3 mm, preferably of 0.5 to 2 mm.

The subunits (X) and (Y) in multiparticulate form may also preferably be packaged in a capsule or be pressed into a tablet, wherein the final formulation in each case proceeds in such a manner that the subunits (X) and (Y) are also retained in the resultant dosage form.

The multiparticulate subunits (X) and (Y) of identical shape should also not be visually distinguishable from one another so that the abuser cannot separate them from one another by simple sorting. This may, for example, be achieved by the application of identical coatings which, apart from this disguising function, may also incorporate further functions, such as, for example, controlled release of one or more active ingredients or provision of a finish resistant to gastric juices on the particular subunits.

In a further preferred embodiment of the present invention, subunits (X) and (Y) are in each case arranged in layers relative to one another.

The layered subunits (X) and (Y) are preferably arranged for this purpose vertically or horizontally relative to one another in the dosage form according to the invention, wherein in each case one or more layered subunits (X) and one or more layered subunits (Y) may be present in the dosage form, such that, apart from the preferred layer sequences (X)-(Y) or (X)-(Y)-(X), any desired other layer sequences may be considered, optionally in combination with layers containing components (a) and/or (b).

Another preferred dosage form according to the invention is one in which subunit (Y) forms a core which is completely enclosed by subunit (X), wherein a separation layer (Z) may be present between said layers. Such a structure is preferably also suitable for the above-stated multiparticulate forms, wherein both subunits (X) and (Y) and an optionally present separation layer (Z), which must satisfy the hardness requirement according to the invention, are formulated in one and the same multiparticulate form. In a further preferred embodiment of the dosage form according to the invention, the subunit (X) forms a core, which is enclosed by subunit (Y), wherein the latter comprises at least one channel which leads from the core to the surface of the dosage form.

The dosage form according to the invention may comprise, between one layer of the subunit (X) and one layer of the subunit (Y), in each case one or more, preferably one, optionally swellable separation layer (Z) which serves to separate subunit (X) spatially from (Y).

If the dosage form according to the invention comprises the layered subunits (X) and (Y) and an optionally present separation layer (Z) in an at least partially vertical or horizontal arrangement, the dosage form preferably takes the form of a tablet, a coextrudate or a laminate.

In one particularly preferred embodiment, the entirety of the free surface of subunit (Y) and optionally at least part of the free surface of subunit(s) (X) and optionally at least part of the free surface of the optionally present separation layer(s) (Z) may be coated with at least one barrier layer (Z') which prevents release of component (c) and/or (e) and/or (d) and/or (f). The barrier layer (Z') must also fulfil the hardness conditions according to the invention.

Another particularly preferred embodiment of the dosage form according to the invention comprises a vertical or horizontal arrangement of the layers of subunits (X) and (Y) and at least one push layer (p) arranged therebetween, and optionally a separation layer (Z), in which dosage form the entirety of the free surface of layer structure consisting of subunits (X) and (Y), the push layer and the optionally present separation layer (Z) is provided with a semipermeable coating (E), which is permeable to a release medium, i.e. conventionally a physiological liquid, but substantially impermeable to the active ingredient and to component (c) and/or (d) and/or (f), and wherein this coating (E) comprises at least one opening for release of the active ingredient in the area of subunit (X).

A corresponding dosage form is known to the person skilled in the art, for example under the name oral osmotic therapeutic system (OROS), as are suitable materials and methods for the production thereof, inter alia from U.S. Pat. No. 4,612,008, U.S. Pat. No. 4,765,989 and U.S. Pat. No. 4,783,337. The corresponding descriptions are hereby introduced as a reference and are deemed to be part of the disclosure.

In a further preferred embodiment, the subunit (X) of the dosage form according to the invention is in the form of a tablet, the edge face of which and optionally one of the two main faces is covered with a barrier layer (Z') containing component (c) and/or (d) and/or (f).

The person skilled in the art will understand that the auxiliary substances of the subunit(s) (X) or (Y) and of the optionally present separation layer(s) (Z) and/or of the barrier layer(s) (Z') used in formulating the dosage form according to the invention will vary as a function of the arrangement thereof in the dosage form according to the invention, the mode of administration and as a function of the particular active ingredient of the optionally present components (a) and/or (b) and/or (e) and of component (c) and/or (d) and/or (f). The materials which have the requisite properties are in each case known per se to the person skilled in the art.

If release of component (c) and/or (d) and/or (f) from subunit (Y) of the dosage form according to the invention is prevented with the assistance of a cover, preferably a barrier layer, the subunit may consist of conventional materials known to the person skilled in the art, providing that it contains at least one polymer (C) to fulfil the hardness condition of the dosage form according to the invention.

If a corresponding barrier layer (Z') is not provided to prevent release of component (c) and/or (d) and/or (f), the materials of the subunits should be selected such that release

of the particular component (c) and/or (d) from subunit (Y) is virtually ruled out. The materials which are stated below to be suitable for production of the barrier layer may preferably be used for this purpose. The materials for the separation layer and/or barrier layer must contain at least one polymer (C) in order to fulfil the hardness conditions.

Preferred materials are those which are selected from the group consisting of alkylcelluloses, hydroxyalkylcelluloses, glucans, scleroglucans, mannans, xanthans, copolymers of poly[bis(p-carboxyphenoxy)propane and sebacic acid, preferably in a molar ratio of 20:80 (commercially available under the name Polifeprosan 20®), carboxymethylcelluloses, cellulose ethers, cellulose esters, nitrocelluloses, polymers based on (meth)acrylic acid and the esters thereof, polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, halogenated polyvinyls, polyglycolides, polysiloxanes and polyurethanes and the copolymers thereof.

Particularly suitable materials may be selected from the group consisting of methylcellulose, ethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxybutylmethylcellulose, cellulose acetate, cellulose propionate (of low, medium or high molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethylcellulose, cellulose triacetate, sodium cellulose sulfate, polymethyl methacrylate, polyethyl methacrylate, polybutyl methacrylate, polyisobutyl methacrylate, polyhexyl methacrylate, polyisodecyl methacrylate, polylauryl methacrylate, polyphenyl methacrylate, polymethyl acrylate, polyisopropyl acrylate, polyisobutyl acrylate, polyoctadecyl acrylate, polyethylene, low density polyethylene, high density polyethylene, polypropylene, polyethylene glycol, polyethylene oxide, polyethylene terephthalate, polyvinyl alcohol, polyvinyl isobutyl ether, polyvinyl acetate and polyvinyl chloride.

Particularly suitable copolymers may be selected from the group consisting of copolymers of butyl methacrylate and isobutyl methacrylate, copolymers of methyl vinyl ether and maleic acid with high molecular weight, copolymers of methyl vinyl ether and maleic acid monoethyl ester, copolymers of methyl vinyl ether and maleic anhydride and copolymers of vinyl alcohol and vinyl acetate.

Further materials which are particularly suitable for formulating the barrier layer are starch-filled polycaprolactone (WO98/20073), aliphatic polyesteramides (DE 19 753 534 A1, DE 19 800 698 A1, EP 0 820 698 A1), aliphatic and aromatic polyester urethanes (DE 19822979), polyhydroxyalkanoates, in particular polyhydroxybutyrates, polyhydroxyvalerates, casein (DE 4 309 528), polylactides and copolylactides (EP 0 980 894 A1). The corresponding descriptions are hereby introduced as a reference and are deemed to be part of the disclosure.

The above-stated materials may optionally be blended with further conventional auxiliary substances known to the person skilled in the art, preferably selected from the group consisting of glyceryl monostearate, semi-synthetic triglyceride derivatives, semi-synthetic glycerides, hydrogenated castor oil, glyceryl palmitostearate, glyceryl behenate, polyvinylpyrrolidone, gelatine, magnesium stearate, stearic acid, sodium stearate, talcum, sodium benzoate, boric acid and colloidal silica, fatty acids, substituted triglycerides, glycerides, polyoxyalkylene glycols and the derivatives thereof.

If the dosage form according to the invention comprises a separation layer (Z'), said layer, like the uncovered subunit (Y), may preferably consist of the above-stated materials described for the barrier layer. The person skilled in the art will understand that release of the active ingredient or of component (c) and/or (d) from the particular subunit may be controlled by the thickness of the separation layer.

The dosage form according to the invention may comprise one or more active ingredients at least partially in controlled release form, wherein controlled release may be achieved with the assistance of conventional materials and methods known to the person skilled in the art, for example by embedding the active ingredient in a controlled release matrix or by the application of one or more controlled release coatings. Active ingredient release must, however, be controlled such that the above-stated conditions are fulfilled in each case, for example that, in the event of correct administration of the dosage form, the active ingredient or active ingredients are virtually completely released before the optionally present component (c) and/or (d) can exert an impairing effect.

Controlled release from the dosage form according to the invention is preferably achieved by embedding the active ingredient in a matrix. The auxiliary substances acting as matrix materials control active ingredient release. Matrix materials may, for example, be hydrophilic, gel-forming materials, from which active ingredient release proceeds mainly by diffusion, or hydrophobic materials, from which active ingredient release proceeds mainly by diffusion from the pores in the matrix.

Physiologically acceptable, hydrophobic materials which are known to the person skilled in the art may be used as matrix materials. Polymers, particularly preferably cellulose ethers, cellulose esters and/or acrylic resins are preferably used as hydrophilic matrix materials. Ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxymethylcellulose, poly(meth)acrylic acid and/or the derivatives thereof, such as the salts, amides or esters thereof are very particularly preferably used as matrix materials.

Matrix materials prepared from hydrophobic materials, such as hydrophobic polymers, waxes, fats, long-chain fatty acids, fatty alcohols or corresponding esters or ethers or mixtures thereof are also preferred. Mono- or diglycerides of C12-C30 fatty acids and/or C12-C30 fatty alcohols and/or waxes or mixtures thereof are particularly preferably used as hydrophobic materials.

It is also possible to use mixtures of the above-stated hydrophilic and hydrophobic materials as matrix materials.

Component (C) and the optionally present component (D), which serve to achieve the breaking strength of at least 500 N which is necessary according to the invention may furthermore also optionally serve as additional matrix materials.

If the dosage form according to the invention is intended for oral administration, it may also preferably comprise a coating which is resistant to gastric juices and dissolves as a function of the pH value of the release environment. By means of this coating, it is possible to ensure that the dosage form according to the invention passes through the stomach undissolved and the active ingredient is only released in the intestines. The coating which is resistant to gastric juices preferably dissolves at a pH value of between 5 and 7.5.

Corresponding materials and methods for the controlled release of active ingredients and for the application of coatings which are resistant to gastric juices are known to the person skilled in the art, for example from "Coated Pharmaceutical Dosage Forms—Fundamentals, Manufacturing Techniques, Biopharmaceutical Aspects, Test Methods and Raw Materials" by Kurt H. Bauer, K. Lehmann, Hermann P. Osterwald, Rothgang, Gerhart, 1st edition, 1998, Medpharm Scientific Publishers. The corresponding literature description is hereby introduced as a reference and is deemed to be part of the disclosure.

Method for Determining Breaking Strength

A) In order to verify whether a polymer may be used as component (C), the polymer is pressed to form a tablet with a diameter of 10 mm and a height of 5 mm using a force of 150 N at a temperature which at least corresponds to the softening point of the polymer and is determined with the assistance of a DSC diagram of the polymer. Using tablets produced in this manner, breaking strength is determined with the apparatus described below in accordance with the method for determining the breaking strength of tablets published in the European Pharmacopoeia 1997, page 143-144, method no. 2.9.8. The apparatus used for the measurement is a series 3300 universal tester, single column benchtop model no. 3345 from Instron®, Canton, Mass., USA. The clamping tool used is a pressure piston with a diameter of 25 mm, which can be subjected to a load of up to 1 kN (item no. 2501-3 from Instron®).

An Instron® universal tester, single column benchtop model no. 5543, with the above-stated clamping tool may also be used to carry out the measurement.

The tablets deemed to be resistant to breaking under a specific load include not only those which have not broken but also those which may have suffered plastic deformation under the action of the force.

Providing that the dosage form is in tablet form, breaking strength may be determined using the same measurement method.

The following Examples illustrate the invention purely by way of example and without restricting the general concept of the invention.

EXAMPLES

Tramadol hydrochloride was used as the active ingredient in a series of Examples. Tramadol hydrochloride was used, despite tramadol not being an active ingredient which conventionally has abuse potential, because it is not governed by German narcotics legislation, so simplifying the experimental work. Tramadol is moreover a member of the opioid class with excellent water solubility.

Example 1

Components	Per tablet	Complete batch
Tramadol hydrochloride	100 mg	100 g
Polyethylene oxide, NF, MFI (190° C. at 21.6 kg/10 min) <0.5 g MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	200 mg	200 g
Total weight	300 mg	300 g

Tramadol hydrochloride and polyethylene oxide powder were mixed in a free-fall mixer. A tabletting tool with top punch, bottom punch and die for tablets with a diameter of 10 mm and a radius of curvature of 8 mm was heated to 80° C. in a heating cabinet. 300 mg portions of the powder mixture were pressed with the heated tool, wherein pressure was maintained for at least 15 seconds by clamping the tabletting tool in a vice.

The breaking strength of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not break when exposed to a force of 500 N.

The tablet could not be comminuted using a hammer, nor with the assistance of a mortar and pestle.

In vitro release of the active ingredient from the preparation was determined in a paddle stirrer apparatus in accordance with Pharm. Eur. The temperature of the release medium was 37° C. and the rotational speed of the stirrer 75 min^{-1}. At the beginning of the investigation, each tablet was placed in a 600 ml portion of artificial gastric juice, pH 1.2. After 30 minutes, the pH value was increased to 2.3 by addition of alkali solution, after a further 90 minutes to pH 6.5 and after a further 60 minutes to pH 7.2. The released quantity of active ingredient present in the dissolution medium at each point in time was determined by spectrophotometry.

Time	Released quantity
30 min	15%
240 min	52%
480 min	80%
720 min	99%

Example 2

300 mg portions of the powder mixture from Example 1 were heated to 80° C. and in placed in the die of the tabletting tool. Pressing was then performed. The tablet exhibits the same properties such as the tablet in Example 1.

Example 3

Raw material	Per tablet	Complete batch
Tramadol hydrochloride	50 mg	100 g
Polyethylene oxide, NF, MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	100 mg	200 g
Total weight	150 mg	300 g

Tramadol hydrochloride and the above-stated components were mixed in a free-fall mixer. A tabletting tool with top punch, bottom punch and die for tablets with a diameter of 7 mm was heated to 80° C. in a heating cabinet. 150 mg portions of the powder mixture were pressed with the heated tool, wherein pressure was maintained for at least 15 seconds by clamping the tabletting tool in a vice.

The breaking strength of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not break when exposed to a force of 500 N.

In vitro release of the active ingredient was determined as in Example 1 and was:

Time	Released quantity
30 min	15%
240 min	62%
480 min	88%
720 min	99%

Example 4

Raw material	Per tablet	Complete batch
Tramadol hydrochloride	100 mg	100 g
Polyethylene oxide, NF, MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	180 mg	180 g
Xanthan, NF	20 mg	20 g
Total weight	300 mg	300 g

Tramadol hydrochloride, xanthan and polyethylene oxide were mixed in a free-fall mixer. A tabletting tool with top punch, bottom punch and die for tablets with a diameter of 10 mm and a radius of curvature of 8 mm was heated to 80° C. in a heating cabinet. 300 mg portions of the powder mixture were pressed with the heated tool, wherein pressure was maintained for at least 15 seconds by clamping the tabletting tool in a vice.

The breaking strength of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not break when exposed to a force of 500 N. The tablets did suffer a little plastic deformation.

In vitro release of the active ingredient was determined as in Example 1 and was:

Time	Released quantity
30 min	14%
240 min	54%
480 min	81%
720 min	99%

The tablets could be cut up with a knife into pieces of an edge length of as small as approx. 2 mm. No further comminution proceeding as far as pulverisation was possible. When the pieces are combined with water, a highly viscous gel is formed. Only with great difficulty could the gel be pressed through a 0.9 mm injection cannula. When the gel was injected into water, the gel did not spontaneously mix with water, but remained visually distinguishable.

Example 5

Raw material	Per tablet	Complete batch
Tramadol hydrochloride	50 mg	100 g
Polyethylene oxide, NF, MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	90 mg	180 g
Xanthan, NF	10 mg	20 g
Total weight	300 mg	300 g

Tramadol hydrochloride, xanthan and polyethylene oxide were mixed in a free-fall mixer. A tabletting tool with a top punch, bottom punch and die for oblong tablets 10 mm in length and 5 mm in width was heated to 90° C. in a heating cabinet. 150 mg portions of the powder mixture were pressed with the heated tool, wherein pressure was maintained for at least 15 seconds by clamping the tabletting tool in a vice.

The breaking strength of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not break when exposed to a force of 500 N. The tablets did suffer a little plastic deformation.

In vitro release of the active ingredient was determined as in Example 1 and was:

Time	Released quantity
30 min	22%
120 min	50%
240 min	80%
360 min	90%
480 min	99%

The tablets could be cut up into pieces of an edge length of as small as approx. 2 mm, but could not be pulverised. When the pieces are combined with water, a highly viscous gel is formed. Only with great difficulty could the gel be pressed through a 0.9 mm injection cannula. When the gel was injected into water, the gel did not spontaneously mix with water, but remained visually distinguishable.

Example 6

A tablet with the following composition was produced as described in Example 1:

Components	Per tablet	Per batch
Oxycodone hydrochloride	20.0 mg	0.240 g
Xanthan, NF	20.0 mg	0.240 g
Polyethylene oxide, NF, MFI (190° C. at 21.6 kg/10 min) <0.5 g MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	110.0 mg	1.320 g
Total weight	150.0 mg	1.800 g

Release of the active ingredient was determined as follows:

In vitro release of the active ingredient from the preparation was determined in a paddle stirrer apparatus in accordance with Pharm. Eur. The temperature of the release medium was 37° C. and the rotational speed 75 rpm. The phosphate buffer, pH 6.8, described in DSP served as the release medium. The quantity of active ingredient present in the solvent at the particular time of testing was determined by spectrophotometry.

Time	Mean
0 min	0%
30 min	17%
240 min	61%
480 min	90%
720 min	101.1%

The breaking strength of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not break when exposed to a force of 500 N.

The tablets could be cut up into pieces of an edge length of as small as approx. 2 mm, but could not be pulverised. When the pieces are combined with water, a highly viscous gel is formed. Only with great difficulty could the gel be pressed

through a 0.9 mm injection cannula. When the gel was injected into water, the gel did not spontaneously mix with water, but remained visually distinguishable.

What is claimed is:

1. An abuse-proofed, thermoformed dosage form comprising one or more active ingredients with abuse potential (A) optionally together with physiologically acceptable auxiliary substances (B), at least one synthetic or natural polymer (C), wherein the polymer (C) has a molecular weight of at least 0.5 million according to rheological measurements, and optionally at least one wax (D), wherein the dosage form exhibits a breaking strength of at least 500 N.

2. A dosage form according to claim **1**, which is in the form of a tablet.

3. A dosage form according to claim **1**, which is in multiparticulate form.

4. A dosage form according to claim **1**, wherein the polymer (C) is at least one polymer selected from the group consisting of polyethylene oxide, polymethylene oxide, polypropylene oxide, polyethylene, polypropylene, polyvinyl chloride, polycarbonate, polystyrene, polyacrylate, copolymers and the mixtures thereof.

5. A dosage form according to claim **1**, wherein the molecular weight is 1-15 million.

6. A dosage form according to claim **1**, which comprises the wax (D) and the wax (D) is at least one natural, semisynthetic or synthetic wax with a softening point of at least 60° C.

7. A dosage form according to claim **6**, wherein the wax (D) is carnauba wax or beeswax.

8. A dosage form according to claim **1**, wherein the active ingredient (A) is at least one active ingredient selected from the group consisting of opiates, opioids, tranquillisers, stimulants, barbiturates and further narcotics.

9. A dosage form according to claim **1**, which additionally comprises at least one of the following components a)-f):

(a) at least one substance which irritates the nasal passages and/or pharynx,

(b) at least one viscosity-increasing agent, which, with the assistance of a necessary minimum quantity of an aqueous liquid, forms a gel with the extract obtained from the dosage form, which gel optionally remains visually distinguishable when introduced into a further quantity of an aqueous liquid,

c) at least one antagonist for the active ingredient or active ingredients with abuse potential,

(d) at least one emetic,

(e) at least one dye as an aversive agent,

(f) at least one bitter substance.

10. A dosage form according to claim **9**, wherein the component (a) irritant substance causes burning, itching, an urge to sneeze, increased formation of secretions or a combination of at least two of these stimuli.

11. A dosage form according to claim **10**, wherein the component (a) irritant substance is based on one or more constituents of at least one hot substance drug.

12. A dosage form according to claim **11**, wherein the hot substance drug is at least one drug selected from the group consisting of Allii sativi bulbus (garlic), Asari rhizoma cum herba (Asarum root and leaves), Calami rhizoma (calamus root), Capsici fructus (capsicum), Capsici fructus acer (cayenne pepper), Curcumae longae rhizoma (turmeric root), Curcumae xanthorrhizae rhizoma (Javanese turmeric root), Galangae rhizoma (galangal root), Myristicae semen (nutmeg), Piperis nigri fructus (pepper), Sinapis albae semen (erucae/white mustard seed), Sinapis nigri semen (black mustard seed), Zedoariae rhizoma (zedoary root) and Zingiberis rhizoma (ginger root).

13. A dosage form according to claim **11**, wherein the constituent of the hot substance drug is an o-methoxy(methyl)phenol compound, an acid amide compound, a mustard oil or a sulfide compound or is derived from such a compound.

14. A dosage form according to claim **11**, wherein the constituent of the hot substance drug is at least one constituent selected from the group consisting of myristicin, elemicin, isoeugenol, β-asarone, safrole, gingerols, xanthorrhizol, capsaicinoids, piperine, glucosinolates, and a compound derived from these constituents.

15. A dosage form according to claim **9**, wherein component (b) is at least one viscosity-increasing agent selected from the group consisting of microcrystalline cellulose with 11 wt. % carboxymethylcellulose sodium (Avicel® RC **591**), carboxymethylcellulose sodium (Blanose®, CMC-Na C**300**P®, Frimulsion BLC-**5**®, Tylose C**300** P®), polyacrylic acid (Carbopol® **980** NF, Carbopol® **981**), locust bean flour (Cesagum® LA-**200**, Cesagum® LID/**150**, Cesagum® LN-**1**), citrus pectin (Cesapectin® HM Medium Rapid Set), waxy maize starch (C*Gel **042010**®), sodium alginate (Frimulsion ALG (E**401**)®), guar flour (Frimulsion BM®, Polygum **26**/**1**-**75**®), iota carrageen (Frimulsion D**021**®), karaya gum, gellan gum (Kelcogel F®, Kelcogel LT**100**®), galactomannan (Meyprogat **150** ®), tara bean flour (Polygum **43**/**1**®), propylene glycol alginate (Protanal-Ester SD-LB®), sodium hyaluronate, apple pectin, pectin from lemon peel, sodium hyaluronate, tragacanth, tara gum (Vidogum SP **200**®), fermented polysaccharide welan gum (K**1**A**96**) and xanthan gum (Xantural **180**®).

16. A dosage form according to claim **9**, wherein component (c) is at least one opiate or opioid antagonist selected from the group consisting of naloxone, naltrexone, nalmefene, nalid, nalmexone, nalorphine, naluphine and a corresponding physiologically acceptable compound.

17. A dosage form according to claim **9**, wherein component (c) is at least one neuroleptic stimulant antagonist.

18. A dosage form according to claim **9**, wherein component (d) emetic is based on one or more constituents of radix ipecacuanha (ipecac root) and/or is apomorphine.

19. A dosage form according to claim **9**, wherein component (e) is at least one physiologically acceptable dye.

20. A dosage form according to claim **9**, wherein component (f) is at least one bitter substance selected from the group consisting of aromatic oils, fruit aroma substances, denatonium benzoate and mixtures thereof.

21. A dosage form according to claim **9**, wherein the active ingredient or active ingredients (A) is/are spatially separated from component (c) and/or (d) and/or (f), wherein the active ingredient or active ingredients (A) is/are optionally present in at least one subunit (X) and components (c) and/or (d) and/or (f) is/are present in at least one subunit (Y), and, when the dosage form is correctly administered, components (c) and/or (d) and/or (f) from subunit (Y) do not exert their effect in the body and/or on taking.

22. A dosage form according to claim **1**, which comprises at least one active ingredient at least partially in controlled release form.

23. A dosage form according to claim **22**, wherein each of the active ingredients with abuse potential (A) is present in a controlled release matrix.

24. A dosage form according to claim **23**, wherein component (C) and/or component (D) also serve as a controlled release matrix material.

25. A process for the production of a dosage form according to claim **1**, comprising:

mixing components (A), (B), (C) and the optionally present component (D) and the optionally present components (a) to (f) to form a resultant mixture, and

press-forming the resultant mixture, optionally after granulation, to yield the dosage form with preceding, simultaneous, or subsequent exposure to heat.

26. A process according to claim **25**, wherein granulation is performed by means of a melt process.

27. A dosage form obtainable by a process according to claim **25**.

28. A method of treating a therapeutic condition in a patient suffering therefrom, said method comprising administering to said patient a dosage form according to claim **1**.

29. The method according to claim **28**, wherein the therapeutic condition is pain.

30. A dosage form according to claim **1**, wherein the polymer (C) is polyethylene oxide having a molecular weight of from 1-15 million g/mol.

31. A dosage form according to claim **1**, wherein the one or more active ingredients with abuse potential (A) is/are selected from the group consisting of oxymorphone, oxycodone, tapentadol and the physiologically acceptable salts thereof.

32. A dosage form according to claim **31**, which is in the form of a tablet.

33. A dosage form according to claim **1**, wherein the content of polymer (C) is at least 30% by weight relative to the total weight of the dosage form.

34. A dosage form according to claim **1**, which is in the form of a tablet, wherein the one or more active ingredients with abuse potential (A) is/are selected from the group consisting of oxymorphone, oxycodone, tapentadol and the physiologically acceptable salts thereof; wherein the polymer (C) is polyethylene oxide having a molecular weight of from 1-15 million g/mol;

and wherein the content of polymer (C) is at least 30% by weight relative to the total weight of the dosage form.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	: 8,309,060 B2
APPLICATION NO.	: 13/346257
DATED	: November 13, 2012
INVENTOR(S)	: Johannes Bartholomaus et al.

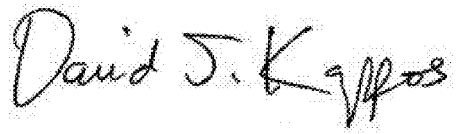
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 19, line 59, “300 mg” should read -- 150 mg --.

Column 24, line 9, “30%” should read -- 60% --.

Column 24, line 18, “30%” should read -- 60% --.

Signed and Sealed this
Twenty-fifth Day of December, 2012



David J. Kappos
Director of the United States Patent and Trademark Office

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TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

November 26, 2013

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: *8,536,130*
ISSUE DATE: *September 17, 2013*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

M. TARVER
Certifying Officer

GRT-NUC00044323



US008536130B2

(12) **United States Patent**
Christoph et al.

(10) **Patent No.: US 8,536,130 B2**
(45) **Date of Patent: Sep. 17, 2013**

(54) **USE OF 1 PHENYL-3-DIMETHYLAMINO-PROPANE COMPOUNDS FOR TREATING NEUROPATHIC PAIN**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 195 days.

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(22) Filed: **Aug. 4, 2010**

(65) **Prior Publication Data**

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(63) Continuation of application No. 12/045,830, filed on Mar. 11, 2008, now abandoned.

(60) Provisional application No. 60/906,220, filed on Mar. 12, 2007.

(30) **Foreign Application Priority Data**

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(51) **Int. Cl.**
A61K 38/00 (2006.01)
A61K 31/275 (2006.01)

(52) **U.S. Cl.**
USPC **514/18.2**; 514/529; 514/646; 514/452; 514/456; 514/434

(58) **Field of Classification Search**
USPC 514/18.2, 529, 646, 452, 456, 434
See application file for complete search history.

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(57) **ABSTRACT**

Use of 1-phenyl-3-dimethylaminopropane compounds for the production of medicaments for treating neuropathic pain, preferably polyneuropathic pain, also preferably diabetic neuropathic pain, more preferably diabetic peripheral neuropathic pain, and furthermore preferably for treating diabetic peripheral neuropathy.

6 Claims, No Drawings

USE OF 1 PHENYL-3-DIMETHYLAMINO-PROPANE COMPOUNDS FOR TREATING NEUROPATHIC PAIN

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 12/045,830, filed Mar. 11, 2008, now abandoned, which in turn claimed priority from U.S. provisional patent application No. 60/906,220, filed Mar. 12, 2007 and Federal Republic of Germany patent application no. DE 10 2007 012 165.4, filed Mar. 12, 2007, the entire disclosures of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

The present invention relates to the use of 1-phenyl-3-dimethylaminopropane compounds for the production of medicaments for treating neuropathic, preferably mononeuropathic and/or polyneuropathic pain, particularly preferably polyneuropathic pain, and also preferably diabetic neuropathic pain, preferably diabetic peripheral neuropathic pain, and furthermore preferably for treating diabetic peripheral neuropathy.

The normal physiological pain sensation, which serves as a protective function for the organism, is transmitted via nerve fibres as a response to corresponding painful stimuli. This is referred to as nociceptive pain. This nociceptive pain may be acute or chronic, somatic or visceral, and may be present with or without an inflammatory component. Appropriate stimuli may be mechanical (e.g. pressure), thermal (e.g. heat) or chemical (e.g. acid). Also, electrical stimuli may be perceived as painful.

In contrast to nociceptive pain—and also in most cases not treatable with the same means—neuropathic pain (a non-nociceptive pain; for a review see Hansson et al., 2001 Neuropathic Pain; Pathophysiology and Treatment in Progress in Pain Research and Management, Vol. 21 eds. Hansson et al. IASP Press, Seattle; Bridges et al., 2001 Br J Anaesthesia 87:12-26) is characterized by the occurrence of spontaneous pain and/or pain triggered by abnormal stimuli. Spontaneously occurring pain results for example from so-called ectopic activity of the pain-conducting nerve fibres. In this case the nerve fibre sends a pain signal from the periphery to the central nervous system even though there was no appropriate stimulus. An example of pain that is triggered by an abnormal stimulus is the phenomenon of allodynia. Allodynia is defined as a painful sensation produced by a normally non-painful stimulus. Allodynia is not restricted to neuropathic pain. Thus, allodynia occurs for example in non-neuropathic conditions such as sunburn or arthritis. The underlying mechanisms of allodynia differ however in principle from one another and can be classified by a detailed medical case history and investigation.

A further example of abnormal pain sensation is hyperalgesia. In this case a normally painful stimulus is perceived as producing a more severe pain than would be the case in a healthy situation. This type of increased pain perception occurs not only in neuropathic pain but also for example in inflammatory pain, where however it has a different cause (inflammation) than in neuropathic pain.

Various metabolic diseases may be the cause of neuropathic changes and may subsequently be implicated in neuropathic pain. An example of such a neuropathy is diabetic neuropathy, which occurs in a large number of patients suffering from diabetes mellitus and may be associated with a large number of clinical symptoms such as a feeling of numbness, tingling sensation, or pain. The most common form of diabetic neuropathy is distal symmetrical sensomotor polyneuropathy.

Neuropathic pain occurs inter alia after damage to peripheral or central nerves and can therefore be induced and observed in animal experiments by targeted lesions of individual nerves. Two possible animal models are the nerve lesion according to Bennett (Bennett and Xie, 1988 Pain 33:87-107) as well as that according to Chung (Kim and Chung, 1992 Pain 50:355-363). In the Bennett model the sciatic nerve is bound unilaterally with loose ligatures; in the Chung model two spinal nerves are bound unilaterally. In both cases the development of symptoms of neuropathic pain can be observed and quantified by means of thermal or mechanical allodynia.

A known animal model for investigating diabetic neuropathy is the induction of diabetes in rodents by administration of a single dose of streptozotocin, an antibiotic extract from *Streptomyces acromogenes*, which selectively damages the 6 cells of the pancreas. After some time the animals exhibit typical symptoms of diabetic neuropathic pain, such as for example mechanical, thermal or chemical hyperalgesia (Courteix et al., 1993 Pain 53:81-88).

To treat neuropathic pain, among other things, gabapentin is used, which however is relatively ineffective, and then only at significant dosages. On the other hand morphine is also often used, the range of side effects of which are, as is known, not without problems. Against the background of the prior art there was therefore a need for compounds with a favorable ratio of effectiveness to side effects, and to provide compounds for the treatment of neuropathic pain.

SUMMARY OF THE INVENTION

An object of the present invention was accordingly to discover compounds that are effective in treating neuropathic pain, in particular polyneuropathic pain and especially diabetic pain.

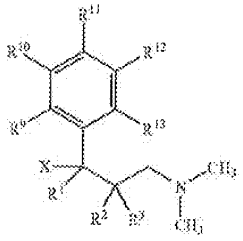
A further object of the invention was to provide a new method of effectively treating neuropathic pain without excessive side effects.

The achievement of these objects is complicated by the fact that a large to overwhelming proportion of the substances effective in treating nociceptive pain—such as acute pain—are not effective at all, or are only slightly effective, in treating neuropathic pain.

It has now surprisingly been found that the compounds disclosed hereinbelow are highly effective in treating neuropathic pain, and surprisingly particularly effective in treating polyneuropathic and diabetic neuropathic pain.

Accordingly, the present invention provides for the use of a 1-phenyl-3-dimethylaminopropane compound corresponding to formula I

I



wherein
X is OH, F, Cl, OC(O)CH_3 or H, preferably OH, F, OC(O)CH_3 or H;
R^1 is saturated and unsubstituted, branched or unbranched C_{1-4}-alkyl, preferably CH_3, C_2H_5, C_4H_9 or t-butyl, in particular CH_3 or C_2H_5;
R^2 and R^3 are independently selected from the group consisting of H and saturated and unsubstituted, branched or unbranched C_{1-4}-alkyl, preferably H, CH_3, C_2H_5, i-propyl or t-butyl, in particular H or CH_3, especially preferably R^3═H; and
three or four of R^9 to R^{13} correspond to H, and the remainder of R^9 to R^{13} are independently selected from the group consisting of H, Cl, F, OH, CF_2H, CF_3, saturated and unsubstituted, branched or unbranched C_{1-4}-alkyl; OR^{14} and SR^{14}, wherein R^{14} is saturated and unsubstituted, branched or unbranched C_{1-3}-alkyl; preferably the remainder of R^9 to R^{13} are independently H, Cl, F, OH, CF_2H, CF_3, OCH_3 or SCH_3; or R^{12} and R^{11} form a 3,4-OCH═CH ring,
or a pharmaceutically acceptable salt thereof
for the treatment of neuropathic pain.

In particular
if R^9, R^{11} and R^{13} correspond to H, one of R^{10} and R^{12} also corresponds to H, while the other is selected from the group consisting of Cl, F, OH, CF_2H, CF_3, OR^{14} or SR^{14}, preferably OH, CF_2H, OCH_3 or SCH_3; or
if R^9 and R^{13} correspond to H and R^{11} corresponds to OH, OCH_3, Cl or F, preferably to Cl, then one of R^{10} and R^{12} also corresponds to H, while the other corresponds to OH, OCH_3, Cl or F, preferably Cl; or
if R^9, R^{10}, R^{12} and R^{13} correspond to H, R^{11} is selected from CF_3, CF_2H, Cl or F, preferably F; or
if R^{10}, R^{11} and R^{12} correspond to H, one of R^9 and R^{13} also corresponds to H, while the other is selected from OH, OC_2H_5 or OC_3H_7.

The compounds optionally may be used in the form of their racemates, their pure stereoisomers, in particular enantiomers or diastereomers, or in the form of mixtures of the stereoisomers, in particular of the enantiomers or diastereomers, in an arbitrary mixture ratio; in the prepared form or in the form of their acids or their bases or in the form of their salts, in particular the physiologically compatible salts, or in the form of their solvates, in particular the hydrates.

The neuropathic pain to be treated may preferably be mononeuropathic and/or polyneuropathic pain, particularly preferably polyneuropathic pain, and furthermore preferably diabetic neuropathic pain, especially preferably diabetic peripheral neuropathic pain. The method of the invention may also preferably be used for treating diabetic neuropathy, and most preferably for treating diabetic peripheral neuropathy.

About 1% of the population suffers from neuropathic pain, in particular polyneuropathic pain, which is one of the most difficult types of pain to treat. There is therefore a need for effective medication for treating in particular diabetic neuropathic pain, especially in patients who are sensitive to the side effects of NSAID analgesics and to μ-opioid agonists, antidepressants and anticonvulsants available on the market, or whose pain cannot be adequately treated with other non-opioid analgesics, antidepressants and anticonvulsants.

Surprisingly it has been found that the aforementioned substances are extremely effective in the two most important in vivo models of neuropathic pain and, what is particularly surprising and should be emphasised, especially in the in vivo model for diabetic neuropathy. The particular selectivity as regards polyneuropathic and diabetic neuropathic pain is shown in further in vivo models (Example 6), and is confirmed by a marked difference in the efficacy (by a factor of 3!). Furthermore, gabapentin was significantly less effective than these compounds.

In particular the present application provides for the use of the substance (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol, a centrally active analgesic, which has a dual mode of action (μ-opioid receptor agonist and an inhibitor of noradrenaline uptake) coupled with low opioid-typical side effects, in contrast to opioids currently used and available on the market, for the treatment of polyneuropathic, preferably diabetic neuropathic and more particularly diabetic peripheral neuropathic pain.

In the context of the present invention alkyl and cycloalkyl radicals are understood to denote saturated and unsaturated (but not aromatic), branched, unbranched and cyclic hydrocarbons, which may be unsubstituted or monosubstituted or polysubstituted. In this connection C_{1-2}-alkyl denotes C1- or C2-alkyl, C_{1-3}-alkyl denotes C1-, C2- or C3-alkyl, C_{1-4}-alkyl denotes C1-, C2-, C3- or C4-alkyl, C_{1-5}-alkyl denotes C1-, C2-, C3-, C4- or C5-alkyl, C_{1-6}-alkyl denotes C1-, C2-, C3-, C4-, C5- or C6-alkyl, C_{1-7}-alkyl denotes C1-, C2-, C3-, C4-, C5-, C6- or C7-alkyl, C_{1-8}-alkyl denotes C1-, C2-, C3-, C4-, C5-, C6-, C7- or C8-alkyl, C_{1-10}-alkyl denotes C1-, C2-, C3-, C4-, C5-, C6-, C7-, C8, —C9- or C10-alkyl and C_{1-18}-alkyl denotes C1-, C2-, C3-, C4-, C5-, C6-, C7-, C8-, C9-, C10-, C11-, C12-, C13-, C14-, C15-, C16-, C17- or C18-alkyl. In addition C_{3-4}-cycloalkyl denotes C3- or C4-cycloalkyl, C_{3-5}-cycloalkyl denotes C3-, C4 or C5-cycloalkyl, C_{3-6}-cycloalkyl denotes C3-, C4-, C5- or C6-cycloalkyl, C_{3-7}-cycloalkyl denotes C3-, C4-, C5-, C6- or C7-cycloalkyl, C_{3-8}-cycloalkyl denotes C3-, C4-, C5-, C6-, C7- or C8-cycloalkyl, C_{4-5}-cycloalkyl denotes C4- or C5-cycloalkyl, C_{4-6}-cycloalkyl denotes C4-, C5- or C6-cycloalkyl, C_{4-7}cycloalkyl denotes C4-, C5-, C6- or C7-cycloalkyl, C_{5-6}-cycloalkyl denotes C5- or C6-cycloalkyl and C_{5-7}-cycloalkyl denotes C5-, C6- or C7-cycloalkyl. With regard to cycloalkyl the term also includes saturated cycloalkyls in which one or two carbon atoms are replaced by a heteroatom S, N or O. The term cycloalkyl however in addition also includes in particular monounsaturated or polyunsaturated, preferably monounsaturated, cycloalkyls without a heteroatom in the ring, provided that the cycloalkyl does not form an aromatic system. The alky and cycloalkyl radicals are preferably methyl, ethyl, vinyl(ethenyl), propyl, allyl(2-propenyl), 1-propinyl, methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1,1-di-methylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, hexyl, 1-methylpentyl, cyclopropyl, 2-methylcyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cycloheptyl, cyclooctyl, but also adamantyl. CHF_2, CF_3 or CH_2OH as well as pyrazolinone, oxopyrazolinone, [1,4]dioxane or dixolane.

At the same time, in connection with alkyl and cycloalkyl—unless expressly defined otherwise—the term "substituted" within the meaning of the present invention denotes the substitution of at least one (optionally also several) hydrogen atom(s) by F, Cl, Br, I, NH_2, SH or OH, in which "polysubstituted" and "substituted" in the case of polysubstitution is understood to mean that the substitution occurs multiply with the same or different substituents on different as well as on the same atoms, for example triple substitution on the same C atom as in the case of CF_3, or at different sites, as in the case of —CH(OH)—CH═CH—$CHCl_2$. Particularly preferred substituents in this connection are F, Cl and OH. With regard to cycloalkyl the hydrogen atom may also be replaced by OC_{1-3}-alkyl or C_{1-3}-alkyl (in

each case monosubstituted or polysubstituted, or unsubstituted) in particular by methyl, ethyl, n-propyl, i-propyl, CF_3, methoxy or ethoxy.

The term $(CH_2)_{3-6}$ is understood to denote —CH_2—CH_2—CH_2—, —CH_2—CH_2—CH_2—CH_2—, —CH_2—CH_2—CH_2—CH_2— and —CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—, the term $(CH_2)_{1-4}$ is understood to denote —CH_2—, —CH_2—CH_2—, —CH_2—CH_2—CH_2— and —CH_2—CH_2—CH_2—CH_2—, and similarly the term $(CH_2)_{4-5}$ is understood to denote —CH_2—CH_2—CH_2—CH_2— and —CH_2—CH_2—CH_2—CH_2—CH_2—, etc.

An aryl radical is understood to denote ring systems with at least one aromatic ring, but without heteroatoms in even only one of the rings. Examples are phenyl, naphthyl, fluoranthenyl, fluorenyl, tetralinyl or indanyl, in particular 9H-fluorenyl or anthracenyl radicals, which may be unsubstituted or monosubstituted or polysubstituted.

A heteroaryl radical is understood to denote heterocyclic ring systems with at least one unsaturated ring, which may contain one or more heteroatoms from the group nitrogen, oxygen and/or sulphur and may also be monosubstituted or polysubstituted. Examples of heteroaryl compounds that may be mentioned include furan, benzofuran, thiophene, benzothiophene, pyrrole, pyridine, pyrimidine, pyrazine, quinoline, isoquinoline, phthalazine, benzo[1,3,5]thiadiazole, benzothiazole, indole, benzotriazole, benzodioxolane, benzodioxane, carbazole, indole and quinazoline.

The term salt is understood to denote any form of the active constituent according to the invention in which this adopts an ionic form or is charged, and is coupled to a counter ion (a cation or anion) or is present in solution. The term is also understood to include complexes of the active constituent with other molecules and ions, in particular complexes that are complexed via ionic interactions. In particular the term is understood to denote (and this is also a preferred embodiment of the invention) physiologically compatible salts, in particular physiologically compatible salts with cations or bases and physiologically compatible salts with anions or acids or also a salt formed with a physiologically compatible acid or a physiologically compatible cation.

The term physiologically compatible is understood to mean that the substance, in particular the salt as such, is compatible when used in humans or mammals, and therefore for example does not act in a non-physiological manner (e.g. is not toxic).

The term physiologically compatible salt with anions or acids is understood within the meaning of the present invention to denote salts of at least one of the compounds according to the invention—generally protonated, for example on the nitrogen atom—as cation with at least one anion, which are physiologically compatible, especially when used in humans and/or mammals. In particular the term is understood within the meaning of the present invention to denote the salt formed with a physiologically compatible acid, namely salts of the respective active constituent with inorganic or organic acids, which are physiologically compatible, especially when used in humans and/or mammals. Examples of physiologically compatible salts of specific acids are salts of the following: hydrochloric acid, hydrobromic acid, sulphuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, malic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid, 1,1-dioxo-1,2-dihydro $1\lambda^6$-benzo[3]isothiazol-3-one (saccharinic acid), monomethylsebacic acid, 5-oxo-proline, hexane-1-sulfonic acid, nicotinic acid, 2-, 3- or 4-aminobenzoic acid, 2,4,6-trimethylbenzoic acid, α-lipoic acid, acetylglycine, acetylsalicylic acid, hippuric acid and/or aspartic acid. The hydrochloride salt is particularly preferred.

The term salt formed with a physiologically compatible acid is understood within the meaning of the present invention to denote salts of the respective active constituent with inorganic or organic acids, which are physiologically compatible, especially when used in humans and/or mammals. The hydrochloride is particularly preferred. Examples of physiologically compatible acids include the following: hydrochloric acid, hydrobromic acid, sulphuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid, 1,1-dioxo-1,2-dihydro $1\lambda^6$-benzo[3]isothiazol-3-one (saccharinic acid), monomethylsebacic acid, 5-oxo-proline, hexane-1-sulfonic acid, nicotinic acid, 2-, 3- or 4-aminobenzoic acid, 2,4,6-trimethylbenzoic acid, α-lipoic acid, acetylglycine, acetylsalicylic acid, hippuric acid and/or aspartic acid.

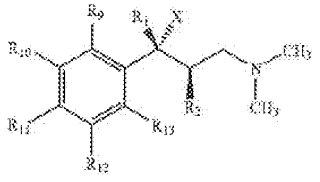
The term physiologically compatible salts with cations or bases is understood within the meaning of the present invention to denote salts of at least one of the compounds according to the invention—generally a (deprotonated) acid—as anion with at least one, preferably inorganic, cation, which are physiologically compatible, especially when used in humans and/or mammals. Particularly preferred are the salts of the alkali and alkaline earth metals, but also salts with NH_4^+, in particular however (mono) or (di) sodium, (mono) or (di) potassium, magnesium or calcium salts.

The term salt formed with a physiologically compatible cation is understood within the meaning of the present invention to denote salts of at least one of the respective compounds as anion with at least one inorganic cation, which are physiologically compatible, especially when used in humans and/or mammals. Particularly preferred are the salts of the alkali and alkaline earth metals, but also NH_4^+, in particular however (mono) or (di)sodium, (mono) or (di)potassium, magnesium or calcium salts.

The compounds used according to the invention and their preparation are in principle known from DE 44 26 245 A1 with regard to the 1-phenyl-3-dimethylaminopropane compounds according to the general Formula I. All compounds other than these specific compounds can easily be prepared by the person skilled in the art in a similar way to the synthesis pathways described there.

In a particularly preferred variant of this embodiment, with regard to the 1-phenyl-3-dimethylaminopropane compounds of the general Formula I used according to the invention where R^3=H, these are present in the form of the diastereomers with the relative configuration Ia

Ia



in particular in mixtures with a larger proportion of this diastereomer compared to the other diastereomer, or are used as an isolated diastereomer.

It is particularly preferred if the 1-phenyl-3-dimethylaminopropane compound of Formula I used according to the invention is selected from the group consisting of:

(2RS,3RS)-1-dimethylamino-3-(3-methoxyphenyl)-2-methyl-pentan-3-ol,
(+)-(2R,3R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methyl-pentan-3-ol,
(2R,3R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methyl-pentan-3-ol,
(−)-(2S,3S)-1-dimethylamino-3-(3-methoxyphenyl)-2-methyl-pentan-3-ol,
(2S,3S)-1-dimethylamino-3-(3-methoxyphenyl)-2-methyl-pentan-3-ol,
(2RS,3RS)-3-(3,4-dichlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
(2RS,3RS)-3-(3-difluoromethylphenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
(2RS,3RS)-1-dimethylamino-2-methyl-3-(3-methylsulfanylphenyl)-pentan-3-ol,
(3RS)-1-dimethylamino-3-(3-methoxyphenyl)-4,4-dimethylpentan-3-ol,
(2RS,3RS)-3-(3-dimethylamino-1-ethyl-1-hydroxy-2-methylpropyl)-phenol,
(1RS,2RS)-3-(3-dimethylamino-1-hydroxy-1,2-dimethylpropyl)-phenol,
(+)-(1R,2R)-3-(3-dimethylamino-1-hydroxy-1,2-dimethylpropyl)-phenol,
(1R,2R)-3-(3-dimethylamino-1-hydroxy-1,2-dimethylpropyl)phenol,
(−)-(1S,2S)-3-(3-dimethylamino-1-hydroxy-1,2-dimethylpropyl)-phenol,
(1S,2S)-3-(3-dimethylamino-1-hydroxy-1,2-dimethylpropyl)phenol,
(RS,RS)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol,
(−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl) phenol,
(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol,
(+)-(1S,2S)-3-(3-dimethylamino-1-ethyl-2-methylpropyl) phenol,
(1S,2 S)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol,
(+)-(1R,2R)-acetic acid-3-dimethylamino-1-ethyl-1-(3-methoxy-phenyl)-2-methyl propyl ester,
(2RS,3RS)-3-(4-chlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
(+)-(2R,3R)-3-(3-dimethylamino-1-ethyl-1-hydroxy-2-methylpropyl)-phenol,
(2RS,3RS)-4-dimethylamino-2-(3-methoxyphenyl)-3-methylbutan-2-ol and
(+)-(2R,3R)-4-dimethylamino-2-(3-methoxyphenyl)-3-methylbutan-2-ol; and
physiologically compatible salts thereof. Hydrochloride salts are preferred.

Particularly preferred substances include:
(RS,RS)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol,
(−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl) phenol,
(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol,
(−)-(1S,2S)-3-(3-dimethylamino-1-ethyl-2-methylpropyl) phenol,
(1S,2S)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol, and physiologically compatible salts thereof.

Especially preferred compounds are:
(−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl) phenol,
(1R,2R)-3-(3-Dimethylamino-1-ethyl-2-methylpropyl)phenol, or physiologically compatible salts thereof.

The pharmaceutical compositions of the invention, which comprise one or more of the aforementioned compounds according to the invention, are useful for treating neuropathic pain, preferably mono- and/or polyneuropathic pain, particularly preferably polyneuropathic pain, furthermore preferably diabetic neuropathic pain, more preferably diabetic peripheral neuropathic pain, and in addition preferably for treating diabetic neuropathy, and particularly preferably for treating diabetic peripheral neuropathy. In accordance with the invention the compositions contain at least one aforementioned active constituent used according to the invention, as well as optionally suitable additives and/or auxiliary substances.

Suitable additives and/or auxiliary substances within the scope of the present invention include all substances known to persons skilled in the art for producing galenical formulations. The selection of these auxiliary substances as well as the amounts to be used depend on whether the medicament is to be administered orally, intravenously, intraperitonealy, intradermally, intramuscularly, intranasally, buccally or topically. For oral administration, suitable preparations may take the form of tablets, chewable tablets, coated pills, capsules, granules, drops, juices or syrups, while for parenteral, topical and inhalative administration, suitable preparations may be formulated as solutions, suspensions, readily reconstitutable dry preparations as well as sprays. A further possible form is as suppositories for rectal administration. Examples of percutaneous administration forms include use in a depot in dissolved form, in a carrier film or a plaster, optionally with the addition of agents promoting penetration of the skin.

Examples of auxiliary substances and additives for oral administration forms include disintegrants, lubricants, binders, fillers, mold release agents, optionally solvents, taste enhancers, sugars, in particular carriers, diluents, colorants, antioxidants, etc. For suppositories there may be used inter alia waxes or fatty acid esters, and for parenteral application agents there may be used carriers, preservatives, suspension aids, etc. The compounds according to the invention may be released in a delayed manner from orally, rectally or percutaneously usable preparation forms. In the medical indications for use according to the invention corresponding Retard formulations, in particular in the form of a "once daily" preparation, which need to be taken only once a day, are especially preferred for use in treating many medical indications for which the active substances of the invention are suitable.

The amounts of active constituent to be administered to patients vary depending on the patient's weight, type of application, and the severity of the medical condition. Preferred are medicaments that contain at least 0.05 to 90.0% of the active constituent, in particular low active dosages, in order to avoid side effects. Normally 0.1 to 5000 mg/kg, in particular 1 to 500 mg/kg and preferably 2 to 250 mg/kg of body weight of at least one compound used according to the invention are administered. However, the administration of 0.01-5 mg/kg, preferably 0.03 to 2 mg/kg and especially 0.05 to 1 mg/kg of body weight is also preferred and customary.

Examples of suitable auxiliary substances for inclusion in the pharmaceutical compositions according to the invention include water, ethanol, 2-propanol, glycerol, ethylene glycol, propylene glycol, polyethylene glycol, polypropylene glycol, glucose, fructose, lactose, sucrose, dextrose, molasses, starch, modified starch, gelatin, sorbitol, inositol, mannitol, microcrystalline cellulose, methylcellulose, carboxymethylcellulose, cellulose acetate, shellac, cetyl alcohol, polyvi-

nylpyrrolidone, paraffins, waxes, natural and synthetic gums, acacia gum, alginates, dextran, saturated and unsaturated fatty acids, stearic acid, magnesium stearate, zinc stearate, glyceryl stearate, sodium lauryl sulfate, edible oils, sesame oil, coconut oil, ground nut oil, soya bean oil, lecithin, sodium lactate, polyoxyethylene and polyoxypropylene fatty acid esters, sorbitan fatty acid esters, sorbic acid, benzoic acid, citric acid, ascorbic acid, tannic acid, sodium chloride, potassium chloride, magnesium chloride, calcium chloride, magnesium oxide, zinc oxide, silicon dioxide, titanium oxide, titanium dioxide, magnesium sulphate, zinc sulphate, calcium sulphate, potassium carbonate, calcium phosphate, dicalcium phosphate, potassium bromide, potassium iodide, talcum, kaolin, pectin, crospovidone, agar and bentonite.

Medicaments and pharmaceutical compositions according to the invention may be prepared using agents, equipment, methods and processes known in the prior art for producing pharmaceutical formulations, such as are described, for example, in "Remington's Pharmaceutical Sciences", edited by A. R. Gennaro, 17th Ed., Mack Publishing Company, Easton, Pa. (1985), in particular in Part 8, Chapters 76 to 93.

Thus, for example, for a solid formulation such as a tablet, the active constituent of the medicament can be granulated with a pharmaceutical carrier, for example conventional tablet constituents such as maize starch, lactose, sucrose, sorbitol, talcum, magnesium stearate, dicalcium phosphate or pharmaceutically acceptable gums, and pharmaceutical diluents, such as for example water, in order to form a solid composition that contains the active constituent in homogeneous distribution. A homogeneous distribution is understood here to mean that the active constituent is distributed uniformly over the whole composition, so that the latter can be subdivided without any problem into identically active unit dose forms such as tablets, pills or capsules. The solid composition is then subdivided into unit dose forms. The tablets or pills of the medicament according to the invention or of the compositions according to the invention can also be coated or compounded in some other way so as to produce a dose form having delayed release. Suitable coating agents are inter alia polymeric acids and mixtures of polymeric acids with materials such as for example schellac, cetyl alcohol and/or cellulose acetate.

Even if the medicaments prepared according to the invention exhibit only slight side effects, it can for example be advantageous, in order to avoid certain forms of dependence, to employ apart from the aforementioned compound according to the invention also morphine antagonists, in particular naloxone, naltrexone and/or levallorphan. In tests it was found for example for morphine and compound 10 (see Example 0 hereinafter) that the substances are also effective with naloxone in treating neuropathic pain.

The invention also relates to a method for treating neuropathic pain, for treating neuropathic, preferably mononeuropathic and/or polyneuropathic pain, particularly preferably polyneuropathic pain, and in addition preferably for treating diabetic neuropathic pain, preferably diabetic peripheral neuropathic pain, and in addition preferably for treating diabetic neuropathy, particularly preferably diabetic peripheral neuropathy, in which at least one of the aforementioned compounds is used according to the invention.

The following examples are intended to describe the invention in more detail, without however restricting the subject-matter of the invention.

EXAMPLES

Example 0

Tested Substances

The following compounds were tested and are hereinafter correspondingly abbreviated as compound (or Comp.) 1, etc. in Table 1:

TABLE 1

Name:	Compound
(2RS,3RS)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol; hydrochloride	1
(2S,3S)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol; hydrochloride	2
(2R,3R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol; hydrochloride	3
(1RS,2RS)-3-(3-dimethylamino-1-hydroxy-1,2-dimethylpropyl)-phenol; hydrochloride	5
(1S,2S)-3-(3-dimethylamino-1-hydroxy-1,2-dimethylpropyl)phenol; hydrochloride	6
(1R,2R)-3-(3-dimethylamino-1-hydroxy-1,2-dimethylpropyl)phenol, hydrochloride	7
(2RS,3RS)-3-(difluoromethylphenyl)-1-dimethylamino-2-methylpentan-3-ol; hydrochloride	8
(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol; hydrochloride	9
(1S,2S)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol, hydrochloride	10
3-(3-dimethylamino-1,2-dimethylpropenyl)-phenol; hydrochloride	14

Additionally:
Morphine Mor
Gabapentin GBP

Example 1

Bennett

Neuropathic Pain in Rats

The effectiveness in treating neuropathic pain was investigated in the Bennett model (chronic constriction injury; Bennett and Xie, 1988, Pain 33: 87-107).

Sprague-Dawley rats weighing 140-160 g are provided with four loose ligatures of the right sciatic nerve under nembutal narcosis. The animals develop a hypersensitivity in the paw innervated by the damaged nerve, which after a healing phase of one week is quantified over about four weeks by means of a 4° C. cold metal plate (cold allodynia). The animals are observed for two minutes on this plate and the number of retractive movements of the damaged paw are measured. The effect of the substance is determined with reference to the base value before application of the substance, at four different times over a period of one hour (15, 30, 45 and 60 minutes after application) and the resultant area under the curve (AUD) as well as the inhibition of cold allodynia at the individual measurement points is expressed in percent effect with reference to the vehicle control (AUD) and to the initial value (individual measurement points). The cohort size is n=10.

The results are summarized together with those from Example 2 in the following Table 2.

Example 2

Chung

In Vivo Experiments According to Chung

Spinal nerve ligatures according to Kim & Chung (1992 Pain 50, 355-363) were applied to the left L5/L6 spinal nerves of male Sprague-Dawley rats. Four to six days after the operation the tactile threshold baseline (withdrawal threshold) was measured on the ipsilateral and contralateral rear paw by an electronic von Frey anaesthesiometer (IITC Life Science, USA). After the test and measurement of the baseline, morphine, gabapentin and some of the aforementioned compounds used according to the invention were administered. The tactile withdrawal thresholds were measured 30 minutes after the administration. The results are expressed as ED50 and % maximal possible effect (% MPE) on the ipsilateral side, in which the baseline is taken as 0% and the withdrawal threshold of a control group is taken as 100% MPE.

The results together with those from Example 1 are summarized in Table 2:

TABLE 2

Testing of the inhibition of neuropathic pain in rats after intraperitoneal (i.p.) or per oral (p.o.) administration

Compound	Cold allodynia ED50 mg/kg i.p. (95% confidence region) [band width of the measurement values]	Tactile allodynia ED50 mg/kg i.p. (95% confidence region) [band width of the measurement values]
Morphine	7.1 [5.7-9.4]	4.6 [3.8-5.7]
Gabapentin	214 (p.o.)	92.6
1	11.1 [9.9-12.3]	10 [
2	26.0	....
3	9.2	....
5	15.0	....
6	32.6	4.65
7	11.1	....
8	17.1	....
9	13	8.15 [3.8-14.5]
10	1.2 [0.6-3.1]	1.5 [0.74-12.54]
14	3.6	....

The compounds all show a marked and dose-dependent inhibition of cold allodynia in Bennett animals and of tactile allodynia in Chung animals. Moreover, in Chung animals in some cases a surprisingly long action duration of up to 30 hours after i.p. application is observed.

Example 3

In Vivo Experiments in Rats with Diabetic Neuropathy

Male Sprague-Dawley rats weighing 160-180 g received an intra-peritoneal injection of streptozotocin (75 mg/kg body weight) dissolved in pH 4.6 citrate buffer. One week later diabetic animals were identified by measuring the blood glucose level, and those with a blood glucose level of ≧17 mM were included in the study. Three and four weeks after administration of streptozotocin the mechanical reaction threshold was measured in diabetic animals by the method of Randall and Selitto (1957 Arch. Int. Pharmacody. 61:409-419) before (pre-test) and at various times after administration of the test substance or vehicle (post-test). Diabetic animals exhibit a reduced mechanical reaction threshold and thus a mechanical hyperalgesia compared to control animals that had simultaneously received vehicle solution instead of streptozotocin. The maximum pressure exerted on the rear paw was 250 g. The end point of the mechanical reaction threshold in grams was determined based on the reaction of the animal (withdrawal of the rear paw, vocalisation or evasive reaction). The size of the cohort in the individual dose stages was n=10. The maximum possible response in percent (% MPE=% of maximum possible effect) was calculated according to the formula:

$$\% \text{ MPE} = (\text{post-test} - \text{pre-test}) / (250 - \text{pre-test}) \times 100.$$

ED50 values (dose at which 50% maximum inhibition occurred) were determined by regression analysis from the % MPE values at the time of the maximum effect.

TABLE 3

Investigation of the inhibition of diabetic neuropathic pain in rats after intraperitoneal (i.p.) substance administration

Compound	Mechanical hyperalgesia ED50 mg/kg i.p. (95% confidence region)	Mechanical hyperalgesia Maximum effect in % MPE at (dose mg/kg i.p.)
Morphine	3.0 (1.8-4.0)	89% (10 mg/kg)
Gabapentin	225 (186-274)	80% (464 mg/kg)
Tramadol	9.2 (7.0-11.8)	86% (21.5 mg/kg)
Compound 9	8.9 (7.1-11.1)	100% (31.6 mg/kg)

Of the tested compounds, compound 9 achieved the highest maximum effect.

Example 4

Tolerance to Morphine

The underlying question is the action of a test substance having a presumably opioid action mechanism in patients who are tolerant or treatment-resistant to morphine. In Bennett animals (according to Example 1) that have developed a tolerance to morphine, the tested compounds still exhibited a significant anti-allodynic action. The action of test substances in naïve (non-morphine-tolerant) animals and morphine-tolerant animals is compared in Table 4. Morphine (Mor) understandably no longer exhibits any effect, whereas the other tested compounds produce a marked inhibition of cold allodynia in these animals. Morphine [10 mg/kg i.p.], Compound 9 [10 and 21.5 mg/kg i.p.], Compound 10 [0.46 and 1 mg/kg i.p.], Compound 4 [21.5 mg/kg i.p.] and Compound 11 [21.5 mg/kg i.p.] were tested analogously to Example 1.

TABLE 4

Examination of the inhibition of neuropathic pain in rats after (intraperitoneal (i.p.) substance administration to naive and morphine-tolerant animals in % AUD.

Compound [dose mg/kg i.p.]	Cold allodynia (% AUD) Morphine-tolerant animals	Cold allodynia (% AUD) Naive animals
Morphine [10]	~22.0	78.6
9 [10]	37.3	49.3
9 [21.5]	36.7	53.4
10 [0.46]	22.9	29.0
10 [1]	39.9	42.7
10 [2.15]	13.0	59.2
4 [21.5]	75.2	65.5
11 [21.5]	42.6	69.2

Example 5

Parenteral Application Form

20 g of Compound 9 are dissolved in 1 liter of water for injection at room temperature and then adjusted by addition of NaCl to isotonic conditions.

Example 6

Comparison of Mononeuropathic and Polyneuropathic Pain

Experimental Procedure

Male Sprague Dawley rats (140-180 g, Janvier, France) are kept under standard conditions (06.00-18.00 hours light, 18.00-06.00 hours darkness; 20°-24° C. room temperature; 35-70% relative atmospheric humidity, tap water and standard feed as desired) in groups of five animals in Macrolon type 4 cages.

Mononeuropathy (Spinal Nerve Ligature, SNL)

Under pentobarbital narcosis (Narcoren, 60 mg/kg i.p., Merial GmbH, Germany) the spinal nerves L5 and L6 are tightly bound unilaterally on the left side with a silk thread (NC silk black, USP 5/0, metric 1, Braun Melsungen AG, Germany) (Kim and Chung, Pain 1992; 50: 355-63). After the operation the animals were allowed to recover for one week and within this time developed a hypersensitivity on the ipsilateral (left) paw. The hypersensitivity to a pressure stimulus can be measured using an electronic von Frey filament (Somedic, Sweden). For this purpose the animals are placed on a grating under a hood. After the animals became accustomed to the surroundings the damaged (ipsilateral, left) and undamaged (contralateral, right) rear paws are subjected to increasing pressure on the underside of the paw until the animal tries to retract the corresponding paw. The median value of five tests defines the withdrawal threshold of a test time point. The animals are tested on both rear paws before and at various times after administration of the substance or vehicle. For each animal the difference between the test value and pre-test for the ipsilateral and contralateral side is determined, and the result is expressed as the mean value (MW) and standard error of the mean (SEM) for the groups consisting in each case of 10 animals. The difference between the mean difference values of the ipsilateral and contralateral side defines the hypersensitivity induced by mononeuropathy. The statistical significance of the effect of a substance is determined on the basis of the difference values compared to the vehicle group for the ipsilateral and contralateral side, by means of bifactorial variance analysis and post hoc analysis according to Bonferroni.

Polyneuropathy (Streptozotocin-Induced Diabetic Neuropathy, STZ)

Rats receive a single i.p. dose of Streptozotocin (STZ, Sigma Aldrich Chemie, Germany) or vehicle (0.1 mM citrate buffer, pH 4.6). After one week the blood sugar values are determined and animals treated with STZ that have a blood sugar value of ≧17 mM are classed as diabetic in the experiment. Diabetic animals develop a hypersensitivity in the rear paws. The hypersensitivity to a pressure stimulus can be measured using a pressure pain instrument (algesiometer; Ugo Basile, Italy) according to the method of Randall and Selitto (Arch. Int. Pharmacodyn. 1957; 111: 409-19) in diabetic animals compared to healthy control animals of the same weight, in the third week after STZ treatment. After the animals had become accustomed to the surroundings, the rear right paw of damaged (diabetic) and undamaged (healthy) animals was subjected to increasing pressure on the upper side of the paw until the corresponding paw is withdrawn or the animal gives a vocal response. This value defines the withdrawal threshold of a test time point. Diabetic and healthy animals are tested before and at various times after administration of the substance or vehicle. For each animal the difference between the test value and pre-test is determined, and for the groups, each consisting of ten animals, the result is expressed as the mean value (MW) and standard error of the mean (SEM). The difference between the mean difference values of the diabetic and healthy animals defines the polyneuropathy-induced hypersensitivity. The statistical significance of the effect of a substance is determined on the basis of the difference values with respect to the vehicle group for diabetic and healthy animals by means of bifactorial variance analysis and post hoc analysis according to Bonferroni.

Results

Mononeuropathic Pain

(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride 9 (0.1-10 mg/kg, i.v., Table 1) shows a dose-dependent increase of the withdrawal threshold on the ipsilateral rear paw. The statistically significant minimal effective dose is 1 mg/kg. The mean difference value between the ipsilateral withdrawal threshold of healthy control animals and the ipsilateral withdrawal threshold of mononeuropathic animals in this series of experiments is 36 g. Complete inhibition of the mononeuropathically-induced withdrawal threshold reduction is thus achieved at values (test value−re-test value) of ≧36 g on the ipsilateral side. Time points at which this value is reached or exceeded are given in bold type in boxes in the table. Contralateral measurement values are not included in this analysis. In the highest dosage group of 10 mg/kg i.v. full inhibition of the mononeuropathically-induced withdrawal threshold reduction is reached after 30 minutes. The contralateral withdrawal threshold is also raised in a dose-dependent manner. The statistically significant minimal effective dose is 10 mg/kg.

TABLE 1

(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride (9) mononeuropathy

Dose (mg/kg, i.v.)	Side		30 min	60 min	180 min
Vehicle	Ipsi	MW	0.70	0.06	-1.33
		SEM	1.16	1.31	1.09
		Significance	n.s.	n.s.	n.s.
	Contra	MW	-4.06	0.83	-3.79
		SEM	2.63	3.77	2.90
		Significance	n.s.	n.s.	n.s.
0.1	Ipsi	MW	1.74	-0.59	-2.24
		SEM	1.55	1.44	1.15
		Significance	n.s.	n.s.	n.s.
	Contra	MW	0.06	-3.13	-4.30
		SEM	4.52	4.12	3.01
		Significance	n.s.	n.s.	n.s.
0.316	Ipsi	MW	5.78	2.21	1.68
		SEM	2.34	2.93	1.41
		Significance	n.s.	n.s.	n.s.
	Contra	MW	0.39	-6.20	2.21
		SEM	4.71	3.03	3.81
		Significance	n.s.	n.s.	n.s.
1	Ipsi	MW	12.86	7.09	2.01
		SEM	2.42	0.80	0.64
		Significance	*	n.s.	n.s
	Contra	MW	2.90	2.45	-6.65
		SEM	3.32	3.92	2.45
		Significance	n.s.	n.s.	n.s.
3.16	Ipsi	MW	18.43	20.32	11.06
		SEM	2.90	2.39	1.45
		Significance	*	*	*
	Contra	MW	8.02	2.85	-0.34
		SEM	4.13	3.09	3.81
		Significance	n.s.	n.s.	n.s.
10	Ipsi	MW	42.05	19.47	13.65
		SEM	3.50	1.52	1.40
		Significance	*	*	*
	Contra	MW	31.85	10.62	4.51
		SEM	3.23	4.92	4.17
		Significance	*	n.s.	n.s.

(test value − pre-test value (g); * $p < 0.05$ with respect to vehicle; n.s. = not significant with respect to vehicle)

Polyneuropathic Pain

(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl) hydrochloride 9 (0.1-1 mg/kg, i.v., Table 2) shows a dose-dependent increase of the withdrawal threshold in the rear paw of diabetic rats. The statistically significant minimal effective dose is 0.3 mg/kg. The mean difference value between the withdrawal threshold of naive control animals and the withdrawal threshold of polyneuropathic animals is in this series of experiments 43 g. Complete inhibition of the polyneuropathically-induced withdrawal threshold reduction is thus achieved at values (test value−pre-test value) of ≧43 g in diabetic animals. Time points at which this value is reached or exceeded are shown in grey in the table. Measurement values of naive animals are not included in this analysis. In the highest dosage group of 1 mg/kg i.v. complete inhibition of the polyneuropathically-induced withdrawal threshold reduction is reached after 15 minutes and 30 minutes. The withdrawal threshold of healthy control animals is also raised in a dose-dependent manner. The statistically significant minimal effective dose is 1 mg/kg.

TABLE 2

(1R, 2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl) hydrochloride (9) polyneuropathy

Dose (mg/kg, i.v.)	Group		15 min	30 min	45 min	60 min
0.1	Diabetes	MW	1.0	-2.0	6.0	-2.0
		SEM	6.4	5.5	3.4	5.5
Vehicle		MW	3.0	2.0	-11.0	0.0
		SEM	4.2	3.6	3.5	3.7
		Significance	n.s.	n.s.	n.s.	n.s.
0.1	Naive	MW	4.0	-12.0	-2.0	-5.0
		SEM	4.8	7.7	5.3	6.2
Vehicle		MW	-9.0	-2.0	-5.0	-3.0
		SEM	4.8	5.1	4.5	2.1
		Significance	n.s.	n.s.	n.s.	n.s.
0.316	Diabetes	MW	35.0	30.0	24.0	16.0
		SEM	9.2	6.3	6.9	4.8
Vehicle		MW	-6.0	-5.0	0.0	1.0
		SEM	3.7	6.7	6.0	3.5
		Significance	*	*	*	n.s.
0.316	Naive	MW	17.0	-5.0	-5.0	2.0
		SEM	3.3	7.3	4.5	2.5
Vehicle		MW	-6.0	-5.0	-14.0	2.0
		SEM	6.7	5.8	6.7	4.4
		Significance	n.s.	n.s.	n.s.	n.s.
1	Diabetes	MW	54.0	49.0	34.0	27.0
		SEM	10.8	8.7	6.5	6.2
Vehicle		MW	1.0	-10.0	4.0	4.0
		SEM	5.9	3.3	6.4	3.4
		Significance	*	*	*	*
1	Naive	MW	42.0	28.0	-2.0	7.0
		SEM	7.6	7.4	6.3	4.5
Vehicle		MW	-4.0	-5.0	-15.0	-2.0
		SEM	5.6	8.7	3.1	3.6
		Significance	*	*	n.s.	n.s.

(test value − pre-test value (g); * $p < 0.05$ with respect to vehicle; n.s. not significant with respect to vehicle)

1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride 9 produces a dose-dependent increase of the pressure-mediated withdrawal threshold in mononeuropathic and polyneuropathic pain. In both pain models (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol produces a selective inhibition of the pathologically induced pain response, without at the same time influencing the normal pain response. A clear difference is found in the level of effectiveness of (1R,2R)-3-(3-dimethylamino-1-

ethyl-2-methyl-propyl)-phenol in both models. Whereas in the polyneuropathic pain model a significant inhibition is already detectable at 0.316 mg/kg i.v., a significant inhibition in the mononeuropathic pain model occurs only at 1 mg/kg i.v., i.e. at a three times higher dosage. A similar behavior is observed at the dosage at which the maximum effect is achieved. In the polyneuropathic pain model complete inhibition is reached at 1 mg/kg i.v., whereas in the mononeuropathic pain model complete inhibition is reached only at 10 mg/kg i.v., i.e. at a ten times higher dosage. These data show that 1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol is particularly suitable for the treatment of polyneuropathic pain states.

The foregoing description and examples have been set forth merely to illustrate the invention and are not intended to be limiting. Since modifications of the described embodiments incorporating the spirit and substance of the invention may occur to persons skilled in the art, the invention should be construed broadly to include all variations within the scope of the appended claims and equivalents thereof.

What is claimed is:

1. A method of treating polyneuropathic pain in a subject suffering therefrom, said method comprising administering to said subject an effective polyneuropathic pain inhibiting amount of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol

or a pharmaceutically acceptable salt thereof.

2. A method according to claim 1, comprising administering a hydrochloride salt of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol.

3. A method according to claim 1, wherein said polyneuropathic pain is diabetic polyneuropathic pain.

4. A method according to claim 1, wherein said polyneuropathic pain is peripheral polyneuropathic pain.

5. A method according to claim 1, wherein said polyneuropathic pain is peripheral diabetic polyneuropathic pain.

6. A method of treating diabetic polyneuropathy in a subject suffering therefrom, said method comprising administering to said subject a pharmacologically effective amount of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol

or a pharmaceutically acceptable salt thereof.

* * * * *

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(19) **United States**

(12) **Reissued Patent**

Buschmann et al.

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(45) **Date of Reissued Patent: Apr. 24, 2007**

(54) **1-PHENYL-3-DIMETHYLAMINOPROPANE COMPOUNDS WITH A PHARMACOLOGICAL EFFECTS**

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(58) **Field of Classification Search** 544/86; 549/362, 348; 558/190, 273; 560/32, 37, 560/66, 250, 252; 514/231.8, 114, 452, 456, 514/488, 534, 546, 653, 654
See application file for complete search history.

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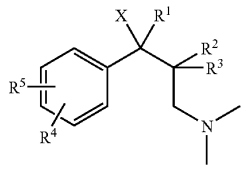
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(57) **ABSTRACT**

1-phenyl-3-dimethylaminopropane compounds corresponding to the formula I

I



a method of preparing them, and the use of these substances as analgesic active ingredients in pharmaceutical compositions.

141 Claims, No Drawings

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1-PHENYL-3-DIMETHYLAMINOPROPANE COMPOUNDS WITH A PHARMACOLOGICAL EFFECTS

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

CROSS REFERENCE TO RELATED APPLICATION

This application is a reissue of U.S. Pat. No. 6,248,737.

BACKGROUND OF THE INVENTION

The present invention relates to 1-phenyl-3-dimethylaminopropane compounds, to a method of preparing them, and to the use of these substances as pharmaceutical active ingredients.

The treatment of chronic and non-chronic pain situations is of great importance in medicine. This is reflected in the large number of publications. Thus, for example, 1-naphthyl-3-aminopropane-1-ols with an analgesic-narcotic effect are known from EP 176 049. Secondary and tertiary alcohols with γ-amino groups are described in J. Pharm. Sci. 59, 1038 (1970) and in J. Prakt. Chem. 323, 793 (1981); phenyl-dimethylaminopropanols containing a para-substituted phenyl radical are described in Chem. Abstr. 54, 20963c (1960) and in Chem. Abstr. 63, 6912e (1965). These compounds also possess analgesic properties. In contrast, the 3-dimethylaminopropan-1-ols containing 2-phenyl radicals described in DE 32 42 922 have an antidepressant effect. The 1-phenyl-propan-1-ols described in J. Pharm. Sci. 57, 1487 (1968) have different pharmacological effects depending on the γ-aza ring.

Opioids have been used for many years as analgesics for the treatment of pain, although they give rise to a series of side effects, for example addiction and dependency, respiratory depression, gastrointestinal inhibition and obstipation. They can therefore only be given over an extended period of time or in higher doses subject to special precautionary measures such as special prescription regulations (Goodman, Gilman in "The Pharmacological Basis of Therapeutics", Pergamon Press, New York (1990)).

Tramadol hydrochloride—(1RS,2RS)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride—assumes a special position amongst centrally-acting analgesics, since this active ingredient gives rise to a pronounced inhibition of pain without the side effects which are known for opioids (J. Pharmacol. Exptl. Ther.4 267, 331 (1993)). Tramadol is a racemate and consists of identical amounts of (+) and (−) enantiomer. In vivo the active ingredient forms the metabolite O-desmethyltramadol, which is likewise present as a mixture of enantiomers. Investigations have shown that both the enantiomers of tramadol and the enantiomers of tramadol metabolites contribute to the analgesic effect (J. Pharmacol. Exp. Ther. 260, 275 (1992)).

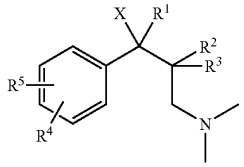
SUMMARY OF THE INVENTION

The underlying object of the present invention was to provide substances with an analgesic effect, which are suitable for the treatment of severe pain without giving rise to the side effects which are typical of opioids.

A further object was to provide analgesic substances which do not exhibit the side effects, for example nausea and vomiting, which occur during treatment with tramadol in some cases.

It has been found that these stringent requirements are fulfilled by certain 1-phenyl-3-dimethylaminopropane compounds. These substances are characterized by a pronounced analgesic effect which is significantly enhanced compared with that of tramadol.

The present invention accordingly relates to 1-phenyl-3-dimethylaminopropane compounds of formula I



in which

X represents OH, F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group;

R^1 is a C_{1-4}-alkyl group;

R^2 represents H or a C_{1-4}-alkyl group and R^3 represents H or a straight chain C_{1-4}-alkyl group, or R^2 and R^3 together constitute a C_{4-7} cycloalkyl radical, and

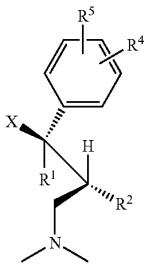
if R^5 is H, R^4 represents meta-O-Z, where Z is H, C_{1-4}-alkyl, $PO(OC_{1-4}\text{-alkyl})_2$, $CO(OC_{1-5}\text{-alkyl})$, $CONH—C_6H_4—(C_{1-3}\text{-alkyl})$ or $CO—C_6H_4—R^7$, wherein R^7 is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^8)_2$, where R^8 is C_{1-4}-alkyl or 4-morpholino, or R^4. represents meta-S-C_{1-3}-alkyl, meta-Cl, meta-F or meta-$CR^9R^{10}R^{11}$, ortho-OH, ortho-O-C_{2-3}-alkyl, para-F or para-$CR^9R^{10}R^{11}$, where R^9, R^{10} and R^{11} represent H or F, or

if R^5 represents Cl, F, OH or O—C_{1-3}-alkyl in the para-position, R^4 represents Cl, F, OH or O—C_{1-3}-alkyl in the meta-position, or

R^4 and R^5 together represent 3,4-OCH═CH— or 3,4-OCH═CHO—, as diastereoisomers or enantiomers in the form of free bases or salts of physiologically acceptable acids.

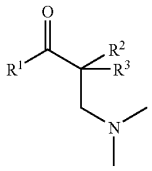
1-phenyl-3-dimethylaminopropane compounds of formula I are preferred in which X constitutes OH, F, Cl or H; R^1 represents a C_{1-4}-alkyl group; R^2 represents H or CH_3, and R^3 represents H or CH_3, and if R^5 is H, R^4 represents OC_{1-3}-alkyl, —OH, —S—C_{1-3}-alkyl, F, Cl, CH_3, —CF_2H or —CF_3 in the meta-position, or para-CF_3, or if R5 is a para-Cl or para-F, R^4 represents meta-Cl or meta-F, or R^4 and R^5 together represent 3,4-OCH═CH—.

1-phenyl-3-dimethylaminopropane compounds of formula I are particularly preferred in which the R^2 and R^3 radicals have different meanings, in the form of their diastereoisomers of configuration Ia

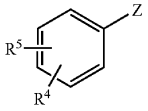


The present invention also relates to a method of preparing 1-phenyl-3-dimethylaminopropane compounds of for-

mula I, in which the variable X represents OH, which is characterized in that a β-dimethylaminoketone of formula II

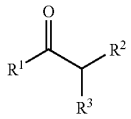


is reacted with an organometallic compound of formula III



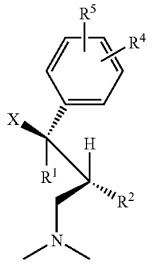
in which Z represents MgCl, MgBr, MgI or Li, to form a compound of formula I in which X represents OH.

The reaction of a β-dimethylaminoketone with a Grignard reagent of formula III, in which Z represents MgCl, MgBr or MgI, or with an organolithium compound of formula III, can be carried out in an a liphatic ether, for example diethyl ether and/or tetrahydrofuran, at temperatures between −70° C. and +60° C. Organolithium compounds of formula II can be obtained by the replacement of halogen by lithium, for example, by reacting a compound of formula III, in which Z represents Cl, Br or I, with a solution of n-butyllithium in n-hexane. β-dimethylaminoketones of formula II can be obtained from ketones of general formula IV

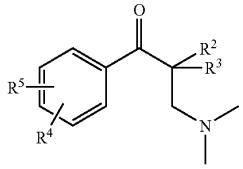


by reaction with dimethylamine hydrochloride and formaldehyde in glacial acetic acid or in a C_{1-4}-alkyl alcohol or by reaction with dimethylammonium ethylene chloride in acetonitrile using acetyl chloride as a catalyst (Synthesis 1973, 703).

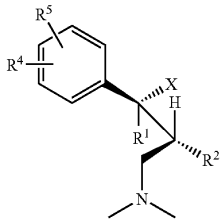
Upon reaction of a β-dimethylaminoketone of formula II, in which the variables R^2 and R^3 have different meanings, with an organometallic compound of formula III, 1-phenyl-3-dimethylaminopropane compounds of formula I are obtained having the relative configuration of formula Ia



in which the X and the dimethylamino group are disposed threo in relation to each other. In contrast, if the reaction for the preparation of 1-phenyl-1-hydroxy-3-aminopropanes were carried out according to the method disclosed in DD 124 521, i.e. if β-aminoketones corresponding to the formula



were reacted with an alkyl Grignard reagent R^1MgHal, this would result in compounds with the relative configuration Ib



in which the [OH] *X* group and the dimethylamino radical are disposed erythro in relation to each other.

1-phenyl-3-dimethylaminopropane compounds of formula I, in which R^4 and/or R^5 constitute the OH group, can be prepared from the corresponding 1-(4(5)-methoxyphenyl)-3-dimethylaminopropanol compounds by selective ether cleavage with diisobutylaluminium hydride in an aromatic hydrocarbon, for example toluene, at a temperature between 60 and 130° C. (Synthesis 1975, 617).

The present invention also relates to a method of preparing 1-phenyl-3-dimethylaminopropane compounds of formula I, in which X represents H, which is characterized in that a compound of formula I, in which X represents Cl, is reacted with zinc borohydride, zinc cyanoborohydride and/or tin cyanoborohydride.

The reaction is usually conducted in a solvent, for example diethyl ether and/or tetrahydrofuran, at a temperature between 0° C. and 30° C.

Compounds of formula I, in which X is H and R^4 and/or R^5 constitute the OH group, can be prepared from the corresponding methoxyphenyl compounds by heating them for several hours with concentrated hydrobromic acid (Chem. Rev. 54, 615 (1954); J. Am. Chem. Soc. 74, 1316 (1952)).

The present invention further relates to a method of preparing 1-phenyl-3-dimethylaminopropane compounds of formula I, where X represents F, which is characterized in that a compound of formula I, in which X represents OH, is reacted with dimethylaminosulfur trifluoride in a solvent.

Suitable solvents include dichloromethane, 1,1,2-trichloroethane and/or toluene. The reaction is usually conducted at a temperature between −50° C. and +30° C. (Org. React. 35, 513 (1988)). If a compound of formula I with X═OH is used in which R^4 and/or R^5 constitute OH groups, these OH groups must be protected before reaction with the fluorine compound, for example by reaction with benzoyl chloride.

The present invention also relates to a method of preparing 1-phenyl-3-dimethylaminopropane compounds of formula I, in which X represents Cl, which is characterized in that a compound of formula I, in which X represents OH, is reacted with thionyl chloride.

The reaction is usually conducted in the absence of solvent at a temperature between 0° C. and 20° C. Replacement of OH by Cl is effected while maintaining the configuration.

The present invention also relates to a method of preparing 1-phenyl-3-dimethylaminopropane compounds of formula I, in which X represents an $OCOR^6$ group where R^6 is a C_{1-3}-alkyl, which is characterized in that a compound of formula I, in which X represents OH, is reacted with an acid chloride Cl—$COOR^6$.

The reaction is preferably conducted in a solvent, for example dichloromethane, toluene and/or tetrahydrofuran, at a temperature between −10° C. and +30° C.

1-phenyl-3-dimethylaminopropane compounds of formula I, in which R^5 is H and R^4 is a meta-phosphate group, meta-carbonate group, meta-carbamate group or meta-carboxylate group, can be obtained by the reaction of the corresponding 1-(3-hydroxyphenyl)-3-dimethylaminopropane compounds of formula I in the form of their alkali salts with an alkali salt of a dialkyl chlorophosphate, with an alkyl chloroformate, with an aryl isocyanate or with a carboxylic acid chloride. These reactions are usually conducted in a solvent, for example toluene, dichloromethane, diethyl ether and/or tetrahydrofuran, at temperatures between −15° C. and +110° C. (Drugs of the Future 16, 443 (1991); J. Med. Chem. 30, 2008 (1987) and 32, 2503 (1989); J. Org. Chem. 43, 4797 (1978); Tetrahedron Lett. 1977, 1571; J. Pharm. Sci. 57, 774 (1968)).

The compounds of formula I can be converted in a known manner into their salts with physiologically acceptable acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid and/or aspartic acid. Salt formation is preferably effected in a solvent, for example diethyl ether, diisopropyl ether, alkyl acetates, acetone and/or 2-butanone. Moreover, trimethylchlorosilane in aqueous solution is suitable for the preparation of hydrochlorides.

1-phenyl-3-dimethylaminopropane compounds of formula I are toxicologically harmless, so that they are suitable as pharmaceutical active ingredients in drugs.

Accordingly, the present invention also relates to the use of a 1-phenyl-3-dimethylaminopropane compound of formula I as a pharmaceutical active ingredient. Compounds of formula I are preferably used for the treatment of pain.

In addition to at least one 1-phenyl-3-dimethylaminopropane compound of formula I, the analgesics according to the invention may contain carriers, fillers, solvents, diluents, colorants and/or binders. The selection of auxiliary substances and of the amounts of the same to be used depends on whether the drug is to be administered orally, intravenously, intraperitoneally, intradermally, intramuscularly, intranasally or locally, for example for infections of the skin, of the mucous membranes or of the eye. Preparations in the form of tablets, dragees, capsules, granules, drops, liquids and syrups are suitable for oral application. Solutions, suspensions, readily reconstitutable dry preparations, and sprays are suitable for parenteral, topical and inhalative applications. Compounds of formula I according to the invention in a deposit in dissolved form or in a patch, optionally with the addition of a skin penetration promoter, are suitable preparations for percutaneous application. Forms of preparations which can be administered orally or percutaneously may effect delayed release of the compounds of formula I according to the invention.

The amount of active ingredient to be administered to patients varies depending on the patient's weight, on the manner of administration, the indication and the degree of severity of the illness. 50 to 500 mg/kg of at least one 1-phenyl-3-dimethylaminopropane compound of formula I are usually administered.

EXAMPLES

The yields of the compounds prepared have not been optimised.

All temperatures are uncorrected.

Unless otherwise indicated, petroleum ether with a boiling point of 50–70° C. was used. The term "ether" denotes diethyl ether.

Silica gel 60 (0.040–0.063 mm) manufactured by E. Merck, Darmstadt, was used as the stationary phase for column chromatography.

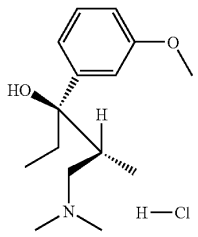
This layer chromatography investigations were conducted using prefabricated silica gel 60 F 254 HPTLC plates manufactured by E. Merck, Darmstadt.

Racemate separation was effected on a Chiracel OD column.

The mixture ratios of the mobile phases for all chromatographic investigations are expressed as volume/volume.

RT denotes room temperature; m.p. denotes melting point.

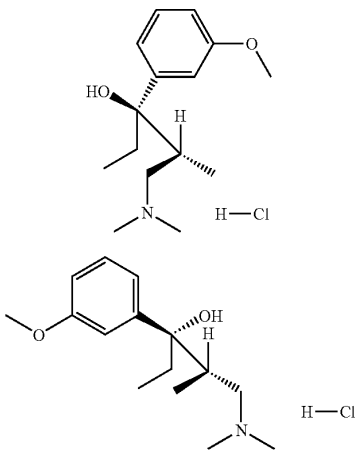
Example 1



(2RS,3RS)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol Hydrochloride(1)

207.63 g (1.11 mole) 3-bromoanisole dissolved in 400 ml dry tetrahydrofuran were added drop-wise to 26.99 g (1.11 mole) magnesium turnings in 150 ml dry tetrahydrofuran so that the reaction mixture boiled gently. After the addition of 3-bromoanisole was complete the mixture was heated under reflux for one hour and thereafter was cooled to 5–10° C. 128.30 g (0.89 mole) 1-dimethylamino-2-methylpentan-3-one dissolved in 400 ml tetrahydrofuran were added at this temperature. The reaction mixture was allowed to stand overnight and then cooled again to 5–10° C. The Grignard solution was decomposed by the addition of 300 ml of 20% ammonium chloride solution. The reaction mixture was diluted with 400 ml ether, the organic phase was separated off and the aqueous phase was extracted twice with 250 ml ether. The combined organic phases were dried over sodium sulphate. After removing the solvent by distillation, the residue (212 g) was taken up in 3200 ml 2-butanone and added to 120.60 g (1.11 mole) trimethylchlorosilane and 20 ml water. 121.5 g of hydrochloride (1) (38% theoretical) with a melting point of 198–199° C. crystallised out at 4–5° C.

Example 2



Enantiomers of (1):

(−)-(2S,3S)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol Hydrochloride(−1)

and

(+)-(2R,3R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol Hydrochloride(+1).

The base was released from (1) with dichloromethane/sodium hydroxide solution. After drying the solution dichloromethane was distilled off under vacuum. The racemate was then separated on the chiral HPLC column. The hydrochlorides, which had a melting point of 150–151° C., were prepared from the enantiomers obtained by reaction with trimethylchlorosilane/water in 2-butanone.

(−1):

yield: 42% theoretical

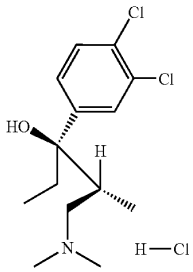
$[\alpha]_{D}^{RT}$=−31.8° (c=0.99; methanol)

(+1):

yield: 41% theoretical

$[\alpha]_{D}^{RT}$+33.0° (c=0.96; methanol)

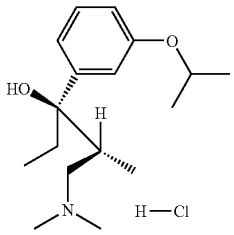
Example 3



(2RS,3RS)-3-(3,4-dichlorophenyl)-1-dimethylamino-2-methylpentan-3-ol Hydrochloride (2)

39 g of crude mixture were prepared analogously to Example 1 from 15 g (105 mmol) 1-dimethylamino-2-methylpentan-3-one, 35.5 g (157 mmole) 4-bromo-1,2-dichlorobenzene and 3.8 g (157 mmole) magnesium turnings. This mixture was introduced on to a 7×40 cm column packed with silica gel and eluted with 4:1 ethyl acetate/methanol. 14.9 g of base were obtained, from which 11.2 g of hydrochloride (2) (31% theoretical) with a melting point of 183–184° C. were obtained with trimethylchlorosilane/water in 2-butanone/diisopropyl ether.

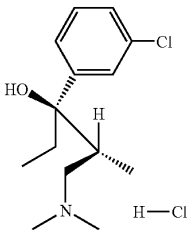
Example 4



(2RS,3RS)-3-(3-isopropoxyphenyl)-1-dimethylamino-2-methylpentan-3-ol Hydrochloride (3)

25 g of crude mixture were prepared analogously to Example 1 from 14.3 g (100 mmol) 1-dimethylamino-2-methylpentan-3-one, 20.0 g (157 mmole) 1-bromo-3-isopropoxybenzene and 2.79 g (115 mmole) magnesium turnings. This mixture was introduced on to a 7×40 cm column packed with silica gel and eluted with 15:1 ethyl acetate/methanol. 9.0 g of base were obtained, from which 8.3 g of hydrochloride (3) (26% theoretical) with a melting point of 133–134° C. were obtained with trimethylchlorosilane/water in 2-butanone.

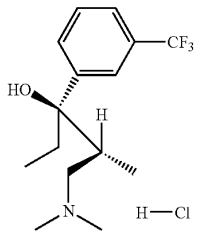
Example 5



(2RS,3RS)-3-(3-chlorophenyl)-1-dimethylamino-2-methylpentan-3-ol Hydrochloride (4)

63 g of crude mixture were obtained under the conditions cited for Example 1 from 38.0 g (270 mmole) 1-dimethylamino-2-methylpentan-3-one, 74.7 g (390 mmol) 1 -bromo-3-chlorobenzene and 9.50 g (390 mmole) magnesium turnings. This mixture was introduced on to a 7×45 cm column packed with silica gel and eluted with 7:1 diisopropyl ether/methanol. 12.8 g of base were obtained, from which 10.8 g of hydrochloride (4) (14% theoretical) with a melting point of 160–162° C. were obtained with trimethylchlorosilane/water in 2-butanone/ether.

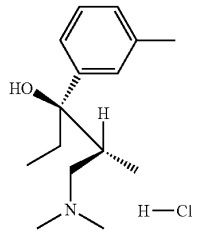
Example 6



(2RS,3RS)-1-dimethylamino-2-methyl-3-(3-trifluoromethylphenyl)-pentan-3-ol Hydrochloride(5)

21.2 g of crude mixture were obtained under the conditions cited for Example 1 from 14.3 g (100 mmole) 1-dimethylamino-2-methylpentan-3-one, 29.3 g (130 mmole) 1-bromo-3-trifluoromethylbenzene and 3.2 g (130 mmole) magnesium turnings. This mixture was introduced on to a 6×40 cm column packed with silica gel and eluted with 10:1 diisopropyl ether/methanol. 9.1 g of base were obtained, from which 7.8 g of hydrochloride (5) (18.5% theoretical) with a melting point of 189–190° C. was obtained with trimethylchlorosilane/water in 2-butanone.

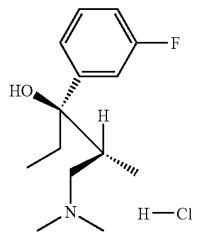
Example 7



(2RS,3RS)-1-dimethylamino-2-methyl-3-(3-m-tolyl)-pentan-3-ol Hydrochloride (6)

75 g of crude mixture were obtained as in Example 1 from 47.3 g (330 mmole) 1-dimethylamino-2-methylpentan-3-one, 64.6 g (400 mmole) 3-bromotoluene and 9.72 g (400 mmole) of magnesium turnings. This mixture was introduced on to a 7×50 cm column packed with silica gel and eluted with 7:1 diisopropyl ether/methanol. 24.3 g of base were obtained, from which 21.5 g of hydrochloride (6) (24% theoretical) with a melting point of 154–155° C. were obtained with trimethylchlorosilane/water in 2-butanone.

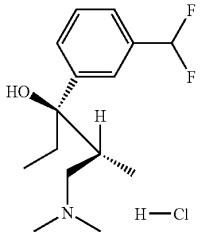
Example 8



(2RS, 3RS)-1-dimethylamino-3-(3-fluorophenyl)-2-methylpentan-3-ol Hydrochloride (7)

70 g of crude mixture were obtained under the conditions cited for Example 1 from 54.0 g (380 mmole) 1-dimethylamino-2-methylpentan-3-one, 82.5 g (470 mmole) 1-bromo-3-fluorobenzene and 9.23 g (470 mmole) magnesium turnings. This mixture was introduced on to a 7×50 cm column packed with silica gel and eluted with 1:1 ethyl acetate/methanol. 13.0 g of base were obtained, from which 11.2 g of hydrochloride (7) (11.5% theoretical) with a melting point of 145–146° C. was obtained with trimethylchlorosilane/water in 2-butanone.

Example 9

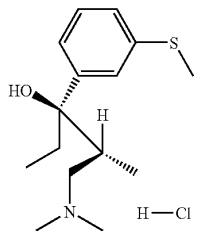


(2RS,3RS)-3-(3-difluoromethylphenyl)-1-dimethylamino-2-methylpentan-3-ol Hydrochloride(8)

7.0 g (34 mmole) 1-bromo-3-difluoromethylbenzene, prepared from 3-bromobenzaldehyde and diethylaminosulphur trifluoride in dichloromethane according to Org. React. 35, 513 (1988) were dissolved in 110 ml of dry tetrahydrofuran and cooled to −75° C. After the addition of 21.12 ml (34 mmole) of a 1.6 molar solution of n-butyllithium in hexane the mixture was stirred for one hour at −75° C. 4.8 g (34 mmole) 1-dimethylamino-2-methylpentan-3-one dissolved in 15 ml of dry tetrahydrofuran were then added dropwise. The reaction mixture was warmed to room temperature over 2.5 hours.

Work-up was effected by the drop-wise addition of 65 ml of 5% hydrochloric acid with cooling in an ice bath, so that the internal temperature did not exceed 15° C. After phase separation the organic phase was extracted with 40 ml of 5% hydrochloric acid. The combined aqueous phases were washed twice with 50 ml ether. In order to release the base, the mixture was added to concentrated sodium hydroxide solution and extracted with dichloromethane. 7.8 g of crude product were obtained in this manner and was introduced on to a 7×40 cm column packed with silica gel. Elution with 1:1 ethyl acetate/methanol gave 4.89 g of base, from which 4.6 g of hydrochloride (8) (44% theoretical) with a melting point of 194–195° C. was obtained with trimethylchlorosilane/water in 2-butanone.

Example 10

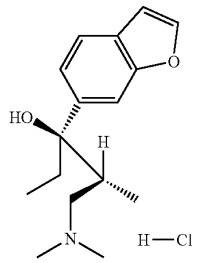


(2RS,3RS)-1-dimethylamino-2-methyl-3-(3-methylsulphanylphenyl)-pentan-3-ol Hydrochloride(9)

38 g of crude mixture were obtained under the conditions cited for Example 1 from 17.6 g (123 mmole)

1-dimethylamino-2-methylpentan-3-one, 25.0 g (123 mmole) 1-bromo-3-methylsulphanylbenzene and 3.0 g (123 mmole) magnesium turnings. This mixture was introduced on to a 7×40 cm column packed with silica gel and eluted with 10:1 ethyl acetate/methanol. 8.35 g of base were obtained, from which 7.2 g of hydrochloride (9) (19% theoretical) with a melting point of 159–160° C. were obtained with trimethylchlorosilane/water in 2-butanone.

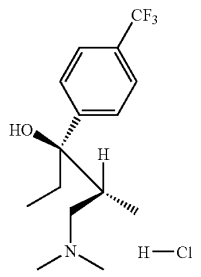
Example 11



(2RS,3RS)-3-benzofuran-6-yl-1-dimethylamino-2-methylpentan-3-ol Hydrochloride(10)

3.45 g (18 mmole) 6-bromobenzofurane (prepared according to EP 355 827) and 6 ml 1,2-dibromoethane, dissolved in 60 ml dry ether, were added drop-wise over 1.5 hours to 2.12 g (87 mmole) magnesium turnings in 30 ml dry ether; after the addition the mixture was heated under reflux for 30 minutes. Thereafter, 2.5 g (18 mmole) 1-dimethylamino-2-methylpentan-3-one dissolved in 7.5 ml ether was added drop-wise over 1.5 hours whilst cooling in an ice bath to maintain an internal temperature of 5–10° C. The reaction mixture was allowed to stand for 12 hours at room temperature, and was then cooled again to 5–10° C. and added to 35 ml of 20% aqueous ammonium chloride solution. After phase separation, the aqueous phase was extracted twice with 50 ml ether. The combined organic phases were dried over sodium sulphate. After removing the solvent by distillation the residue (3.9 g) was introduced on to a 5×16 cm column packed with silica gel 0.95 g of base were obtained by elution with 7:1 diisopropyl ether/methanol, from which 0.82 g of hydrochloride (10) (15.5% theoretical) with a melting point of 162° C. were obtained with trimethylchlorosilane/water in ethyl acetate/2-butanone.

Example 12



(2RS,3RS)-1-dimethylamino-2-methyl-3-(4-trifluoromethylphenyl)-pentan-3-ol Hydrochloride (11)

44 g of crude mixture were obtained as in Example 1 from 20 g (140 mmole) 1-dimethylamino-2-methylpentan-3-one, 31.5 g (140 mmole) 1-bromo-4-trifluoromethylbenzene, 16.5 g (680 mmole) magnesium turnings and 47 ml 1,2-dibromomethane. This mixture was introduced on to a 7×50 cm column packed with silica gel and eluted with 5:1 ethyl acetate/methanol. 16.4 g of base were obtained, from which 12.3 g of hydrochloride (11) (27% theoretical) with a melting point of 170–171° C. were obtained with trimethylchlorosilane/water in 2-butanone.

Example 13

(3RS)-1-dimethylamino-3-(3-methoxyphenyl)-hexan-3-ol Hydrochloride (12)

18.5 g of crude mixture were obtained as in Example 1 from 10 g (70 mmole) 1-dimethylamino-hexan-3-one, 18.7 g (100 mmole) 1-bromo-3-methoxybenzene and 2.3 g (100 mmole) magnesium turnings. This mixture was introduced on to a 6×50 cm column packed with silica gel and eluted with 1:1 ethyl acetate/methanol. 6.84 g of base were obtained, from which 6.15 g of hydrochloride (12) (32% theoretical) with a melting point of 179–180° C. were obtained with trimethylchlorosilane/water in 2-butanone.

Example 14

(3RS)-1-dimethylamino-3-(3-methoxyphenyl)-heptan-3-ol Hydrochloride (13)

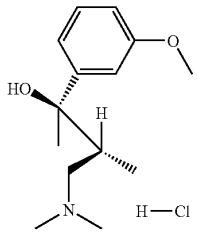
17.3 g of crude mixture were obtained as in Example 1 from 10 g (64 mmole) 1-dimethylamino-heptan-3-one, 15.9 g (157 mmole) 1-bromo-3-methoxybenzene and 2.06 g (85 mmole) magnesium turnings. This mixture was introduced on to a 6×40 cm column packed with silica gel and eluted with ethyl acetate. 5.4 g of base were obtained, from which 4.1 g of hydrochloride (13) (21% theoretical) with a melting point of 150° C. were obtained with trimethylchlorosilane/water in 2-butanone.

Example 15

(3RS)-1-dimethylamino-3-(3-methoxyphenyl)-4,4-dimethylpentan-3-ol Hydrochloride(14)

37 g of crude mixture were obtained as in Example 1 from 18.6 g (118 mmole) 1-dimethylamino-4,4-dimethylpentan-3-one, 28.4 g (152 mmole) 1-bromo-3-methoxybenzene and 3.7 g (152 mmole) magnesium turnings. This mixture was introduced on to a 7×40 cm column packed with silica gel and eluted with 5:1 ethyl acetate/methanol. 2.2 g of base were obtained, from which 1.8 g of hydrochloride (14) (5% theoretical) with a melting point of 213° C. were obtained with trimethylchlorosilane/water in 2-butanone.

Example 16



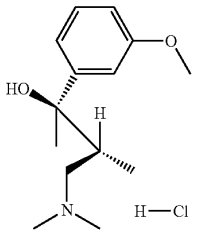
(2RS,3RS)-4-dimethylamino-2-(3-methoxyphenyl)-3-methylbutan-3-ol Hydrochloride(15)

21 g of crude mixture were obtained as in Example 1 from 5.3 g (41 mmole) 4-dimethylamino-3-methylbutan-3-one, 23.0 g (123 mmole) 1-bromo-3-methoxybenzene and 3.0 g (123 mmole) magnesium turnings. This mixture was introduced on to a 4.5×27 cm column packed with silica gel and eluted with 4:1 ethyl acetate/methanol. 4.0 g of base were

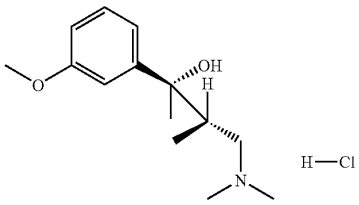
obtained, from which 3.6 g of hydrochloride (15) (32%) theoretical) with a melting point of 124° C. were obtained with trimethylchlorosilane/water in 2-butanone.

Example 17

(+15)



(-15)



Enantiomers of (15):

(−)-(2S,3S)-4-dimethylamino-2-(3-methoxyphenyl)-3-methylbutan-3-ol Hydrochloride (−15)

and

(+)-(2R,3R)-4-dimethylamino-2-(3-methoxyphenyl)-3-methylbutan-3-ol Hydrochloride(+15).

The base was released from hydrochloride (15), which was prepared as in Example 16, with dichloromethane/sodium hydroxide solution. After drying and removal of dichloromethane by distillation, the racemate was then separated into the enantiomers on a chiral HPLC column. The hydrochlorides were obtained from the enantiomers with trimethylchlorosilane/water in 2-butanone.

(−15):

yield: 41% theoretical

m.p.: 117–118° C.

$[\alpha]_{D^{RT}}$=−38.6° (c=1.05; methanol)

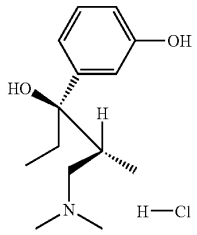
(+15):

yield: 41% theoretical

m.p.: 118–119° C.

$[\alpha]_{D^{RT}}$=+41.0° (c=1.01; methanol)

Example 18

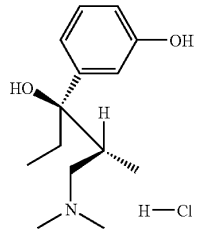


(2RS,3RS)-3-(3-dimethylamino-1-ethyl-1-hydroxy-2-methylpropyl)-phenol Hydrochloride(16).

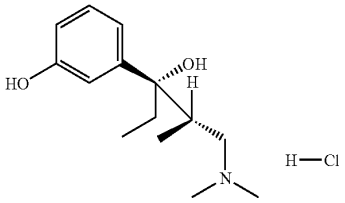
The base was released from compound (1), which was prepared as in Example 1, with dichloromethane/sodium hydroxide solution. After drying the solution, dichloromethane was removed by distillation. 4.3 g (17 mmole) of base were dissolved in 25 ml dry toluene and slowly added drop-wise to 71 ml (85 mmole) of a 1.2 molar solution of diisobutylaluminium hydride in toluene. When the addition was complete, the mixture was heated for 8 hours under reflux and then cooled to room temperature. The reaction mixture was diluted with 25 ml toluene. 9.4 ml ethanol followed by 9.4 ml water were added drop-wise whilst cooling in an ice bath. After stirring for one hour whilst cooling in the ice bath the reaction mixture was freed from aluminium salts by filtration, and the residue was washed three times with 50 ml toluene in each case. Thereafter the combined organic phases were dried and toluene was removed by distillation. 3.95 g of hydrochloride (16) (85% theoretical) with a melting point of 213–214° C. were obtained from the base with aqueous hydrochloric acid solution in acetone.

Example 19

(+16)



(-16)



Enantiomers of (16):

(-) ([2S,3S)] *1S,2S*)-3-(dimethylamino-1-ethyl-1-hydroxy-2-methylpropyl)-phenol Hydrochloride (-16) and

(+) ([2S,3S] *1R,2R*)-3-(dimethylamino-1-ethyl-1-hydroxy-2-methylpropyl)-phenol Hydrochloride (+16)

The enantiomers (−16) and (+16) were prepared under the conditions cited in Example 2.

(−16):

yield: 85% theoretical

m.p.: 208–209° C.

$[\alpha]_{D^{RT}}$=−34.6° (c=0.98; methanol)

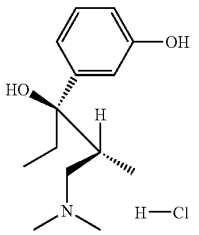
(+16):

yield: 85% theoretical

m.p.: 206–207° C.

$[\alpha]_{D^{RT}}$=+34.4° (c=1.06; methanol)

Example 20



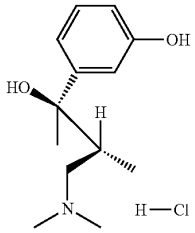
(1RS,2RS)-3-(3-dimethylamino-1-hydroxy-1,2-dimethylpropylphenol Hydrochloride(17)

Compound (17) was prepared under the conditions cited in Example 18 starting from methoxy compound (15) which was obtained as in Example 16.

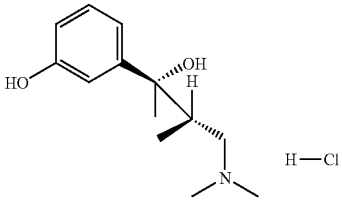
Yield: 85% theoretical

m.p.: 232° C.

Example 21



(+17)



(-17)

Enantiomers of (17):

(−)-(1S,2S)-3-(3-dimethylamino-1-hydroxy-1,2-dimethylpropyl)-phenol Hydrochloride(−17)

and

(+)-(1R,2R)-3-(3-dimethylamino-1-hydroxy-1,2-dimethylpropyl)-phenolhydrochloride(+17)

The enantiomers (−17) and (+17) were prepared under the conditions cited in Example 2.

(−17):

yield: 82% theoretical

m.p.: 204–205° C.

$[\alpha]_{D^{RT}}$=−42.0° (c=0.94; methanol)

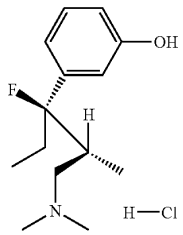
(+17):

yield: 83% theoretical

m.p.: 204–205° C.

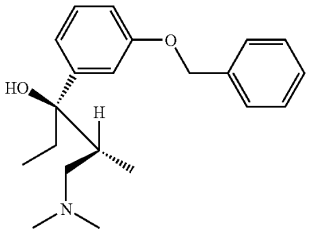
$[\alpha]_{D^{RT}}$=+41.2° (c=1.01; methanol)

Example 22



(+)-(1R,2R)-3-(3-dimethylamino-1-ethyl-1-fluoro-2-methylpropyl)-phenol Hydrochloride(+18)

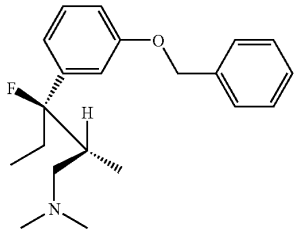
1st Step



(+)-(1R,2R)-3-(3-benzyloxyphenyl)-1-dimethylamino-2-methylpentan-3-ol (+19)

The base was released with dichloromethane/sodium hydroxide solution from enantiomer (+16) obtained as in Example 19, and dichloromethane was removed by distillation after drying the solution. 5.3 g (22 mmole) of base were dissolved in 27 ml of dry dimethylformamide and added in several portions to 1.2 g of 50% sodium hydride. After the addition of 2.8 ml (24 mmole) benzoyl chloride the mixture was heated for three hours at 70° C. The reaction mixture was then cooled to room temperature and poured on to an ice/water mixture. It was extracted three times with 70 ml ether in each case. After drying the combined organic phases over sodium sulphate, the solvent was distilled off and the residue was introduced on to a 4.5×30 cm column packed with silica gel. 6.8 g of base (+19) (92% theoretical) were obtained as a light yellow, highly viscous oil by elution with diisopropyl ether/methanol.

2nd Step



(+)-(2R,3R)-[3-(3-benzyloxyphenyl)-3-fluoro-2-methylpentyl]-dimethylamine(+20)

6.8 g (21 mmole) of (+19), dissolved in 80 ml dichloromethane, were added dropwise at −20° C. to a solution of 3.7 g (23 mmole) diethylaminosulphur trifluoride in 30 ml of dry dichloromethane. After the addition was complete, the mixture was stirred for 30 minutes at this temperature and then warmed to room temperature. After stirring for a further one hour at room temperature, the mixture was cooled to 0–5° C. and hydrolysed with 50 ml water. After phase separation, the aqueous phase was

extracted twice with 50 ml dichloromethane. The combined organic phases were dried and freed from solvent by distillation under vacuum. The crude mixture obtained (8.04 g) was introduced on to a 6×50 cm column packed with silica gel and eluted with 1:1 ethyl acetate/methanol. 3.04 g of base (+20) (40% theoretical) were obtained as a light yellow, viscous oil.

3rd Step:

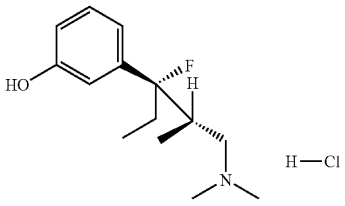
(+)-(1R,2R)-3-(3-dimethylamino-1-ethyl-1-fluoro-2-methylpropyl)-phenol Hydrochloride(+18)

3.0 g (91 mmole) of (+20) were dissolved in 15 ml of dry methanol and added to 0.44 g palladium on activated carbon (10% Pd) in a hydrogenation apparatus. 215 ml hydrogen was consumed after stirring for three hours at room temperature. The catalyst was removed by filtration, and the methanol was removed by distillation. 2.22 g of base were obtained, from which 2.0 g of hydrochloride (+18) (79% theoretical) were obtained with trimethylchlorosilane/water in 2-butanone.

m.p.: 174–176° C.

$[\alpha]_{D}^{RT}$=+29.5° (c=1.08; methanol)

Example 23



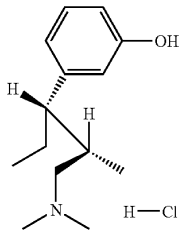
(−)-(1S,2S)-3-(3-dimethylamino-1-ethyl-1-fluoro-2-methylpropyl)-phenol Hydrochloride(−18)

Enantiomer (−18) was obtained in a yield of 29% theoretical from enantiomer (−16) obtained as in Example 19, under the conditions cited in Example 22.

m.p.: 170–172° C.

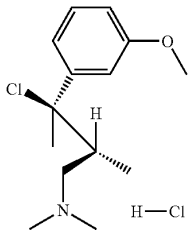
$[\alpha]_{D}^{RT}$=−28.4° (c=1.03; methanol)

Example 24



(+)-(1S,[2R] 2S)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride (+21)

1st Step:



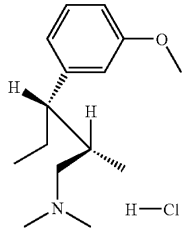
(+)-(2R,3R)-[3-chloro-3-(-3-methoxyphenyl)-2-methylpentyl]-dimethylamine Hydrochloride(+22)

10 g (35 mmole) of (+1), prepared as in Example 2, were added to 10 ml thionyl chloride at room temperature. Nitrogen was subsequently passed over the reaction mixture for two hours to remove excess thionyl chloride. After a fresh addition of 10 ml thionyl chloride the reaction mixture was allowed to stand for 12 hours before excess thionyl chloride was again removed over a period of 2.5 hours by means of a stream of nitrogen. After drying, the residue was dissolved in 10 ml of ice-cold 2-butanone and mixed with stirring with 200 ml ether and then with 140 ml diisopropyl ether. The supernatant solvent phase was decanted off and the remaining oil was again taken up in 10 ml 2-butanone. After the addition of seed crystals, 300 ml diisopropyl ether were added drop-wise with vigorous stirring over three hours, whereupon the hydrochloride crystallised out. 9.8 g of (22) (91% theoretical) were obtained.

m.p.: 120° C. (decomposition)

$[\alpha]_{D}^{RT}$=+24.7° (c=1.01; methanol)

2nd Step:



(+)-([2R]2S, 3S)-[3-(3-methoxyphenyl)-2-methylpentyl]-dimethylamine Hydrocholoride (+23)

46 g of dried zinc chloride were dissolved in 580 ml of dry ether and subsequently added drop-wise to a slurry of 31 g sodium borohydride in 1800 ml ether. After stirring for 12 hours, 500 ml were removed by decantation from the zinc borohydride suspension obtained and added drop-wise to 9.8 g (32 mmole) of (+22) in 200 ml of dry ether. The reaction mixture was stirred for 72 hours at room temperature and then added drop-wise to 40 ml of a saturated ammonium chloride solution with cooling in an ice bath. After phase separation, the ether phase was washed twice with saturated brine; after drying over sodium sulphate the solvent was distilled off under vacuum. 7.3 g of an amine-borane complex were obtained, which were dissolved in 100 ml of dry methanol to isolate the free base. After the addition of 7.5 g triphenylphosphine the mixture was heated for 18 hours under reflux. After removing the solvent by distillation the residue was added to 100 ml of 5% hydrochloric acid, and the hydrochloric acid phase was subsequently washed twice with 50 ml ether. Thereafter the hydrochloric acid phase was made alkaline with concentrated sodium hydroxide solution whilst cooling in an ice bath, and was solvent-extracted twice with 50 ml dichloromethane. After drying the combined organic phases over sodium sulphate the solvent was distilled off under vacuum and the remaining residue (5.2 g) was taken up in 2-butanone. After the addition of trimethylchlorosilane/water, 4.3 g of hydrochloride (+23) (50% theoretical) crystallised out.

m.p.: 163–164° C.

$[\alpha]_{D}^{RT}$=+25.20 (c=0.95; methanol)

3rd Step:

(+)-(1S,[2R] 2S)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol Hydrochloride(+21)

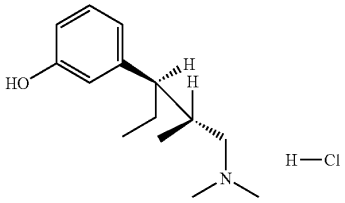
4.3 g (15 mmole) of (+23) from step 2 were added to 100 ml of concentrated hydrobromic acid. The mixture was then heated under reflux for two hours. After cooling to room temperature the reaction mixture was concentrated under the

vacuum from a water pump. The residue was treated with concentrated sodium hydrogen carbonate solution until an alkaline reaction was obtained. After extracting twice with 50 ml dichloromethane in each case the combined organic phases were dried over sodium sulphate. Dichloromethane was then distilled off under vacuum and the residue (4 g) was taken up in 2-butanone. After the addition of trimethylchlorosilane/water, 3.8 g of hydrochloride (+21) (98% theoretical) crystallised out.

m.p.: 194–196° C.

$[\alpha]_{D^{RT}}$=+24.5° (c=1.10; methanol)

Example 25



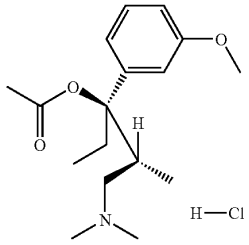
(-)-(1R,[2S] 2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride(-21)

Enantiomer (−21) was obtained in 45% yield under the conditions cited in Example 24 from (−1), which was prepared as in Example 2.

m.p.: 168–170° C.

$[\alpha]_{D^{RT}}$=−27.5° (c=0.97; methanol)

Example 26



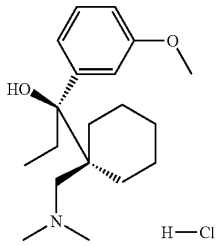
(+)-(1R,2R)-acetic acid-3-dimethylamino-1-ethyl-1-(3-methyoxyphenyl)-2-methylpropyl Ester Hydrochloride(+24)

The base was released from enantiomer (+1), which was prepared as in Example 2, with dichloromethane/sodium hydroxide solution. After drying the solution, dichloromethane was removed by distillation. 3.0 g (39 mmole) acetyl chloride were added drop-wise, whilst cooling in an ice bath, to 10 g (35 mmole) of the base obtained, which had been taken up in 150 ml of dry dichloromethane. After the addition of acetyl chloride was complete, the reaction mixture was warmed to room temperature, and after stirring for two hours was mixed with 100 ml of saturated sodium hydrogen carbonate solution. The organic phase was separated from the aqueous phase and the aqueous phase was extracted twice with 50 ml dichloromethane. The organic phases were combined and dried over sodium sulphate. After removing the solvent by distillation, 13.4 g crude mixture were obtained, from which 10.7 g, of hydrochloride (+24) (93% theoretical) was obtained with trimethylchlorosilane/water in 2-butanone/ethyl acetate.

m.p.: 153° C.

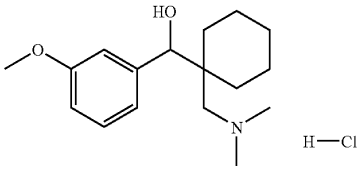
$[\alpha]_{D^{RT}}$=−17.3° (c=1.04; methanol)

Example 27



(1RS)-1-(1-dimethylaminomethyl-cyclohexyl)-1-(3-methoxyphenyl)-propan-1-ol Hydrochloride(25)

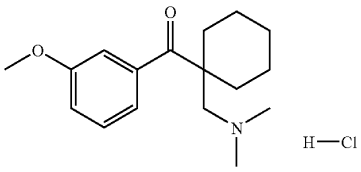
1st Step:



(1RS)-1-(1-dimethylaminomethyl-cyclohexyl)-(3-methoxyphenyl)-methanol Hydrochloride(26)

44 g crude mixture was obtained from 25 g (150 mmole) 1-dimethylaminomethyl-cyclohexane carbaldehyde, 32.9 g (180 mmole) 1-bromo-3-methoxybenzene and 4.3 g (180 mmole) magnesium turnings, under the conditions cited in Example 1. This mixture was introduced on to a 7×40 cm column packed with silica gel and eluted with 4:1 diisopropyl ether/methanol. 38 g of base were obtained, from which 40 g of hydrochloride (26) (85% theoretical) with a melting point of 235° C. were obtained with trimethylchlorosilane/water in 2-butanone.

2nd Step:



(1RS)-(1-dimethylaminomethyl-cyclohexyl)-(3-methoxyphenyl)-methanone Hydrochloride(27)

The base was released from (26) with dichloromethane/sodium hydroxide solution and after drying the solution dichloromethane was removed by distillation. 8.3 g (30 mmole) of base were dissolved in 30 ml n-hexane and added drop-wise to a suspension consisting of 95 g pyridinium chlorochromate (prepared according to Synthesis 1980, 223) absorbed on neutral alumina. After stirring for 72 hours at room temperature the reaction mixture was mixed with 120 ml dichloromethane, stirred for a further 2 hours and then filtered through 30 g alumina. The filter residue was washed three times by decantation with 50 ml dichloromethane and ether in each case. The organic phases were combined with the filtrate and freed from solvent by distillation. The residue obtained was taken up in 60 ml of 2 Normal sodium hydroxide solution and extracted four times with 20 mg

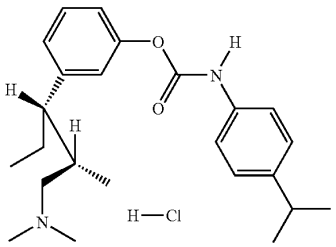
ethyl acetate in each case. After drying the combined organic phases, the solvent was removed by distillation. 4.8 g crude mixture were obtained, which was introduced on to a 6×30 cm column packed with silica gel and eluted, firstly with ethyl acetate, then with 9:1 ethyl acetate/methanol and finally with 4:1 ethyl acetate/methanol. 3.8 g of base were obtained, from which 3.1 g of hydrochloride (27) (33% theoretical) with a melting point of 174° C. were obtained with trichlorosilane/water in 2-butanone.

3rd Step:

(1RS)-1-(1-dimethylaminomethyl-cyclohexyl)-1-(3-methoxyphenyl)-propan-1-ol Hydrochloride(25)

3.0 g crude mixture was obtained, under the conditions cited in Example 1, from 2.8 g (10 mmole) of (27) in the form of the base, 1.4 g (13 mmole) bromoethane and 0.32 g (13 mmole) magnesium turnings, using ether as the solvent. This mixture was introduced on to a 3×20 cm column packed with silica gel and eluted with 19:1 diisopropyl ether/methanol, 2.1 g of base were obtained, from which 1.9 g of hydrochloride (25) (55% theoretical) with a melting point of 230° C. were obtained with trichlorosilane/water in 2-butanone/ethyl acetate.

Example 28



(−)-(2R,3S)-{3[3-(p-isopropyl-phenyl-carbamoyl)-oxy-phenyl]-2-methylpentyl-dimethylamine Hydrochloride(−28)

The base was released from enantiomer (+21), which was prepared as in Example 24, with dichloromethane/sodium hydroxide solution, and after drying the solution dichloromethane was removed by distillation. 2.2 g (10 mmole) of the base obtained were dissolved in 20 ml of dry toluene and mixed with 1.8 g (11 mmole) 4-isopropylphenyl isocyanate. After stirring for 20 hours at room temperature the toluene was removed by distillation. The residue was reacted with trimethylchlorosilane/water in n-propyl acetate to form 3.2 g of hydrochloride (−28) (76% theoretical).

m.p.: 151–152° C.

$[\alpha]_{D^{RT}}$=−5.2° (c=1.11; methanol)

Pharmacological Investigations

Writhing Test on Mice

The analgesic effectiveness of the compounds according to the invention was investigated in the phenylquinone-induced writhing test, modified according to I. C. Hendershot, J. Forsaith in J. Pharmacol. Exptl. Ther. 125, 237 (1959), on mice. Male NMRI mice with a weight between 25 and 30 g were used for this purpose. For each dose of substance, each 10 animals received, 30 minutes after the oral administration of a compound according to the invention, 0.3 ml per mouse of an 0.02% aqueous phenylquinone solution (phenylbenzoquinone manufactured by Sigma, Deisenhofen; solution prepared with the addition of 5% ethanol and kept on a water bath at 45° C.) administered intraperitoneally. Thereafter the animals were placed individually in observation cages. The number of pain-induced stretching movements (writhing reaction-straightening of the body with stretching of the rear extremities) was counted with the aid of a push-button counter. The Ed_{50} value (effective dose with 50% inhibition of writhing reaction) was calculated with a 95% confidence limit by means of regression analysis (evaluation program supplied by Martens EDV-Service, Eckental) from the dose-dependent decrease in the writhing reaction, by comparison with mice tested in parallel to which only phenylquinone had been administered. All the compounds according to the invention which were investigated exhibited a pronounced analgesic effect. The results are summarized in the following Table:

TABLE

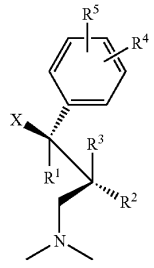
Example	Compound according to the invention	Writhing inhibition ED_{50} [mg/kg per os]	% Inhibition 25 mg/kg per os
1	(1)	5.8	
2	(−1)	22.3	
2	(+1)	1.1	
3	(2)	13.2	
4	(3)		−81.3
5	(4)	15.5	
6	(5)	8.3	
7	(6)	11.8	
8	(7)	27.3	
9	(8)	12.9	
10	(9)	12.8	
11	(10)	12.9	
13	(12)	19.9	
15	(14)	10.5	
16	(15)	3.8	
17	(+15)		−95.2
18	(16)		−100.0
19	(−16)	16.1	
19	(+16)	1.0	
20	(17)		−87.0
21	(−17)		−58.3
21	(+17)		−97.2
22	(+18)	15.7	
24	(+21)	1.9	

The foregoing description and examples have been set forth merely to illustrate the invention and are not intended to be limiting. Since modifications of the disclosed embodiments incorporating the spirit and substance of the invention may occur to persons skilled in the art, the invention should be construed to include all variations within the scope of the appended claims and equivalents thereof.

What is claimed is:

[1. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer having a configuration corresponding to formula Ia':

Ia'



X represents OH, F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group;

R^1 is a C_{1-4}-alkyl group;

R^2 represents H or a C_{1-4}-alkyl group, and

R^3 is different from R^2 and represents H or a straight chain C_{1-4}-alkyl group, and

R^5 represents H, and R^4 represents meta-O—Z,

where Z is H, C_{1-3}-alkyl, $PO(OC_{1-4}alkyl)_2$, $CO(OC_{1-5}$-alkyl), CONH—C_6H_4—(C_{1-3}-alkyl) or CO—C_6H_4—R^7, in which R^7 is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^8)_2$, where R^8 is C_{1-4}-alkyl or 4-morpholino,

or R^4 represents meta-S-C_{1-3}-alkyl, meta-Cl, meta-F, meta-$CR^9R^{10}R^{11}$, ortho-OH, ortho-O—C_{2-3}-alkyl, para-F or para-$CR^9R^{10}R^{11}$, where R^9, R^{10} and R^{11} independently represent H or F, or

R^5 represents para-Cl, para-F, para-OH or para-O—C_{1-3}-alkyl, and R^4 represents meta-Cl, meta-F, meta-OH or meta-O—C_{1-3}-alkyl, or

R^4 and R^5 together represent 3,4-OCH═CH— or 3,4-OCH═CHO—; or a salt thereof with a physiologically acceptable acid.]

[2. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 1, wherein

X represents OH, F, Cl or H;

R^1 represents a C_{1-4}-alkyl group;

R^2 represents H or CH_3;

R^3 is different from R^2 and represents H or CH_3, and

R^5 represents H, and R^4 represents meta-OC_{1-3}-alkyl, meta-OH, meta-S—C_{1-3}-alkyl, meta-F, meta-Cl, meta-CH_3, meta-CF_2H, meta-CF_3 or para-CF_3, or

R^5 represents para-Cl or para-F, and R^4 represents meta-Cl or meta-F, or

R^4 and R^5 together represent 3,4-OCH═CH—.]

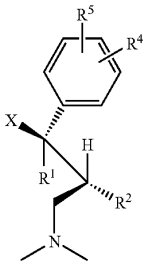
[3. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 1, wherein X represents OH, F, Cl or an $OCOR^4$ group in which R^6 is a C_{1-3}-alkyl group.]

[4. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 1, wherein R^2 is C_{1-4}-alkyl.]

[5. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 1, wherein R^9, R^{10} and R^{11} represent F.]

6. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer having a configuration corresponding to [the] formula Ia,

Ia



wherein

X represents OH, F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group;

R^1 is a C_{1-4}-alkyl group;

R^2 represents a C_{1-4}-alkyl group, and

R^5 represents H, and R^4 represents meta-O—Z,

where Z is H, C_{1-3}-alkyl, $PO(OC_{1-4}alkyl)_2$, $CO(OC_{1-5}$-alkyl), CONH—C_6H_4—(C_{1-3}-alkyl) or CO—C_6H_4—R^7, in which R^7 is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^8)_2$, where R^8 is C_{1-4}-alkyl or 4-morpholino, or R^4 represents meta-S—C_{1-3}-alkyl, meta-Cl, meta-F, meta-$CR^9R^{10}R^{11}$, ortho-OH, ortho-O—C_{2-3}-alkyl, para-F or para-$CR^9R^{10}R^{11}$, where R^9, R^{10} and R^{11} independently represent H or F, or

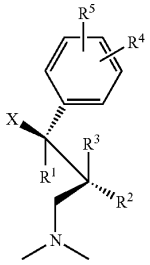
R^5 represents para-Cl, para-F, para-OH or para-O—C_{1-3}-alkyl, and R^4 represents meta-Cl, meta-F, meta-OH or meta-O—C_{1-3}-alkyl, or

R^4 and R^5 together represent 3,4-OCH═CH— or 3,4-OCH═CHO—;

or a salt thereof with a physiologically acceptable acid.

[7. An analgesic composition comprising at least one 1-phenyl-3-dimethylaminopropane diastereoisomer having a configuration corresponding to formula Ia':

Ia'



wherein

X represents OH, F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group;

R^1 is a C_{1-4}-alkyl group;

R^2 represents H or a C_{1-4}-alkyl group, and

R^3 is different from R^2 and represents H or a straight chain C_{1-4}-alkyl group, and

R^5 represents H, and R^4 represents meta-O—Z,

where Z is H, C_{1-3}-alkyl, $PO(OC_{1-4}alkyl)_2$, $CO(OC_{1-5}$-alkyl), CONH—C_6H_4—(C_{1-3}-alkyl) or CO—C_6H_4—R^7, in which R^7 is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^8)_2$, where R^8 is C_{1-4}-alkyl or 4-morpholino,

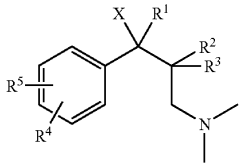
or R^4 represents meta-S—C_{2-3}-alkyl, meta-Cl, meta-F, meta-$CR^9R^{10}R^{11}$, ortho-OH, ortho-O—C_{2-3}-alkyl, para-F or para-$CR^9R^{10}R^{11}$, where R^9, R^{10} and R^{11} independently represent H or F, or

R^5 represents para-Cl, para-F, para-OH or para-O—C_{1-3}-alkyl, and R^4 represents meta-Cl, meta-F, meta-OH or meta-O—C_{1-3}-alkyl, or

R^4 and R^5 together represent 3,4-OCH═CH— or 3,4-OCH═CHO—; or a salt thereof with a physiologically acceptable acid, and at least one conventional pharmaceutical carrier or adjuvant.]

8. A method of treating a mammal suffering from pain, said method comprising administering to said mammal an effective analgesic amount of a 1-phenyl-3-dimethylaminopropane compound corresponding to formula I

I



wherein

X represents OH, F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group;

R^1 is a C_{1-4}-alkyl group;

R^2 represents H or a C_{1-4}-alkyl group and R^3 represents H or a straight chain C_{1-4}-alkyl group, or R^2 and R^3 together form a C_{4-7} cycloalkyl radical, and

R^5 represents H, and R^4 represents meta-O—Z, where Z is H, C_{1-3}-alkyl, $PO(OC_{1-4}alkyl)_2$, $CO(OC_{1-5}$-alkyl), $CONH—C_6H_4—(C_{1-3}$-alkyl) or $CO—C_6H_4—R^7$, in which R^7 is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^8)_2$, where R^8 is C_{1-4}-alkyl or 4-morpholino,

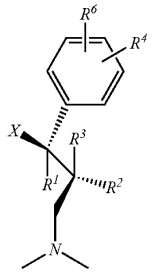
or R^4 represents meta-S—C_{1-3}-alkyl, meta-Cl, meta-F, meta-$CR^9R^{10}R^{11}$, ortho-OH, ortho-O—C_{2-3}-alkyl, para-F or para-$CR^9R^{10}R^{11}$, where R^9, R^{10} and R^{11} independently represent H or F, or

R^5 represents para-Cl, para-F, para-OH or para-O—C_{1-3}-alkyl, and R^4 represents meta-Cl, meta-F, meta-OH or meta-O—C_{1-3}-alkyl, or

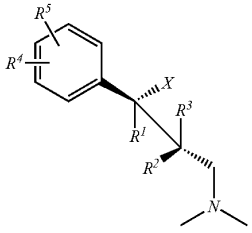
R^4 and R^5 together represent 3,4-OCH═CH— or 3,4-OCH═CHO—, or a salt thereof with a physiologically acceptable acid.

9. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer having a configuration corresponding to at least one of formulae Ia' and Ic';

Ia'



Ic'



wherein

X represents OH, F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group,

R^1 is a C_{1-4}-alkyl group,

R^2 represents a C_n-alkyl group, wherein n=1–4,

R^3 is different from R^2 and represents H or a straight chain C_m-alkyl group, wherein 0<m<n, and

R^5 represents H, and R^4 represents meta-O—Z, where Z is H, C_{1-3}-alkyl, $PO(OC_{14}$-alkyl$)_2$, $CO(OC_{1-5}$-alkyl), $CONH—C_6H_4—(C_{1-3}$-alkyl) or $CO—C_6H_4—R^7$, in which R^7 is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^8)_2$, where R^8 is C_{1-4}-alkyl or 4-morpholino,

or R^4 represents meta-S—C_{1-3}-alkyl, meta-Cl, meta-F, meta-$CR^9R^{10}R^{11}$, ortho-OH, ortho-O—C_{2-3}-alkyl, para-F or para-$CR^9R^{10}R^{11}$, where R^9, R^{10} and R^{11} independently represent H or F, or

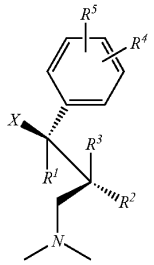
R^5 represents para-Cl, para-F, para-OH or para-O—C_{1-3}-alkyl, and R^4 represents meta-Cl, meta-F, meta-OH or meta-O—C_{1-3}-alkyl, or

R^4 and R^5 together represent 3,4-OCH═CH— or 3,4-OCH═CHO—,

or a salt thereof with a physiologically acceptable acid.

10. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer having a configuration corresponding to formula Ia':

Ia'



wherein

X represents OH, F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group,

R^1 is a C_{1-4}-alkyl group,

R^2 represents a C_{1-4}-alkyl group, and

R^3 is different from R^2 and represents H or a straight chain C_{1-3}-alkyl group, such that X and the dimethylamino group are disposed threo in relation to each other, and

R^5 represents H, and R^4 represents meta-O—Z, where Z is H, C_{1-3}-alkyl, $PO(OC_{14}$-alkyl$)_2$, $CO(OC_{1-5}$-alkyl), $CONH—C_6H_4—(C_{1-3}$-alkyl) or $CO—C_6H_4—R^7$, in which R^7 is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^8)_2$, where R^8 is C_{1-4}-alkyl or 4-morpholino,

or R^4 represents meta-S—C_{1-3}-alkyl, meta-Cl, meta-F, meta-$CR^9R^{10}R^{11}$, ortho-OH, ortho-O—C_{2-3}-alkyl, para-F or para-$CR^9R^{10}R^{11}$, where R^9, R^{10} and R^{11} independently represent H or F, or

R^5 represents para-Cl, para-F, para-OH or para-O—C_{1-3}-alkyl, and R^4 represents meta-Cl, meta-F, meta-OH or meta-O—C_{1-3}-alkyl, or

R^4 and R^5 together represent 3,4-OCH═CH— or 3,4-OCH═CHO—,

or a salt thereof with a physiologically acceptable acid.

11. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 10, wherein R^5 is H, and R^4 is meta-OCH_3.

12. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 10, wherein R^5 is H, and R^4 is meta-OH.

13. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 10, wherein

X represents OH, F, Cl, or H;

R^1 is a C_{1-4}-alkyl group;

R^2 represents CH_3;

R^3 is H; and

R^5 represents H, and R^4 represents meta-O—C_{1-3}-alkyl, meta-OH, meta-S— C_{1-3}-alkyl, meta-F, meta-Cl, meta-CH_3, meta-CF_2H, meta-CF_3, or para-CF_3, or

R^5 represents para-Cl, or para-F, and R^4 represents meta-Cl, or meta-F, or

R^4 and R^5 together represent 3,4-OCH═CH—.

14. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 10, wherein X represents OH, F, Cl, or an $OCOR^6$group in which R^6 is a C_{1-3}-alkyl group.

15. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 10, wherein R^2 is CH_3, and R^3 is H.

16. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 10, wherein R^9, R^{10} and R^{11} represent F.

17. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 10, wherein X represents OH.

18. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 10, wherein X represents F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group.

19. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 6, wherein R^5 is H and R^4 is meta-OCH_3.

20. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 6, wherein R^5 is H and R^4 is meta-OH.

21. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 6, wherein X represents OH, F, Cl, or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group.

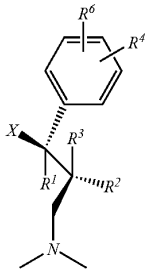
22. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 6, wherein R^9, R^{10} and R^{11} represent F.

23. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 6, wherein X represents OH.

24. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 6, wherein X represents F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group.

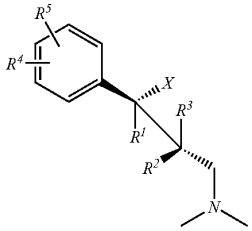
25. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer having a configuration corresponding to at least one of formulae Ia' and Ic':

Ia'



-continued

Ic'



wherein

X represents OH, F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group,

R^1 is a C_{1-4}-alkyl group,

R^2 represents a C_{1-4}-alkyl group, and

R^3 is different from R^2 and represents H or a straight chain C_{1-3}-alkyl group, such that X and the dimethylamino group are disposed threo in relation to each other, and

R^5 represents H, and R^4 represents meta-O—Z, where Z is H, C_{1-3}-alkyl, $PO(OC_{1-4}\text{-alkyl})_2$, $CO(OC_{1-5}\text{-alkyl})$, $CONH—C_6H_4—(C_{1-3}\text{-alkyl})$ or $CO—C_6H_4—R^7$, in which R^7 is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^8)_2$, where R^8 is C_{1-4}-alkyl or 4-morpholino,

or R^4 represents meta-S—C_{1-3}-alkyl, meta-Cl, meta-F, meta-$CR^9R^{10}R^{11}$, ortho-OH, ortho-O—C_{2-3}-alkyl, para-F or para-$CR^9R^{10}R^{11}$, where R^9, R^{10} and R^{11} independently represent H or F, or

R^5 represents para-Cl, para-F, para-OH or para-O—C_{1-3}-alkyl, and R^4 represents meta-Cl, meta-F, meta-OH or meta-O—C_{1-3}-alkyl, or

R^4 and R^5 together represent 3,4-OCH═CH— or 3,4-OCH═CHO—,

or a salt thereof with a physiologically acceptable acid.

26. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 25, wherein

X represents OH, F, Cl, or H;

R^1 is a C_{1-4}-alkyl group;

R^2 represents CH_3;

R^3 is H; and

R^5 represents H, and R^4 represents meta-OC_{1-3}-alkyl, meta-OH, meta-S— C_{1-3}-alkyl, meta-F, meta-Cl, meta-CH_3, meta-CF_2H, meta-CF_3, or para-CF_3, or

R^5 represents para-Cl, or para-F, and R^4 represents meta-Cl, or meta-F, or

R^4 and R^5 together represent 3,4-OCH═CH—.

27. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 25, wherein R^5 is H and R^4 is meta-OCH_3.

28. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 25, wherein R^5 is H and R^4 is meta-OH.

29. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 25, wherein X represents OH, F, Cl or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group.

30. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 25, wherein R^2 is CH_3, and R^3 is H.

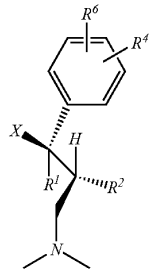
31. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 25, wherein R^9, R^{10} and R^{11} represent F.

32. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 25, wherein X represents OH.

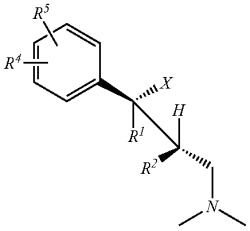
33. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 25, wherein X represents F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group.

34. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer having a configuration corresponding to at least one of formulae Ia and Ic:

Ia



Ic



wherein

X represents OH, F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group;

R^1 is a C_{1-4}-alkyl group;

R^2 represents a C_{1-4}-alkyl group, and

R^5 represents H, and R^4 represents meta-O—Z, where Z is H, C_{1-3}-alkyl, $PO(OC_{1-4}\text{-alkyl})_2$, $CO(OC_{1-5}\text{-alkyl})$, $CONH—C_6H_4—(C_{1-3}\text{-alkyl})$ or $CO—C_6H_4—R^7$, in which R^7 is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^8)_2$, where R^8 is C_{1-4}-alkyl or 4-morpholino,

or R^4 represents meta-S—C_{1-3}-alkyl, meta-Cl, meta-F, meta-$CR^9R^{10}R^{11}$, ortho-OH, ortho-O—C_{2-3}-alkyl, para-F or para-$CR^9R^{10}R^{11}$, where R^9, R^{10} and R^{11} independently represent H or F, or

R^5 represents para-Cl, para-F, para-OH or para-O—C_{1-3}-alkyl, and R^4 represents meta-Cl, meta-F, meta-OH or meta-O—C_{1-3}-alkyl, or

R^4 and R^5 together represent 3,4-OCH═CH— or 3,4-OCH═CHO—;

or a salt thereof with a physiologically acceptable acid.

35. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 34, wherein R^5 is H and R^4 is meta-OCH_3.

36. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 34, wherein R^5 is H and R^4 is meta-OH.

37. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 34, wherein X represents OH, F, Cl or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group.

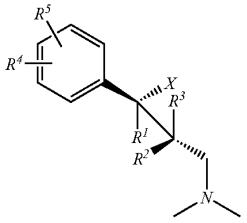
38. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 34, wherein R^9, R^{10} and R^{11} represent F.

39. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 34, wherein X represents OH.

40. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 34, wherein X represents F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group.

41. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer having a configuration corresponding to formula Ic':

Ic'



wherein

X represents OH, F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group,

R^1 is a C_{1-4}-alkyl group,

R^2 represents a C_{1-4}-alkyl group, and

R^3 is different from R^2 and represents H or a straight chain C_{1-3}-alkyl group, such that X and the dimethylamino group are disposed threo in relation to each other, and

R^5 represents H, and R^4 represents meta-O—Z, where Z is H, C_{1-3}-alkyl, $PO(OC_{1-4}\text{-alkyl})_2$, $CO(OC_{1-5}\text{-alkyl})$, $CONH—C_6H_4—(C_{1-3}\text{-alkyl})$ or $CO—C_6H_4—R^7$, in which R^7 is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^8)_2$, where R^8 is C_{1-4}-alkyl or 4-morpholino, or R^4 represents meta-S—C_{1-3}-alkyl, meta-Cl, meta-F, meta-$CR^9R^{10}R^{11}$, ortho-OH, ortho-O—C_{2-3}-alkyl, para-F or para-$CR^9R^{10}R^{11}$, where R^9, R^{10} and R^{11} independently represent H or F, or

R^5 represents para-Cl, para-F, para-OH or para-O—C_{1-3}-alkyl, and R^4 represents meta-Cl, meta-F, meta-OH or meta-O—C_{1-3}-alkyl, or

R^4 and R^5 together represent 3,4-OCH═CH— or 3,4-OCH═CHO—,

or a salt thereof with a physiologically acceptable acid.

42. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 41, wherein

X represents OH, F, Cl, or H;

R^1 is a C_{1-4}-alkyl group;

R^2 represents CH_3;

R^8 is H; and

R^5 represents H, and R^4 represents meta-OC_{1-3}-alkyl, meta-OH, meta-S—C_{1-3}-alkyl, meta-F, meta-Cl, meta-CH_3, meta-CF_2H, meta-CF_3, or para-CF_3, or

R^5 represents para-Cl, or para-F, and R^4 represents meta-Cl, or meta-F, or

R^4 and R^5 together represent 3,4-OCH═CH—.

43. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 41, wherein R^5 is H and R^4 is meta-OCH_3.

44. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 41, wherein R^5 is H and R^4 is meta-OH.

45. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 41, wherein X represents OH, F, Cl or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group.

46. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 41, wherein R^2 is CH_3, and R^3 is H.

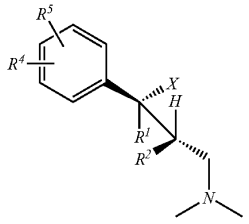
47. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 41, wherein R^9, R^{10} and R^{11} represent F.

48. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 41, wherein X represents OH.

49. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 41, wherein X represents F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group.

50. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer having a configuration corresponding to formula Ic:

Ic



wherein

X represents OH, F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group;

R^1 is a C_{1-4}-alkyl group;

R^2 represents a C_{1-4}-alkyl group, and

R^5 represents H, and R^4 represents meta-O—Z, where Z is H, C_{1-3}-alkyl, $PO(OC_{1-4}\text{-alkyl})_2$, $CO(OC_{1-5}\text{-alkyl})$, $CONH—C_6H_4—(C_{1-3}\text{-alkyl})$ or $CO—C_6H_4—R^7$, in which R^7 is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^8)_2$, where R^8 is C_{1-4}-alkyl or 4-morpholino,

or R^4 represents meta-S—C_{1-3}-alkyl, meta-Cl, meta-F, meta-$CR^9R^{10}R^{11}$, ortho-OH, ortho-O—C_{2-3}-alkyl, para-F or para-$CR^9R^{10}R^{11}$, where R^9, R^{10} and R^{11} independently represent H or F, or

R^5 represents para-Cl, para-F, para-OH or para-O—C_{1-3}-alkyl, and R^4 represents meta-Cl, meta-F, meta-OH or meta-O—C_{1-3}-alkyl, or

R^4 and R^5 together represent 3,4-OCH═CH— or 3,4-OCH═CHO—;

or a salt thereof with a physiologically acceptable acid.

51. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 50, wherein R^5 is H and R^4 is meta-OCH_3.

52. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 50, wherein R^5 is H and R^4 is meta-OH.

53. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 50, wherein X represents OH, F, Cl or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group.

54. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 50, wherein R^9, R^{10} and R^{11} represent F.

55. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 50, wherein X represents OH.

56. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 50, wherein X represents F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group.

57. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 34, wherein the compound is (2S, 3S)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol hydrochloride (−1).

58. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 34, wherein the compound is (+)-(2R, 3R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol hydrochloride (+1).

59. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 34, wherein the compound is (+)-(2R, 3R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol hydrochloride (+1).

60. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 34, wherein the compound is (+)-(1S,2S)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride (+21).

61. (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride (−21).

62. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 34, wherein the compound is (+)-(1RS,2RS)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride (+21).

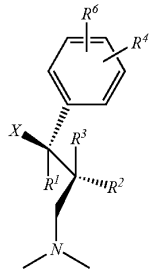
63. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 34, wherein the compound is (+)-(2S,3S)-[3-(3-methoxyphenyl)-2-methylpentyl]-dimethylamine hydrochloride (+23).

64. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 34, wherein the compound is (−)-(2R,3R)-[3-(3-methoxyphenyl)-2-methylpentyl]-dimethylamine hydrochloride (−23).

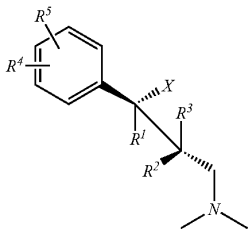
65. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 34, wherein the compound is (+)-(2RS, 3RS)-[3-(3-methoxyphenyl)-2-methylpentyl]-dimethylamine hydrochloride (+23).

66. An analgesic composition comprising at least one 1-phenyl-3-dimethylaminopropane diastereoisomer having a configuration corresponding to at least one of formulae Ia' and Ic':

Ia'



Ic'



wherein

X represents OH, F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group;

R^1 is a C_{1-4}-alkyl group;

R^2 represents a C_{1-4}-alkyl group, and

R^3 is different from R^2 and represents H or a straight chain C_{1-3}-alkyl group, such that X and the dimethylamino group are disposed threo in relation to each other, and

R^5 represents H, and R^4 represents meta-O—Z, C_6H_4—(C_{1-3}-alkyl) or CO—C_6H_4—R^7, in which R^7 is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^8)_2$, where R^8 is C_{1-4}-alkyl or 4-morpholino,

or R^4 represents meta-S—C_{1-3}-alkyl, meta-Cl, meta-F, meta-$CR^9R^{10}R^{11}$, ortho-OH, ortho-O—C_{2-3}-alkyl, para-F or para-$CR^9R^{10}R^{11}$, where R^9, R^{10} and R^{11} independently represent H or F, or

R^5 represents para-Cl, para-F, para-OH or para-O—C_{1-3}-alkyl, and R^4 represents meta-Cl, meta-F, meta-OH or meta-O—C_{1-3}-alkyl, or

R^4 and R^5 together represent 3,4-OCH═CH— or 3,4-OCH═CHO—;

or a salt thereof with a physiologically acceptable acid, and at least one suitable pharmaceutical carrier or adjuvant.

67. An analgesic composition according to claim 66, wherein

X represents OH, F, Cl, or H;

R^1 represents a C_{1-4}-alkyl group;

R^2 represents CH_3;

R^3 is H; and

R^5 represents H, and R^4 represents meta-OC_{1-3}-alkyl, meta-OH, meta-S—C_{1-3}-alkyl, meta-F, meta-Cl, meta-CH_3, meta-CF_2H, meta-CF_3, or

R^5 represents para-Cl, or para-F, and R^4 represents meta-Cl, or meta-F, or

R^4 and R^5 together represent 3,4-OCH═CH—.

68. An analgesic composition according to claim 66, wherein R^5 is H and R^4 is meta-OCH_3.

69. An analgesic composition according to claim 66, wherein R^5 is H and R^4 is meta-OH.

70. An analgesic composition according to claim 66, wherein X represents OH, F, Cl or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group.

71. An analgesic composition according to claim 66, wherein R^2 is CH_2, and R^3 is H.

72. An analgesic composition according to claim 66, wherein R^9, R^{10} and R^{11} represent F.

73. An analgesic composition according to claim 66, wherein X represents OH.

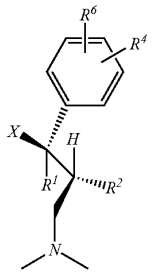
74. An analgesic composition according to claim 66, wherein X represents F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group.

75. An analgesic composition according to claim 66, wherein the 1-phenyl-3-dimethylaminopropane diastereoisomer has a configuration corresponding to formula Ia'.

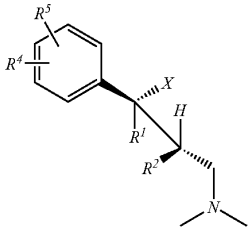
76. An analgesic composition according to claim 66, wherein the 1-phenyl-3-dimethylaminopropane diastereoisomer has a configuration corresponding to formula Ic'.

77. An analgesic composition comprising at least one 1-phenyl-3-dimethylaminopropane diastereoisomer having a configuration corresponding to at least one of formulae Ia and Ic:

Ia



Ic



wherein

X represents OH, F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group;

R^1 is a C_{1-4}-alkyl group;

R^2 represents a C_{1-4}-alkyl group, and

R^5 represents H, and R^4 represents meta-O—Z, where Z is H, C_{1-3}-alkyl, $PO(OC_{1-4}\text{-alkyl})_2$, $CO(OC_{1-5}\text{-alkyl})$, CONH—$C_6H_4$—($C_{1-3}$-alkyl) or CO—$C_6H_4$—$R^7$, in which R^7 is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^8)_2$, where R^8 is C_{1-4}-alkyl or 4-morpholino,

or R^4 represents meta-S—C_{1-3}-alkyl, meta-Cl, meta-F, meta-$CR^9R^{10}R^{11}$, ortho-OH, ortho-O—C_{2-3}-alkyl, para-F or para-$CR^9R^{10}R^{11}$, where R^9, R^{10} and R^{11} independently represent H or F, or

R^5 represents para-Cl, para-F, para-OH or para-O—C_{1-3}-alkyl, and R^4 represents meta-Cl, meta-F, meta-OH or meta-O—C_{1-3}-alkyl, or

R^4 and R^5 together represent 3,4-OCH═CH— or 3,4-OCH═CHO—;

or a salt thereof with a physiologically acceptable acid, and at least one suitable pharmaceutical carrier or adjuvant.

78. An analgesic composition according to claim 77, wherein R^5 is H and R^4 is meta-OCH_3.

79. An analgesic composition according to claim 77, wherein R^5 is H and R^4 is meta-OH.

80. An analgesic composition according to claim 77, wherein X represents OH, F, Cl or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group.

81. An analgesic composition according to claim 77, wherein R^9, R^{10} and R^{11} represent F.

82. An analgesic composition according to claim 77, wherein X represents OH.

83. An analgesic composition according to claim 77, wherein X represents F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group.

84. An analgesic composition according to claim 77, wherein the 1-phenyl-3-dimethylaminopropane diastereoisomer has a configuration corresponding to formula Ia.

85. An analgesic composition according to claim 77, wherein the 1-phenyl-3-dimethylaminopropane diastereoisomer has a configuration corresponding to formula Ic.

86. A method according to claim 8, wherein

X represents OH, F, Cl, or H;

R^1 represents a C_{1-4}-alkyl group;

R^2 represents CH_8;

R^3 represents H, and

R^5 represents H, and R^4 represents meta-OC_{1-8}-alkyl, meta-OH, meta-S—C_{1-3}-alkyl, meta-F, meta-Cl, meta-CH_3, meta-CF_2H, meta-CF_3, or para-CF_3, or

R^5 represents para-Cl, or para-F, and R^4 represents meta-Cl, or meta-F, or

R^4 and R^5 together represent 3,4-OCH═CH—.

87. A method according to claim 8, wherein R^5 is H and R^4 is meta-OCH_8.

88. An method according to claim 8, wherein R^5 is H and R^4 is meta-OH.

89. A method according to claim 8, wherein X represents OH, F, Cl or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group.

90. A method according to claim 8, wherein R^2 is C_{1-4}-alkyl, and R^3 is different from R^2 and is H or C_{1-3} alkyl.

91. A method according to claim 8, wherein R^9, R^{10} and R^{11} represent F.

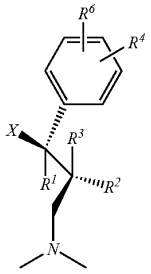
92. A method according to claim 8, wherein X represents OH.

93. A method according to claim 8, wherein X represents F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group.

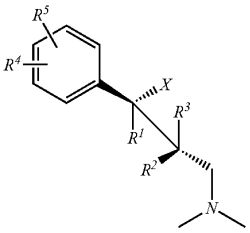
94. A method according to claim 8, wherein X represents H.

95. A method according to claim 8, wherein the compound of formula I has a configuration corresponding to at least one of formulae Ia' and Ic':

Ia'



Ic'



wherein

X represents OH, F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group,

R^1 is a C_{1-4}-alkyl group,

R^2 represents a C_{1-4}-alkyl group, and

R^3 is different from R^2 and represents H or a straight chain C_{1-3}-alkyl group, such that X and the dimethylamino group are disposed threo in relation to each other,

and R^5 represents H, and R^4 represents meta-O—Z,

where Z is H, C_{1-3}-alkyl, $PO(OC_{14}\text{-alkyl})_2$, $CO(OC_{1-5}\text{-alkyl})$, CONH—$C_6H_4$—($C_{1-3}$-alkyl) or CO—$C_6H_4$—$R^7$, in which R^7 is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^8)_2$, where R^8 is C_{1-4}-alkyl or 4-morpholino,

or R^4 represents meta-S—C_{1-3}-alkyl, meta-Cl, meta-F, meta-$CR^9R^{10}R^{11}$, ortho-OH, ortho-O—C_{2-3}-alkyl, para-F or para-$CR^9R^{10}R^{11}$, where R^9, R^{10} and R^{11} independently represent H or F, or

R^5 represents para-Cl, para-F, para-OH or para-O—C_{1-3}-alkyl, and R^4 represents meta-Cl, meta-F, meta-OH or meta-O—C_{1-3}-alkyl, or

R^4 and R^5 together represent 3,4-OCH═CH— or 3,4-OCH═CHO—,

or a salt thereof with a physiologically acceptable acid.

96. A method according to claim 95, wherein

X represents OH, F, Cl, or H;

R^1 represents a C_{1-4}-alkyl group;

R^2 represents CH_3;

R^3 represents H, and

R^5 represents H, and R^4 represents meta-OC_{1-3}-alkyl, meta-OH, meta-S—C_{1-3}-alkyl, meta-F, meta-Cl, meta-CH_3, meta-CF_2H, meta-CF_3, or para-CF_3, or

R^5 represents para-Cl, or para-F, and R^4 represents meta-Cl, or meta-F, or

R^4 and R^5 together represent 3,4-OCH═CH—.

97. A method according to claim 95, wherein R^5 is H and R^4 is meta-OCH_3.

98. An method according to claim 95, wherein R^5 is H and R^4 is meta-OH.

99. A method according to claim 95, wherein X represents OH, F, Cl or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group.

100. A method according to claim 95, wherein R^2 is CH_3, and R^3 is H.

101. A method according to claim 95, wherein R^9, R^{10} and R^{11} represent F.

102. A method according to claim 95, wherein X represents OH.

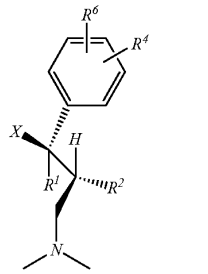
103. A method according to claim 95, wherein X represents F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group.

104. A method according to claim 95, wherein the 1-phenyl-3-dimethylaminopropane diastereoisomer has a configuration corresponding to formula Ia'.

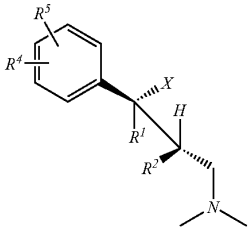
105. A method according to claim 95, wherein the 1-phenyl-3-dimethylaminopropane diastereoisomer has a configuration corresponding to formula Ic'.

106. A method according to claim 8, wherein the compound of formula I has a configuration corresponding to at least one of formulae Ia and Ic:

Ia



Ic



wherein

X represents OH, F, Cl, H or an OCOR^6 group in which R^6 is a C$_{1-3}$-alkyl group;

R^1 is a C$_{1-4}$-alkyl group;

R^2 represents a C$_{1-4}$-alkyl group, and

R^5 represents H, and R^4 represents meta-O—Z, where Z is H, C$_{1-3}$-alkyl, PO(OC$_{1-4}$-alkyl)$_2$, CO(OC$_{1-5}$-alkyl), CONH—C$_6$H$_4$—(C$_{1-3}$-alkyl) or CO—C$_6$H$_4$—R^7, in which R^7 is ortho-OCOC$_{1-3}$-alkyl or meta- or para-CH$_2$N(R^8)$_2$, where R^8 is C$_{1-4}$-alkyl or 4-morpholino, or

R^4 represents meta-S—C$_{1-3}$-alkyl, meta-Cl, meta-F, meta-CR^{9}R^{10}R^{11}, ortho-OH, ortho-O—C$_{2-3}$-alkyl, para-F or para-CR^{9}R^{10}R^{11}, where R^9, R^{10} and R^{11} independently represent H or F, or

R^5 represents para-Cl, para-F, para-OH or para-O—C$_{1-3}$-alkyl, and R^4 represents meta-Cl, meta-F, meta-OH or meta-O—C$_{1-3}$-alkyl, or

R^4 and R^5 together represent 3,4-OCH═CH— or 3,4-OCH═CHO—;

or a salt thereof with a physiologically acceptable acid.

107. A method according to claim 106, wherein X represents OH, F, Cl or an OCOR^6 group in which R^6 is a C$_{1-3}$-alkyl group.

108. A method according to claim 106, wherein R^9, R^{10} and R^{11} represent F.

109. A method according to claim 106, wherein X represents OH.

110. A method according to claim 106, wherein X represents F, Cl, H or an OCOR^6 group in which R^6 is a C$_{1-3}$-alkyl group.

111. A method according to claim 106, wherein the compound is a 1-phenyl-3-dimethylaminopropane diastereoisomer having a configuration corresponding to formula Ia.

112. A method according to claim 106, wherein the compound is a 1-phenyl-3-dimethylaminopropane diastereoisomer having a configuration corresponding to formula Ic.

113. A method according to claim 106, wherein R^5 is H and R^4 is meta-OCH$_3$.

114. A method according to claim 106, wherein R^5 is H and R^4 is meta-OH.

115. A method according to claim 8, wherein the compound is (+)-(1RS,2RS)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride (+21).

116. A method according to claim 8, wherein the compound is (+)-(1S,2S)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride (+21).

117. A method according to claim 8, wherein the compound is (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride (−21).

118. A method according to claim 8, wherein the compound is (+)-(2RS,3RS)-[3-(3-methoxyphenyl)-2-methylpentyl]-dimethylamine hydrochloride (+23).

119. A method according to claim 8, wherein the compound is (+)-(2S,3S)-[3-(3-methoxyphenyl)-2-methylpentyl]-dimethylamine hydrochloride (+23).

120. A method according to claim 8, wherein the compound is (−)-(2R,3R)-[3-(3-methoxyphenyl)-2-methylpentyl]-dimethylamine hydrochloride (−23).

121. A method according to claim 8, wherein the compound is (+)-(2RS, 3RS)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol hydrochloride (+1).

122. A method according to claim 8, wherein the compound is (+)-(2R, 3R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol hydrochloride (+1).

123. A method according to claim 8, wherein the compound is (−)-(2S, 3S)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol hydrochloride (−1).

124. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 6, wherein X is H.

125. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 10, wherein X is H.

126. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 25, wherein X is H.

127. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 34, wherein X is H.

128. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 41, wherein X is H.

129. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 50, wherein X is H.

130. An analgesic composition according to claim 66, wherein X is H.

131. An analgesic composition according to claim 75, wherein X is H.

132. An analgesic composition according to claim 76, wherein X is H.

133. An analgesic composition according to claim 77, wherein X is H.

134. An analgesic composition according to claim 84, wherein X is H.

135. An analgesic composition according to claim 85, wherein X is H.

136. A method according to claim 86, wherein X is H.

137. A method according to claim 95, wherein X is H.

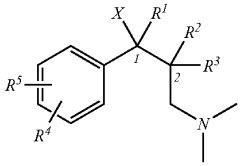
138. A method according to claim 106, wherein X is H.

139. A method according to claim 113, wherein X is H.

140. A method according to claim 114, wherein X is H.

141. An isolated 1-phenyl-3-dimethylaminopropane diastereomer having a configuration corresponding to formula I:

I



wherein

X represents H,

R^1 is a C_{1-4}-alkyl group,

R^2 represents a C_{1-4}-alkyl group,

R^3 is different from R^2 and represents H or a straight chain C_{1-3}-alkyl group,

and

R^5 represents H, and R^4 represents meta-O—Z, where Z is H, C_{1-3}-alkyl, $PO(OC_{1-4}\text{-alkyl})_2$, $CO(OC_{1-5}\text{-alkyl})$, $CONH—C_6H_4—(C_{1-3}\text{-alkyl})$ or $CO—C_6H_4—R^7$, in which R^7 is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^8)_2$, where R^8 is C_{1-4}-alkyl or 4-morpholino,

or R^4 represents meta-S—C_{1-3}-alkyl, meta-Cl, meta-F, meta-$CR^9R^{10}R^{11}$, ortho-OH, ortho-O—C_{2-3}-alkyl, para-F or para-$CR^9R^{10}R^{11}$, where R^9, R^{10} and R^{11} independently represent H or F, or

R^5 represents para-Cl, para-F, para-OH or para-O—C_{1-3}-alkyl, and R^4 represents meta-Cl, meta-F, meta-OH or meta-O—C_{1-3}-alkyl, or

R^4 and R^5 together represent 3,4-OCH═CH— or 3,4-OCH═CHO—, and

wherein carbon atoms at positions 1 and 2 are both asymmetric carbons and the diastereomer has a (1R, 2R) or (1S, 2S) configuration,

or a salt thereof with a physiologically acceptable acid.

142. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 141, wherein R^5 is H, and R^4 is meta-OCH_3.

143. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 141, wherein R^5 is H, and R^4 is meta-OH.

144. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 141, wherein

R^2 represents CH_3;

R^3 is H; and

R^5 represents H, and R^4 represents meta-O—C_{1-3}-alkyl, meta-OH, meta-S— 1-3-alkyl, meta-F, meta-Cl, meta-CH_3, meta-CF_2H, meta-CF_3, or para-CF_3, or

R^5 represents para-Cl, or para-F, and R^4 represents meta-Cl, or meta-F, or

R^4 and R^5 together represent 3,4-OCH═CH—.

145. An isolated 1-phenyl-3-dimethylaminopropane diastereoisomer according to claim 141, wherein R^2 is CH_3, and R^3 is H.

146. An isolated 1-phenyl-3-dimethylaminopropane diastereomer according to claim 141, wherein R^9, R^{10} and R^{11} represent F.

147. A pharmaceutically acceptable salt of (−)-(1R,2R)-3R-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : RE 39,593 E
APPLICATION NO. : 10/462844
DATED : April 24, 2007
INVENTOR(S) : Helmut Buschmann et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

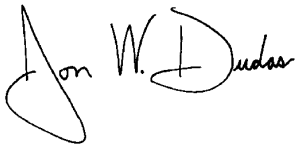
Cols. 25, 27, 29, 32, 34, 35 and 37, In claims 9, 25, 34, 66, 77, 95, and 106, "R^{6}" in formula la should read --R^{5}--.

Col. 35, In claim 86, line 4 should read:

--R^{2} represents CH_3;--

Signed and Sealed this

Seventeenth Day of June, 2008



JON W. DUDAS
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : RE 39,593 E
APPLICATION NO. : 10/462844
DATED : April 24, 2007
INVENTOR(S) : Helmut Buschmann et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In claim 66, Col. 33, lines 7-10 should read:

-- R^5 represents H, and R^4 represents meta-O-Z,

where Z is H, C_{1-3}-alkyl, $PO(OC_{1-4}alkyl)_2$, $CO(OC_{1-5}$-alkyl), $CONH\text{-}C_6H_4\text{-}(C_{1-3}$-alkyl) or $CO\text{-}C_6H_4\text{-}R^7$, in which R^7 is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^8)_2$, where R^8 is C_{1-4}-alkyl or 4-morpholino, --

Signed and Sealed this

Seventeenth Day of February, 2009

John Doll

JOHN DOLL
Acting Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : RE39,593 E
APPLICATION NO. : 10/462844
DATED : April 24, 2007
INVENTOR(S) : Helmut Buschmann et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 42, col. 30, line 52, "R^1 is a C_{1-4}-alkyl group;" should read -- R^1 represents a C_{1-4}-alkyl group; --.

Claim 42, col. 30, line 54, "R^8 is H; and" should read -- R^3 is H; and --.

Claim 59, col. 32, lines 14-15, "(+)-(2R, 3R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol hydrochloride (+1)" should read -- (±)-(2RS, 3RS)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol hydrochloride (±1) --.

Claim 62, col. 32, lines 23-24, "(+)-(1RS,2RS)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride (+21)" should read -- (±)-(1RS,2RS)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride (±21) --.

Claim 65, col. 32, lines 34-35, "(+)-(2RS, 3RS)-[3-(3-methoxyphenyl)-2-methylpentyl]-dimethylamine hydrochloride (+23)" should read -- (±)-(2RS,3RS)-[3-(3-methoxyphenyl)-2-methylpentyl]-dimethylamine hydrochloride (±23) --.

Claim 67, col. 33, line 35, "meta-CF_3, or" should read -- meta-CF_3 or para-CF_3, or --.

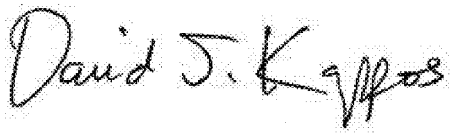
Claim 86, col. 35, line 8, "meta-OC_{1-8}-alkyl," should read -- meta-OC_{1-3}-alkyl, --.

Claim 87, col. 35, line 15, "meta OCH_8" should read -- meta-OCH_3 --.

Claim 115, col. 38, lines 2-3, "(+)-(1RS,2RS)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride (+21)" should read -- (±)-(1RS,2RS)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride (±21) --.

Claim 118, col. 38, lines 12-13, "(+)-(2RS,3RS)-[3-(3-methoxyphenyl)-2-methylpentyl]-dimethylamine hydrochloride (+23)" should read -- (±)-(2RS,3RS)-[3-(3-methoxyphenyl)-2-methylpentyl]-dimethylamine hydrochloride (±23) --.

Signed and Sealed this
Fourth Day of December, 2012



David J. Kappos
Director of the United States Patent and Trademark Office

CERTIFICATE OF CORRECTION (continued)

U.S. Pat. No. RE39,593 E

Claim 121, col. 38, lines 23-24, "(+)-(2RS, 3RS)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol hydrochloride (+1)" should read -- (±)-(2RS, 3RS)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol hydrochloride (±1) --.

Claim 147, col. 40, lines 31-32, "(–)-(1R,2R)-3R-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol" should read -- (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol --.