IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ELAN PHARMA INTERNATIONAL LIMITED,	**REDACTED PUBLIC VERSION**
Plaintiff,	C.A. No. 06-438-GMS
v.	
ABRAXIS BIOSCIENCE, INC.,	
Defendant.	

PLAINTIFF ELAN PHARMA INTERNATIONAL LIMITED'S ANSWERING BRIEF TO DEFENDANT ABRAXIS BIOSCIENCE, INC.'S MOTION TO COMPEL RESPONSES TO INTERROGATORIES AND PRODUCTION OF DOCUMENTS REFERRING TO ABRAXIS OR ABRAXANE

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I. Nature And Stage Of Proceedings

On July 19, 2006, Plaintiff Elan Pharma International Limited ("Elan") filed suit alleging that Abraxis BioScience, Inc. ("Abraxis") infringes U.S. Patent Nos. 5,399,363 (the "'363 Patent") and 5,834,025 (the "'025 Patent") (collectively, the "Patents-In-Suit"). The '363 Patent is directed to a nanoparticulate anticancer drug composition. The '025 Patent is directed to an intravenous method of administering a nanoparticulate drug composition so as to avoid eliciting adverse hemodynamic effects. The accused product, Abraxane®, is a nanoparticulate anticancer drug composition, which is intravenously administered.

Abraxis propounded several interrogatories and requests for production during fact discovery, which ended on August 13, 2007.[1] Several of those interrogatories are directed to Elan's theories of infringement. *See* Abraxis Exh. 6.[2] Further, Abraxis seeks Elan documents referring to Abraxis or Abraxane®. *See* Kruze Decl. ¶ 4. Abraxis has now moved to compel additional responses to these discovery requests. *See* D.I. 234 (the "Motion").

II. Summary Of Argument

Elan does not dispute that Abraxis is entitled to discovery of relevant information pertaining to Elan's theories of infringement in this action and to certain Elan documentation referring or relating to Abraxis or Abraxane®. However, Abraxis's Motion is wholly improper due to Elan's more than adequate discovery responses to date. Contrary to Abraxis's assertions:

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[1] Elan intends in the near future to file a number of requests for discovery relief, including but not limited to requests to extend the fact and expert discovery period, which were made necessary by Abraxis's non-compliance with legitimate Elan discovery requests, most egregiously, by refusing to produce witnesses for timely-noticed depositions and by improperly halting a deposition on grounds of "relevance" without immediately seeking protection from the Court as required by the Federal Rules and by every known precept of proper attorney conduct.

[2] Citations to "Abraxis Exh. __" refer to the Exhibits attached to the Declaration of Diana B. Kruze In Support Of Defendant Abraxis BioScience, Inc.'s Motion To Compel Responses To Interrogatories And Production Of Documents Referring To Abraxis Or Abraxane filed herein at D.I. 236 on August 8, 2007 (hereinafter "Kruze Decl.").

- Elan has provided more than adequate responses regarding its theories of infringement;
- Elan has not resisted the production of documents referring to Abraxis or Abraxane®. The documents produced constitute the full universe of documents within Elan's possession, custody, or control;
- Elan has produced all documents reporting the (very limited) consideration of Abraxane® by Elan. Abraxis is simply wrong in its speculative insistence that there must be extensive additional material relating to Abraxane®. Abraxis had extensive opportunity to depose Elan witnesses, none of whom had any extensive knowledge of or concern with Abraxane®. Elan cannot and need not produce that which does not exist.

III. Statement Of Facts

A. The Revolutionary Inventions Of The Patents-In-Suit

1. U.S. Patent No. 5,399,363 (the "'363 Patent")

Prior to the invention and teachings of the '363 Patent, there existed only one option for formulating anticancer drugs that do not dissolve well in water. That option was to dissolve the drug in something other than water. Bristol Myers Squibb marketed the first commercial formulation of paclitaxel, a known anticancer drug. That first commercial formulation is an intravenous composition called Taxol®. Because paclitaxel is practically insoluble in water, the pacltiaxel in Taxol® is dissolved in a castor oil-alcohol solvent known as Cremophor EL.

Cremophor EL is not only toxic to patients, it also causes very uncomfortable hypersensitivity reactions. It has also been reported that Cremophor EL lessens the effectiveness

of the paclitaxel drug. *See, e.g.*, Elan Exh. 1,[3] U.S. Patent No. 6,432,928 at 2:40-55. The problems associated with Cremophor EL require that patients undergoing chemotherapy with Taxol® be pre-medicated with additional drugs to treat hypersensitivity reactions. Typically, the additional drugs includes antihistamine and steroids, both of which may have their own adverse health effects. Additionally, due to the toxicity of Cremophor EL the maximum tolerated dosage of Taxol® for a patient is limited.

The inventors of the '363 Patent solved the problems associated with formulating poorly water soluble anticancer drugs. They realized that if the drug particles were small enough, the drug need not be dissolved in a toxic solvent for administration to a patient, but rather could dissolve in the patient's bloodstream by virtue of their minute size. The key, however, was not only to be able to create such small drug particles but to maintain the tiny size of those particles. This was because it was known that very small particles have a tendency to clump together to form larger particles; a phenomenon known as "aggregation." The inventors' discovery of nanoparticles that would maintain their small size (stable nanoparticles) would revolutionize formulations of poorly soluble and of insoluble drugs.

The '363 Patent is directed to such stable nanoparticles. The stable nanoparticles have an effective average particle size smaller than 1,000 nanometers (nm).[4] Such particles are so small that they are invisible to the naked eye. The nanoparticles consist essentially of a poorly water soluble crystalline anticancer drug and a non-crosslinked[5] surface modifier. The non-

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[3] Citations to "Elan Exh. __" refer to the Exhibits In Support Of Plaintiff Elan Pharma International Limited's Answering Brief to Defendant Abraxis BioScience, Inc.'s Motion To Compel Responses To Interrogatories And Production Of Documents Referring To Abraxis Or Abraxane filed contemporaneously herewith.

[4] For perspective, the size of a pinhead is about 1,000,000 nm.

[5] A cross-link[age] is "the setting up of chemical links between the molecular chains of polymers." Elan Exh. 2, McGraw-Hill Dictionary of Scientific and Technical Terms (1989) at 456.

crosslinked surface modifier is "adsorbed" (that is, retained but not chemically bonded) onto the surface of the crystalline anticancer drug and is sufficient to stabilize the particle size by preventing clumping or aggregation. The surface modifier prevents clumping by acting as a barrier between the particles[6] such that close contact is minimized and clumping cannot occur. This achievement is important not only for ensuring small particle size and hence ability to dissolve even a poorly-soluble particle, but also because aggregated particles are less efficacious and in some instances are dangerous.

2. U.S. Patent No. 5,834,025 (the "'025 Patent")

The *in vivo* administration of nanoparticles was sometimes found to cause dangerous cardiovascular dysfunctions, such as reductions in blood pressure and cardiac function. But the inventors of the '025 Patent discovered a method of administering a formulation of nanoparticles in a safe manner — a manner by which dangerous cardiovascular dysfunction would be reduced or even eliminated.

The inventors discovered that controlling the rate of administration of a formulation of nanoparticles, such that the nanoparticles are administered at an optimum infusion rate not exceeding 10 milligrams per minute, could reduce or avoid adverse hemodynamic effects.

B. ABRAXANE® — The Accused Product

Abraxane® in its freeze dried formulation is a formulation of nanoparticles containing 100 mg of paclitaxel, and approximately 900 mg of human albumin.[7] The

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[6] Elan Exh. 3, U.S. Patent No. 5,145,684 at 8:22-29 (which is incorporated by reference into the '363 Patent at 1:7-11).

[7] Abraxane is sold as a freeze dried powder that Abraxis instructs physicians to reconstitute with sterile saline water for administration to patients (because unreconstituted powdered drug formulations are physically incapable of being administered intravenously). The liquefied Abraxane suspension thus formed according to Abraxis's

continued ...

nanoparticles have a mean average size of about 130 nm. *See*. REDACTED ; Elan Exh. 6, ABRX0219406 ("Abraxane consists only of albumin-bound paclitaxel particles with a mean size of approximately 130 nanometers").

The human albumin

REDACTED

Thus, Abraxane® is a formulation that includes stable nanoparticles — particles in which the anticancer agent is maintained at submicron (less than 1000 nm) size by a surface modifier.

Although the Abraxane® formulation as a whole contains an over abundance of albumin (approximately 90%),

REDACTED

. Thus, the albumin-dominated Abraxane® formulation taken as a whole may appear amorphous. Indeed, any combination of compounds containing at least 90% of an amorphous substance, human albumin, would appear, taken as a whole, amorphous.

REDACTED . But the claims of the '363 Patent are directed to "particles," not just to combined formulations of particles and excessive amounts of amorphous stabilizers, and the claims of the '025 Patent are directed to a method of

instructions contains nanoparticles of paclitaxel and albumin, excess albumin unbound to the nanoparticle, and saline water for infusion. The form of Abraxane sold as a freeze dried solid powder for reconstitution contains only the nanoparticle of paclitaxel and albumin, and excess unbound albumin. *See, e.g.*, Elan Exh. 4, Abraxane May 2007 Package Insert.

administering such a nanoparticle composition. Thus, Elan's infringement contentions focus upon the drug containing nanoparticles dispersed within Abraxane®.

Abraxis instructs the medical community to prepare freeze dried Abraxane® for intravenous administration by reconstituting the freeze dried cake in saline water. Elan Exh. 4, Abraxane® May 2007 Package Insert. Although Abraxis's package insert literature publicly advises physicians to dose Abraxane® at 260 mg/m^2 over 30 minutes,

REDACTED

C. Abraxis's Interrogatories And Elan's Responses

Prior to any depositions, prior to Abraxis's inadequate and incomplete production of documents pertaining to the Abraxane® formulation and its manufacturing process, and prior to the Court's construing the claims of the Patents-In-Suit, Abraxis propounded its First Set of Interrogatories, which consisted of a sole contention interrogatory requesting: (1) a detailed explanation of why Elan contended that Abraxis infringes the Patents-In-Suit; (2) an element-by-element claim chart illustrating Elan's contentions; and (3) references to the documents and other evidence upon which Elan relied for its contentions.

In response to this premature, compound contention interrogatory, Elan provided Abraxis with an element-by-element claim chart for each asserted claim of the Patents-In-Suit

and identified each component of the nanoparticles within Abraxane® that corresponded to each respective element of each claim of the Patents-In-Suit. Elan supplemented its response to this Interrogatory as discovery progressed and pertinent documents were produced in the course of this litigation

Abraxis's Second Set of Interrogatories, served within two weeks of its First Set of Interrogatories, requested, among other things, an explanation of why Elan contends that Abraxis induces infringement and/or contributorily infringes each claim of the Patents-In-Suit. In response to Abraxis's interrogatory, Elan provided in addition to the claim chart an outline of its infringement contentions, and reserved the right to supplement as discovery progressed and depositions were underway.

Abraxis's Third Set of Interrogatories improperly seeks to shift the burden on issues of validity and enforceability of the Patents-In-Suit to the patentee, Elan. Essentially, for the '363 Patent alone, Abraxis cited over fifty prior art references and asked Elan why each claim of the patent is valid over each of the references. This is not how discovery proceeds in patent litigation, on an issue for which Abraxis carries, at every stage, the burden of proof by clear and convincing evidence. Both Patents-In-Suit are presumed valid by statute. *See* 35 U.S.C. § 282. It would be grossly burdensome to expect or require Elan to produce, under the guise of fact discovery, a claim-by-claim legal analysis of dozens of prior art references on an issue as to which it does not bear the burden of persuasion on validity.

Elan has in good faith responded fully and completely to Abraxis's discovery requests, as well as making available for depositions all those individual witnesses noticed by Abraxis. This approach stands in stark contrast to Abraxis's routine obstruction of discovery by, for instance, **REDACTED**

REDACTED

D. Elan Produced All Non-Privileged, Documents Regarding Abraxis Or Abraxane®

Elan agreed to produce documents responsive to Abraxis's requests for documents regarding Abraxane® or Abraxis. Elan has done so. Abraxis now attempts to mischaracterize the facts underlying the produced documents in order to divert attention from the real issue in this case: Abraxis's infringement of the Patents-In-Suit.

1. REDACTED

Over a decade ago, Dr. Neil Desai, the lead formulation scientist for Abraxane® made it his practice to

REDACTED

REDACTED

REDACTED

2. Elan employees Relied Solely Upon The Representations Of Abraxis That The Paclitaxel In Abraxane® Was Allegedly Amorphous

This is not a lawsuit about whether Elan replicated Abraxane®, or about what Elan employees believed about the nature of Abraxane® — neither of which issues has any relevance to whether Abraxis infringes the claims of the Patents-In-Suit as construed by the Court.

REDACTED

REDACTED

REDACTED

REDACTED

REDACTED

REDACTED

3. No Testing Of Abraxane® Was Required Or Performed Within Elan

Whether Elan internally tested Abraxane® is another issue having no relevance to Abraxis's infringement or any other live issue.

REDACTED

Indeed, Mr. David Czekai, vice president and general manager of Elan NanoSystems, a business unit of Elan, testified explicitly

REDACTED

Dr. Gary Liversidge, lead inventor on nanoparticle technology further corroborated Mr. Czekai during his deposition.

REDACTED

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Dr. Elaine Liversidge further conclusively corroborates that REDACTED

REDACTED

Despite the uncontroverted testimony of three different employees within Elan — each corroborating that REDACTED — Abraxis continues to

insist on further discovery into data on "Elan's Abraxane® testing" that does not exist and would have no legal relevance if it did.

4. Elan's Consideration Of Practicing Its Own Invention By Evaluating Possible Generic Paclitaxel Nanoparticle Formulations Has No Relevance And Is In No Way Culpable

In yet another instance of its misguided and fanatical focus upon Elan's real or imagined conduct that is neither culpable nor relevant in any way to the claims and defenses in this case, Abraxis demands further discovery

REDACTED

Elan is not only the innovator of this technology, it has been at the forefront of the nanoparticulate technology over the last fifteen years.

Abraxis's insistence on further discovery into information that does not exist

REDACTED

Of course, development of potential generics is routine practice in the pharmaceutical industry. It is explicitly authorized and endorsed by the Hatch-Waxman Amendments to the Food, Drug and Cosmetic Act. *See* 21 U.S.C. § 355. Finally, it has nothing to do with Abraxis's infringement or the validity of Elan's Patents-In-Suit.

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REDACTED

burdens Elan and this Court unduly and without legitimate purpose.

5. Elan Does Not Need To Determine The Manufacturing Process Used To Make Abraxane® To Formulate Potential Elan Product

In its final assertion of a demand that is more irrelevant accusation than an attempt to gain information that could establish a claim or defense on a live issue in this case,

REDACTED

Again it must be noted that even if Elan had or has engaged in speculation regarding Abraxis's manufacturing process based on publicly available (and in some cases, inaccurate) documents and information, this would amount to nothing more than idle curiosity and competitive intelligence on Elan's part. Certainly it would have no relevance to absolving Abraxis's infringement or invalidating the Patents-In-Suit.

REDACTED

Elan invented pioneering systems for stabilized nanoparticulate drugs, as reflected in the Patents-In-Suit, over a decade ago. Abraxane® was approved just two years ago.

REDACTED

REDACTED Abraxis then makes the further illogical argument that because among more than 26,000 documents, there was sporadic and isolated reference to or speculation about the manufacture of Abraxane® (in the form of 240 produced documents), the presence of this small number of documents is, by itself, proof that a much larger quantity of documents must exist, and that it is being withheld for nefarious reasons.

No such trove of hidden "Abraxane® manufacturing" documents exists. Elan has produced, as it said it would, all responsive documents, not privileged or protected under attorney work product, to Abraxis. Elan also produced its privilege log over a week ago.

IV. Argument

A. Legal Standard

Pursuant to the Federal Rules of Civil Procedure a party may obtain discovery regarding any matter, not privileged, that is relevant o the claim or defense of a party. *See* Fed. R. Civ. P. 26(b)(1). Generally, however, a motion to compel discovery will be denied if the materials sought are privileged or protected under attorney work product doctrine, regardless of whether the materials fall within the definition of relevance. *See* Fed. R. Civ. P. 26(b)(1), (3). Further, motions to compel discovery may be denied in light of the 1983 amendments to Rule 26 even if the moving party shows that the material sought is relevant and the opposing party fails to show that the material is protected by privileged or work product doctrine, if the discovery demanded is not consistent with the Rules' requirement of proportionality of burdens and good faith discovery practice.

Pursuant to the proportionality requirements, a motion to compel must be denied if the party opposing the discovery shows the Court that: (1) the discovery sought is unreasonably cumulative or duplicative; (2) the discovery sought is obtainable from some other source that is more convenient, less burdensome, or less expensive; (3) the party seeking the

discovery has had ample opportunity by discovery in the action to obtain the information sought; and/or (4) the burden or expense of the proposed discovery outweighs its likely benefit, taking into account the needs of the case, the amount in controversy, the parties' resources, the importance of the issues at stake in the litigation, and the importance of the proposed discovery in resolving the issues. 7 *Moore's Federal Practice* § 37.22[2][d] (3d ed. 1998).

B. Abraxis's Motion To Compel Discovery Should Be Denied

For the reasons stated below, Abraxis's Motion should be denied by this Court.

1. Elan's Response To Abraxis's First Interrogatory

Elan in good faith responded to Abraxis's first interrogatory to the best of its ability without waiving privilege and/or attorney work product. Elan also seasonably supplemented its responses to Abraxis's discovery requests four times as discovery progressed.

(a) The '363 Patent

Abraxis's Motion amounts to, among other things, an attempt by subterfuge to force Elan to disclose privileged attorney and expert work product prior to the exchange of expert reports, currently scheduled to occur on September 14, 2007. Abraxis has no right to this material at this stage. Abraxis has ample notice of the nature of Elan's theory of infringement. In response to Abraxis's contention interrogatory, Elan not only provided a narrative of its infringement contentions regarding the '363 Patent under 35 U.S.C. §§ 271(a), (b), and (c), it also provided an element-by-element claim chart, which cites to evidence to establish that Abraxane® meets the limitations of the asserted claims. Thus, Abraxis's lamentation that Elan has not provided Abraxis with any evidence or most of its contentions for its infringement allegations borders on falsehood.

The specific information sought by Abraxis regarding Elan's evidence that "reconstituted Abraxane®" infringes the '363 Patent can be found in its own documents. REDACTED

REDACTED However, to the extent that Abraxis seeks attorney work product, i.e., any possible underlying tests done by experts for this case at the direction of counsel, such information is clearly protected from discovery until the exchange of expert reports which is currently scheduled to occur on September 14, 2007. *See, e.g., In re Cendant Corp. Securities Litigation,* 343 F.3d 658, 662-63, 665 (3d Cir. 2003); Fed. R. Civ. P. 26(b)(3).

As Abraxis never met its burden of explaining how Elan's contentions regarding infringement under the doctrine of equivalents could be helpful to narrow the issues of the case so early in the case, prior to any deposition, and prior to any *Markman* Order, an early response to Abraxis's contention interrogatory would have been futile. Elan pledged that it would seasonably supplement its response and will do so shortly now that a Markman Order defining the claim terms has issued (as of only last week) that might permit detailed analysis of the scope of equivalents for these terms.

(b) The '025 Patent

Elan has clearly stated that its contention of infringement of the '025 Patent is an induced infringement claim.

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Despite the clarity of Elan's induced infringement claim, however, Abraxis asks this Court to "order Elan to voluntarily dismiss this claim," (Motion at 17), relying on *Refrac International, Ltd. v. Hitachi, Ltd.*, 921 F.2d 1247 (Fed. Cir. 1990), in support of its unfounded and Draconian request. *Refrac,* however, turned on facts starkly different from those here.

There, the plaintiff was found to have acted in bad faith because it had failed to identify the elements of *any* specific product corresponding with the elements of the patent claims, it made no specific reference to literal infringement or infringement by equivalents by any party, and it provided no analysis whatsoever with respect to the asserted patents. *Id.* at 1251. Nothing like that has occurred in this case and so Abraxis's reliance on *Refrac* is simply misplaced.

2. Elan's Response To Abraxis's Second Interrogatory (Indirect Infringement)

As to Abraxis's Interrogatory No. 2, which requests that Elan explain in detail why Abraxis indirectly infringes the Patents-In-Suit, Abraxis identifies four purported deficiencies in Elan's responses to date: (a) identification of the specific accused products; (b) time periods for which Elan alleges indirect infringement; (c) for the '025 Patent, an explanation of how Elan contends that Abraxis instructs doctors to infringe; and (d) the identity of other documents and other evidence upon which Elan relies. Motion at 17-18. Each of these purported deficiencies is simply not present, as illustrated herein.

(a) The Accused Products

In its amended answers to Abraxis's Interrogatory No. 2, for the '363 Patent, Elan specifically identified the forms of Abraxane® products for which Abraxis should be held liable as to inducing and contributory infringement. *See* Abraxis Exh. 20, Plaintiff Elan Pharma International Limited's Fourth Amended Responses And Objections to Abraxis's Second Set Of Interrogatories at 3-6. Specifically, for the '363 Patent, Elan alleges that reconstituted Abraxane® is the accused product for which Abraxis actively induces infringement and/or contributorily infringes the '363 Patent. *See id.* at 4-6. Further, for the '025 Patent, Elan alleges that reconstituted Abraxane® is the accused product for which Abraxis actively induces infringement. *See id.* at 5.

(b) The Relevant Time Period

Elan believes that the relevant time period was implicit in its infringement assertions making clear that Abraxis has actively induced infringement for as long as it has been made, used, sold, and offered for sale in the United States and Abraxis has instructed physicians to reconstitute it and administer it at infringing infusion rates. For clarity, Elan states herein that the relevant time period for which it asserts indirect infringement is January 2005 through the present and continuing forward until Abraxis's infringement ceases.

(c) Abraxis's Instructions To Physicians

Abraxis asserts that "Elan only cites numerous copies of Abraxis's package insert" in support of its contention that Abraxis meets the "10 mg/min" claim limitation of the '025 Patent. Motion at 18. This is factually incorrect. Elan has pointed specifically to Exhibit A to its amended answers to Abraxis's Interrogatory No. 1 to provide evidence of the relevant infusion rate. *See* Elan's Fourth Amended Responses and Objections to Abraxis's Second Set of Interrogatories at 5. Therein, Elan has identified numerous documents, including **REDACTED** **REDACTED** that evidence Abraxis's encouragement to physicians and those administering Abraxane® to patients to do so **REDACTED**, which would fall within the scope of the "10 mg/min" infusion rate limitation of the '025 Patent. *See* Exhibit A to Elan's Fourth Amended Responses to Abraxis's First Set of Interrogatories for Claims 1 and 13 of the '025 Patent.

(d) Identification Of Documents And Other Evidence

Elan has supplemented its interrogatory responses as further discovery has been completed. Elan again plans to supplement, specifically to include additional **REDACTED** that have been produced by Abraxis and to include relevant portions of the deposition testimony **REDACTED**

3. Abraxis's Third Interrogatory (Conception And Reduction To Practice)

Abraxis's Interrogatory No. 3, which requests for each claim of the Patents-In-Suit, a description of the dates and circumstances of its conception, design, development, actual reduction to practice, first written description, first disclosure to another, first offer for sale, and first public use is overly broad, unduly burdensome and oppressive. In this regard, Interrogatory No. 3 seeks Elan to provide descriptions of dates and circumstances for eight separate inquiries for each of thirty separate claims (the '363 Patent has 17 issued claims and the '025 Patent has 20 issued claims) issued in the Patents-In-Suit. Thus, Abraxis actually seeks information amounting to 296 separate interrogatories (8 queries x 37 claims). Further, Abraxis's request also seeks information regarding claims that are not asserted in this lawsuit. Thus, discovery on the non-asserted claims would be improper because it would not be germane to any claim or defense herein.

Despite the objectionable overbreadth and impermissible scope of Abraxis's interrogatory, Elan in good faith responded to Interrogatory No. 3 by specifically identifying documents by Bates numbers for each of the eight inquires noted in Abraxis's Interrogatory. Regarding the conception and reduction to practice inquiries, not only did Elan produce and direct Abraxis to the laboratory notebooks of the inventors, Elan also made each of the inventors available for deposition. Although the timing of reduction to practice may indeed be relevant to the issue of validity, Abraxis has not explained why it is incumbent upon Elan to essentially produce a specific date, ultimately reaching a quasi legal conclusion, instead of providing all of the underlying factual evidence that could support a conclusion about the timing. Instructive on this issue is *Kimberly-Clark Corp. v. Tyco Healthcare Retail Group*, No. 05-C-985, 2007 WL 218721, at *3-4 (E.D. Wis. Jan. 26, 2007), in which the Court found that providing the laboratory notebooks and the inventors for deposition was sufficient in response to an

Interrogatory regarding conception and reduction to practice. Elan has no information not now available to Abraxis to determine the requested information, so the burdens are at worst equal, and no relief is required.

4. Abraxis's Fourth Interrogatory (Willfulness)

The relevant inquiry for willfulness requires a showing of "objective recklessness," which involves proof by "clear and convincing evidence that the infringer acted despite an objectively high likelihood that its actions constituted infringement of a valid patent." *In re Seagate Tech., LLC*, No. 830, 2007 WL 2358677, at *5 (Fed. Cir. Aug. 20, 2007) (*en banc*). In response to Abraxis's Interrogatory No. 4, Elan provided Abraxis with the date of December 19, 2000 as the latest date by which Abraxis received actual notice of the '363 Patent. Elan explained the circumstances by which the '363 Patent was cited by the United States Patent and Trademark Office in reference to certain claims then pending in a patent application assigned to Abraxis. Further to Elan's response to Interrogatory No. 4, it reserved its right to supplement its answers as discovery progressed and as additional information is discovered.

Pursuant to this reservation, Elan is currently in the process of supplementing its response to this particular interrogatory based on newly-acquired information that establishes that

REDACTED

REDACTED

Accordingly, Elan will be supplementing its response to this Interrogatory shortly, to establish a much earlier date for Abraxis's notice of the Patents-In-Suit, and to specify particular evidence indicative of Abraxis's intent to copy Elan's invention. Abraxis's motion to compel discovery should accordingly be denied.

5. Abraxis's Fifth Interrogatory (Injunction)

Interrogatory No. 5 seeks information on which Elan will rely upon to prove its contention that it is entitled to a temporary, preliminary, and/or permanent injunction. Such an

inquiry seeks the invasive disclosure of the mental impressions, conclusions, opinions and legal theories of legal counsel, and differs substantially from a permissible inquiry, which asks a party to identify the facts and documents underlying a given contention. *See* Fed. R. Civ. P. 33(c); *Capacchione v. Charlotte-Mecklenburg Schs.*, 182 F.R.D. 486, 489 (W.D.N.C. 1998); 7 *Moore's Federal Practice* § 32.02[2][b] (3d ed. 1998).

Despite Abraxis's objectionable interrogatory, Elan responded by not only explaining bases for its contention for injunctive relief, but also by identifying documents to support such contentions. *See* Abraxis Exh. 20, Elan Pharma International Limited's Fourth Amended Responses and Objections to Abraxis's Second Set of Interrogatories at 20-21. Accordingly, Abraxis's motion should be denied.

6. Abraxis's Sixth Interrogatory (Damages)

Abraxis's Interrogatory No. 6 requests not only an explanation of why Elan is entitled to damages, but also a detailed description of the theory by which Elan contends it is entitled to such damages, including the mathematical calculations used to arrive at the amount of damages, the dates upon the calculations are based, and the identity of documents and other evidence that support the calculations.

Interrogatory No. 6 is not only premature, it requests information that is immune from discovery because of attorney-client privilege and/or work product doctrine as applied to the work product of a consulting expert.

REDACTED , Abraxis has failed to produce the necessary data for Elan to compute damages. **REDACTED**

REDACTED Elan, however, has pledged to supplement its answer and will timely supplement with expert analysis from its damages expert after receiving such necessary documents and in accordance with the Court's Scheduling Order,

which requires the exchange of opening expert reports on September 14, 2007. Thus, not only is this interrogatory premature, it seeks information protected under the work product doctrine. *Moore U.S.A. Inc. v. The Standard Register Co.*, No. 98-CV-485C(F), 2000 WL 876884, at *4 (W.D.N.Y. May 26, 2000) (holding response to interrogatory proper and complete to the extent it discloses damages to which plaintiff believed is will be entitled). Accordingly, Abraxis's motion to compel discovery on damages should be denied.

7. Abraxis's Seventh Interrogatory (Communications Regarding Patents)

Abraxis's Interrogatory No. 7 requests every communication with another party about the Patents-In-Suit or the '684 Patent, each instance in which Elan has offered a license under these patents, and each instance in which Elan threatened legal action based on these patents. Elan objected to this interrogatory on multiple proper grounds, but nevertheless provided a complete response.

Elan responded that it: (1) had not threatened or initiated litigation relating to the Patents-In-Suit; (2) had not threatened or initiated litigation relating to the '684 Patent; and (3) had followed and relied upon the procedures related to non-party confidential information in the Stipulated Protective Order. And as Abraxis itself concedes: "Elan has provided Abraxis with a list of licensees and a log of documents withheld on confidentiality grounds," as required by the Stipulated Protective Order. *See* Motion at 24.

Elan diligently pursued permission to disclose responsive information from non-parties. When Elan identified information in its possession, custody, or control that was responsive and subject to a contractual confidentiality agreements with third-parties, Elan then

sent letters to the third-parties seeking permission to disclose the information.[8] Abraxis complains about two redacted licenses (*See* Motion at 24), but fails to mention that these redactions were made at the direction of the non-party, as indicated in the log.

Abraxis also fails to mention that, despite the procedures concerning non-party confidential information outlined in the Stipulated Protective Order, it has directly subpoenaed many non-parties to produce the very information logged by Elan as confidential, including communications with non-parties.[9] Abraxis subpoenaed twelve third parties for licenses they held from Elan. Further, Elan granted EntreMed and Santen permission to produce confidential documents in its possession on July 31, 2007. Abraxis has separately received documents in response to its subpoenas from at least Acusphere, Ingredient Innovations International, Lyotropic Therapeutics, Inc., Nexstar Pharmaceuticals, Inc., Merck & Co., Inc., Wyeth-Ayerst Laboratories.

After subpoena some other non-parties have also agreed to allow Elan to produce documents, which Elan has done and will continue to do. For example, Bristol Myers Squibb and Santen have now both granted Elan the right to produce licenses responsive to Abraxis's Request. Accordingly Abraxis was provided with the Santen documents on August 21, 2007 and the Bristol Myers Squibb documents on August 9, 2007.

Abraxis's complaints about Elan's response to Interrogatory 7 are disingenuous. Elan followed the procedures in the Stipulated Protective Order seeking permission to produce confidential information from non-parties, produced such information, and continues to produce such information.

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[8] Elan has provided Abraxis with four Non-Party Confidentiality Logs, the latest of which is Elan's Amended Third Non-Party Confidentiality Log, dated June 29, 2007.

[9] The non-parties Abraxis subpoenaed are Elan's customers.

8. Abraxis's Tenth Interrogatory (Enforceability And Invalidity)

Issued patents have a strong presumption of validity in infringement proceedings. *Al-Site Corp. v. VSI Int'l, Inc.*, 174 F.3d 1308, 1323 (Fed. Cir. 1999). The burden of establishing invalidity rests on the party asserting such invalidity. *Id.; Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1050 (Fed. Cir. 1988). Moreover, the presumption of validity operates to place the burden of production of evidence and the burden of persuasion on the party who attacks the patent with regard to fact issues relating to the legal conclusion of invalidity. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1354 (Fed. Cir. 1983).

Abraxis attempts to shift the burden of production of evidence and the burden of persuasion onto Elan by requiring a detailed explanation and evidence upon which Elan relies to prove the validity and enforceability of the Patents-In-Suit. This is improper because it shifts the burden of proof onto the patent owner, and is a ploy to have Elan do Abraxis's work of identifying the closest prior art of the undifferentiated mass of references cited by Abraxis. Indeed, there could be no other logical reason for Abraxis to cite within the fifty-plus references it asserts against the '363 Patent, many that have already been considered by the United States Patent and Trademark Office during prosecution of that particular patent. It is well established that it is especially difficult to meet the burden of showing, by clear and convincing evidence, the invalidity of a patent when the prior art was before the Patent Office Examiner during prosecution of the application. *Hewlett-Packard Co. v. Bausch & Lomb, Inc.*, 909 F.2d 1464 (Fed. Cir. 1990). To the extent that the references were already considered by the Patent Office, this Interrogatory certainly borders on harassment.

Abraxis's Interrogatory is not even limited to the asserted claims of the Patents-In-Suit. Instead, Abraxis seeks a detailed explanation of why the "Patents-In-Suit are enforceable and valid." Further, Abraxis requests that the detailed explanation specifically

address the more than fifty allegedly invalidating individual references cited by Abraxis. Surely, Abraxis's unduly broad and compound Interrogatory would grossly exceed the limitation of 50 interrogatories, including subparts as provided by Delaware Local Rule 26.1 and set forth in October 30, 2006 Joint Status Report. *See* D.I. 11. For the '363 Patent alone, analysis of each of the 50-plus references against the 20 claims recited therein compel Elan effectively to address 1000 discrete interrogatories. The Court in *Martin Marietta Materials, Inc. v. Bedford Reinforced Plastics, Inc.*, No. 3:2003-57, 2007 WL 1300772 (W.D. Pa. May 2, 2007), held that a similar compound interrogatory need not be answered by the patent owner because such interrogatory created an undue burden on the patent owner.

Accordingly, Abraxis's motion compel a response to Interrogatory No. 10 should be denied.

9. Abraxis's Eleventh Interrogatory (Standing)

A party may produce or specify business records in lieu of a verbal answer to an interrogatory when: (a) the answer to an interrogatory may be derived or ascertained from the business records; (b) the burden of deriving or ascertaining the answer is substantially the same for the party serving the interrogatory as for the party served; and (c) the specification of documents is in sufficient detail to permit the interrogating party to locate and to identify, as readily as can the party served, the records from which the answer may be ascertained. Fed. R. Civ. P. 33(d).

In response to Abraxis's Interrogatory No. 11, which requests an explanation as to why Elan believes it has standing to sue for infringement of the Patents-In-Suit, Elan relied on Rule 33(d) and directed Abraxis to specified business records, namely the asset purchase agreement and assignment documents that establish that the chain of title of the Patents-In-Suit (as well as the continuing business operations associated with them) vests ultimately with Elan.

Indeed, the documents were identified with specificity by Elan, and the details of the transfers of ownership of the Patents-In-Suit and related business units can be ascertained from the documents themselves. Moreover, the burden of analyzing the conveyance documents would be the same for both Abraxis and Elan. Elan is obliged only to give the specified documentary information to Abraxis under Rule 33(d). It is not required to explain or interpret it. *Caliper Techs. Corp. v. Molecular Devices Corp.*, 213 F.R.D. 555 (N.D. Cal. 2003) (denying Caliper's request for a narrative response in spite of MDC responding by producing business records under Fed. R. Civ. P. 33(d)).

Abraxis's motion to compel a narrative response should accordingly be denied.

10. Abraxis's Twelfth Interrogatory (Nanoparticulate Paclitaxel)

In response to Abraxis's Interrogatory No. 12, which demands information on Elan's supposed attempts to develop a nanoparticulate paclitaxel composition, Elan once again properly relied upon Rule 33(d) and directed Abraxis to business records, by identifying specific Bates ranges of documents from which details of Elan's limited attempts to develop a nanoparticulate paclitaxel composition can be ascertained.

Abraxis's Motion relies upon two cases for the proposition that Elan's citation to allegedly-voluminous documents fails Rule 33(d)'s requirements. *See* Motion at 28. The responses to interrogatories given by the parties in Abraxis's cited cases, however, are distinguishable from the detailed response Elan provided for this interrogatory. In responding to interrogatories seeking information about the states' purchases of fine paper, the plaintiffs in *In re Fine Paper Antitrust Litigation* merely responded that documents containing the relevant information had already been produced in the litigation, without specifying where or when. *In re Fine Paper Antitrust Litig.*, 685 F.2d 810, 823 (3d Cir. 1982). The Court found that merely directing the party to the undifferentiated mass of business records already produced in the case

is an abuse of Rule 33(d). *Id.* Elan, however, has not merely said that the response to Abraxis's interrogatory is somewhere in its entire production of documents. Instead, Elan has identified the Bates ranges of documents that are believed to be specifically responsive to Abraxis's interrogatory. For example, instead of identifying all lab notebooks as a place where the response might be found, Elan identified specific pages of specific lab notebooks that contain information believed responsive to the interrogatory.

In Abraxis's other cited case, in responding to an interrogatory requesting the identity of each refinery and terminal in the United States that received shipments of crude oil from a particular source, defendant identified 53,000 pages of documents, of which only a handful produced contain the requested information. *Bowoto v. Chevron Corp.*, No. C 99-02506, 2006 WL 2507454, at *2 (N.D. Cal. Aug. 29, 2006). The facts of this case, however, are inapposite as Elan did not identify such a voluminous production wherein only a few documents possessed the information requested, as Abraxis would have the Court believe. Instead, Elan has identified with specificity reasonable Bates ranges that are responsive to Abraxis's interrogatory, without identifying a large amount of additional non-responsive documents. For example, in identifying responsive lab notebooks, Elan went to the effort of specifically identifying only the responsive pages of the lab notebooks rather than identifying the entirety of the books.

Moreover, the burden of analyzing the identified documents would be the same for both Abraxis and Elan, especially as Elan has, though not obligated to, pre-classified certain identified documents for Abraxis's benefit. For instance, Elan divided the specified documents into several categories including lab notebooks, presentations/charts, study reports, folder label/test reports, folder/images, folder label/internal memorandum, correspondence, procedure,

notes, articles, emails, patents, contracts, patent assignments, and proposals, all of which supererogatory categorization effort Abraxis's Motion ignores.

Accordingly, Abraxis's motion to compel more detailed responses should be denied.

11. Abraxis's Thirteenth Interrogatory (Contribution To Patents)

Abraxis's Interrogatory No. 13 requests a detailed description regarding the timing and specific contributions each inventor made to every claim in the of the Patents-In-Suit and the '684 Patent.[10] Elan responded to this interrogatory by referring to its answer to Abraxis's Interrogatory No. 3, which asks Elan to "describe the dates and circumstances of [each claims] conception, design, development [and] actual reduction to practice."

Abraxis's Interrogatory No. 13 and 3 are related in that they both request information about the circumstances surrounding the invention embodied in each claim of the Patents-in-Suit. An "inventor" is an individual who contributes to at least one claim of a patent. *Stern v. The Trustees of Columbia Univ.*, 434 F.3d 1375, 1378 (Fed. Cir. 2006); *Bd. of Educ. ex rel. Bd. of Tr. of Fla. State Univ. v. Am. BioScience, Inc.*, 333 F.3d 1330, 1340 (Fed. Cir. 2003) ("Invention requires conception."). Thus, the circumstances surrounding an inventor's conception of an invention necessarily also reflect the inventor's contribution to the invention. Accordingly, the documents Elan already identified under Rule 33(d) in answering Abraxis's Interrogatory No. 3 are equally sufficient to answer Abraxis's Interrogatory No. 13.

Unlike Abraxis's Interrogatory No. 3, Interrogatory No. 13 also demands information relating to the '684 Patent. The '684 Patent is not at issue in this litigation.

[10] The inventors of these patents are listed on the face of each patent.
See the '684 Patent, Elan Exh. 3; Abraxis; the '363 Patent, Abraxis Exh. 5; the '025 Patent, Abraxis Exh. 6:
'684: Gary G. Liversidge; Kenneth C. Cundy; John F. Bishop; David A. Czekai
'363: Gary G. Liversidge; Elaine Liversidge; Pramod P. Sarpotdar
'025: Lawrence de Garavilla; Elaine M. Liversidge; Gary G. Liversidge

Nevertheless, Abraxis asks for a detailed description of the timing and specific contributions of each named inventor on a claim-by-claim basis. (The '684 Patent has 20 claims and 4 inventors.) It also requests Elan to identify evidence supporting the contributions of each named inventor. Thus, Abraxis's request seeks information regarding claims that are not asserted in this lawsuit. Discovery on such non-asserted claims is improper because it is not germane to any claim or defense. *Cf. In re PE Corp. Secs. Litig.*, 221 F.R.D. 20, 24 (D.Conn. 2003) (noting that the 2000 amendment to Rule 26(b) establishes that discoverable facts should be germane to claim or defense alleged in pleading). Accordingly, inclusion of the '684 Patent in Interrogatory No. 13 is improper and Elan requests that it be permitted to refrain from responding at all to this burdensome portion of the interrogatory.

With respect to the Patents-in-Suit, Interrogatory No. 13 is overbroad because it requests an analysis of each of the named inventors' contribution to each patent claim, some of which are not asserted in this lawsuit. Discovery on such non-asserted claims is improper because it is not germane to any claim or defense. Accordingly, inclusion of non-asserted claims in Interrogatory No. 13 is improper.

Despite the objectionable overbreadth and impermissible scope of Abraxis's interrogatory, Elan in good faith responded to Interrogatory No. 13 by specifically identifying documents with reference to Interrogatory No. 3 under Rule 33(d). Not only did Elan produce and direct Abraxis to the laboratory notebooks of the inventors, Elan also made each of the inventors available for deposition. Abraxis took extensive testimony from the named inventors. Thus, the burden of extracting or further analyzing the information Abraxis demands (whether from the laboratory notebooks or the recorded testimony of the named inventors) would be identical for Abraxis and Elan.

C. Documents Referring To Abraxis Or Abraxane®

Abraxis's arguments on this topic are not only drawn out across six pages of text, they are redundant of earlier pages of text in its Opening Brief In Support of Abraxis's Motion To Compel Discovery. Elan will sum up for purposes of clarity and conciseness what it has already stated.

Simply put, Elan has produced all responsive documents it has to date identified within its possession, custody, and control referring to Abraxis or Abraxane®, unless the documents were privileged or protected from discovery based on attorney work product or another valid privilege. Indeed, Elan has already produced its privileged log. Elan does not know what phantom documents Abraxis thinks Elan is withholding that are responsive to this request, or to what more robust assurance to this effect Abraxis thinks it is entitled. Sworn testimony, certified interrogatory responses, and other discovery responses produced under the aegis of the Federal Rules, are all that Elan can offer, and they all refute the existence of some purposefully-withheld motherlode of responsive Elan documents referencing Abraxis or Abraxane®.

The illogic of Abraxis's vehement arguments on the "phantom Abraxane®/Abraxis documents" issues is obvious when one considers the fundamentally non-serious basis asserted for Abraxis's belief that there exist such phantom documents that have been improperly withheld. Abraxis comes to this illogical conclusion precisely because Elan *did* produce 240 documents responsive to this request, and because many of those documents were in the public domain. If the best efforts of Elan and its counsel to locate responsive, non-privileged documents had uncovered instead of 240, only 120, such documents, it is not clear whether Abraxis would insist that the hypothetical phantom Abraxis/Abraxane® document cache was twice as big, or only half as big.

In the world of what is real, and following Elan's diligent search, there is no such cache of documents known or believed by Elan to exist. Elan cannot prove the non-existence of documents with affirmative evidence, any more than it can prove any negative proposition. But nor do the Rules require it to do so.

Abraxis consistently jumps to conclusions about what documents should exist or must exist based on nothing more than its unfounded hunches and speculation.

REDACTED

Counsel for Elan has informed the Court (and Abraxis), through its opposition to Abraxis's unfounded Motion pursuant to Fed. R. Civ. P. 11, that Elan had identified a more than sufficient basis for filing the complaint for patent infringement against Abraxis and that testing of Abraxane® had been performed. Abraxis now attempts to take counsel's statements out of context to suggest that such testing took place *at Elan* and that thus (yet again) there simply *must* (based presumably again upon the scientific "one would expect to see" standard) exist a hidden mass of documentation for such non-existent testing. *See* Motion. Again, Abraxis makes this inference despite the sworn testimony of three Elan witnesses that **REDACTED**

If the testing took place, Abraxis's cross-examination of these witnesses should have revealed it, unless Abraxis intends to take the next egregious step and allege a conspiracy to falsify testimony by Elan.

Abraxis's demands in the Motion for "Abraxane® testing" information, while couched largely in terms of phantom testing by Elan, is, at the end of the day a covert attempt to secure a broad order compelling revelation of *all* tests or analyses of Abraxane®. If such an Order were improvidently granted, Abraxis clearly plans to compel Elan to disclose and produce any underlying testing or analyses of crystallinity and other properties of Abraxane® conducted, for instance, by technologists working upon direction of Elan's counsel in developing Elan's pre-filing identification and further confirmation of the infringing nature of Abraxane®.

But the law establishes clearly that such attorney-directed information development and analysis is protected under the attorney work product doctrine, at least until the time that an expert involved in such analysis is designated as a testifying expert. *See generally In re Cendant Corp. Securities Litigation*, 343 F.3d 658. Nevertheless, Abraxis prays that this Court should compel Elan to produce all its protected testing or alternatively preclude Elan from

using the tests as evidence at trial. Abraxis's argument is not only Draconian, it is not at all the law.

Abraxis relies on *Glaxo, Inc. v. Torpharm, Inc.* No. 95 C 4686, 1996 WL 411487 (N.D. Ill. July 18, 1996), to support its contention that *any* testing results relating Abraxane® (including testing by a consulting expert, if any) are discoverable and should be produced by compulsion. Abraxis again presents to this Court an inapposite precedent. In *Glaxo,* defendant sought and the court compelled tests conducted by plaintiff's technical experts in the course of a *past litigation*. Not only was the defendant in *Glaxo* not a party to the past litigation, it propounded discovery requests relating to other litigations.

> Defendants seek a variety of documents, most of which relate to tests conducted by Glaxo or disclosure of documents from past litigation. Although the test results are discoverable, most of defendant's document production requests are overly broad, particularly those relating to companion litigation. For the purposes of the discussion below, companion litigation refers to lawsuits conducted by Glaxo against companies described as Novopharm, Genpharm, and Geneva in the parties briefs.

Id., at * 2. Nothing in *Glaxo* supports Abraxis's brash attempt to breach an important privilege. Not only is *Glaxo* not controlling on the facts here, for the reasons discussed above, Abraxis's characterization of it as "strikingly similar to the [case] at bar" (Motion at 35), is not a fair characterization of either the precedent or of the circumstances of this action.

V. Conclusion

For the foregoing reasons, the Court should deny in its entirety Abraxis's Motion to Compel.

ASHBY & GEDDES

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Dated: August 22, 2007
183497.1

EXHIBIT 1

US006432928B1

(12) **United States Patent**
Szente et al.

(10) **Patent No.: US 6,432,928 B1**
(45) **Date of Patent: Aug. 13, 2002**

(54) **COMPLEXES AND THEIR COMPOSITIONS**

(75) Inventors: **Lajos Szente**; **Jozsef Szejtli**; **Maria Vikmon nee Kiraly**; **Julia Szeman**, all of Budapest (HU)

(73) Assignee: **Chinoin Gyogyszer es Vegyeszeti Termekek Gyara Rt.**, Budapest (HU)

(*) 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.: **08/836,390**

(22) PCT Filed: **Nov. 2, 1995**

(86) PCT No.: **PCT/HU95/00055**

§ 371 (c)(1),
(2), (4) Date: **Aug. 1, 1997**

(87) PCT Pub. No.: **WO96/14872**

PCT Pub. Date: **May 23, 1996**

(30) **Foreign Application Priority Data**

Nov. 11, 1994 (HU) 9403237

(51) **Int. Cl.**[7] **A61K 31/715**; C08B 37/16
(52) **U.S. Cl.** **514/58**; 536/103
(58) **Field of Search** 536/103; 514/58

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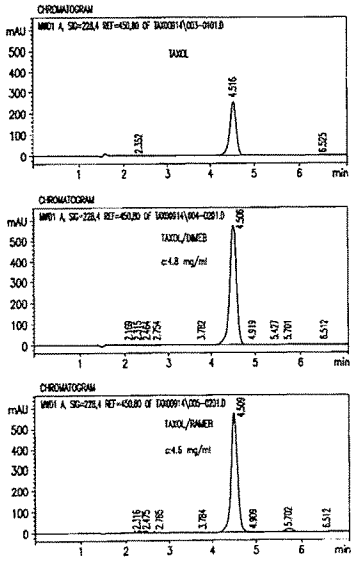
Primary Examiner—James O. Wilson
Assistant Examiner—Everett White
(74) *Attorney, Agent, or Firm*—Birch, Stewart, Kolasch & Birch, LLP

(57) **ABSTRACT**

This invention provides inclusion complexes of Taxol ((2aR-(aα,4β,4aβ,6β,9α(αR*,βS*),11α,12α,12aα,12bα))-β-(benzoylamino)-α-hydroxy-benzene-propanoic acid 6,12-b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclo-deca-(3,4)-benz-(1,2-b)-oxeth-9-yl-ester)) or Taxotere (butoxycarbonyl-10-desacetyl-N-debenzoyl-Taxol) or Taxus extracts formed with a cyclodextrin derivative and a co-solvent. This invention relates to pharmaceutical composition with increased water-solubility and stability. This invention provides the process for the preparation of an inclusion complex of Taxol or Taxotere or a brevifolia extract of Taxus formed with a cyclodextrin derivative and a co-solvent. This invention relates to pharmaceutical composition, containing as active ingredient an effective amount of an inclusion complex of Taxol or Taxotere or a Taxus brevifolia extract formed with a cyclodextrin derivative, preferably heptakis-2,6-0 dimethyl-β-cyclodextrin, random methylated β-cyclodextrin, succinylmethyl-β-cyclodextrin and a co-solvent together with usual filling, diluting and other auxiliaries generally used in the pharmaceutical industry.

22 Claims, 2 Drawing Sheets



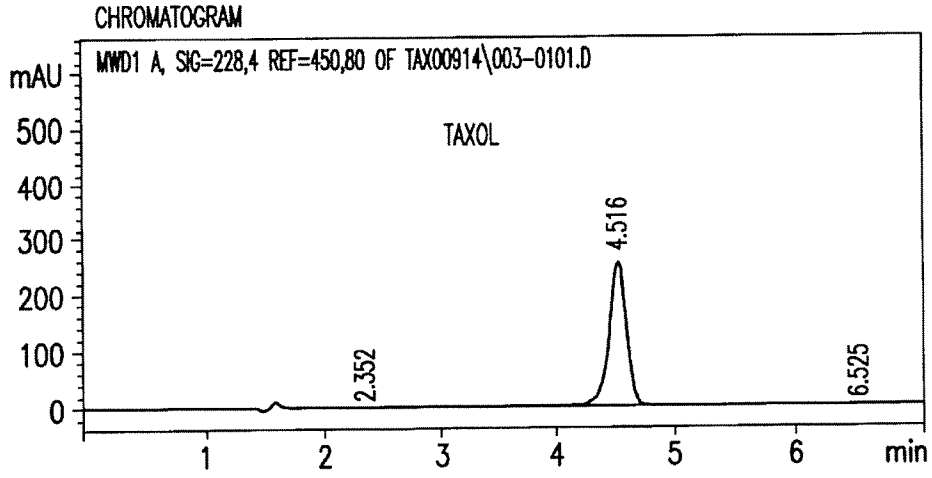


FIG.1A

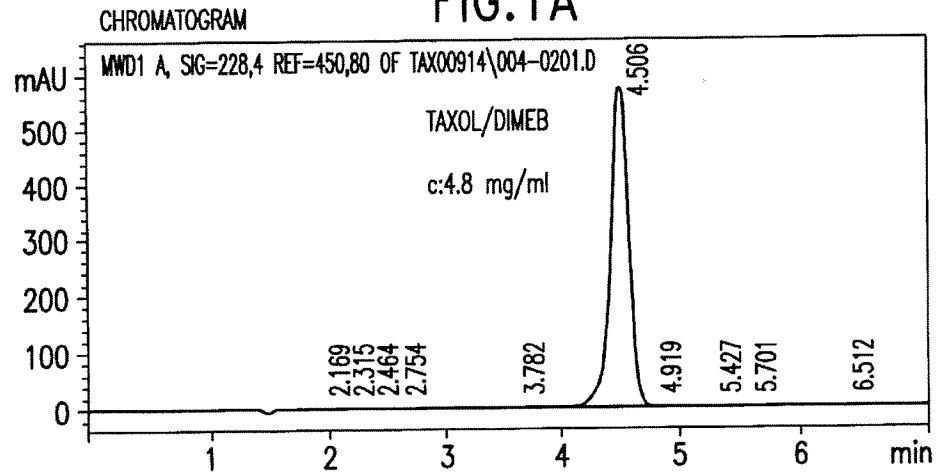


FIG.1B

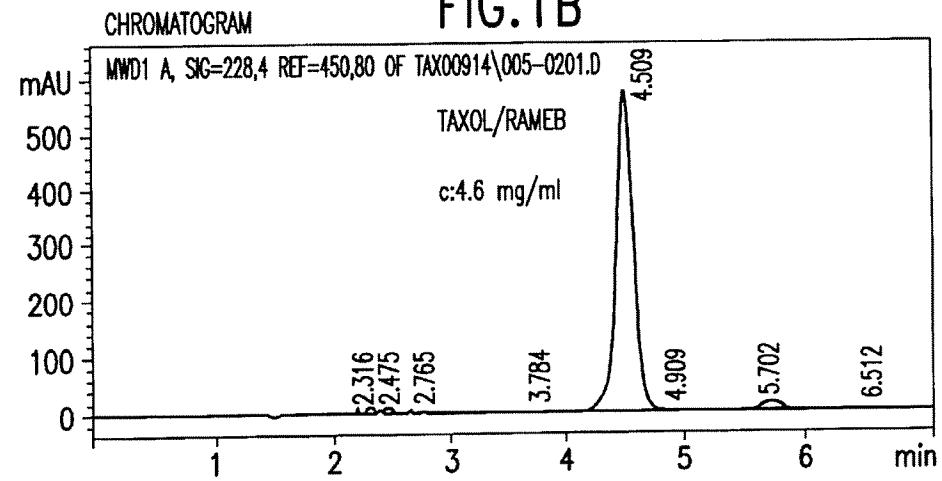


FIG.1C

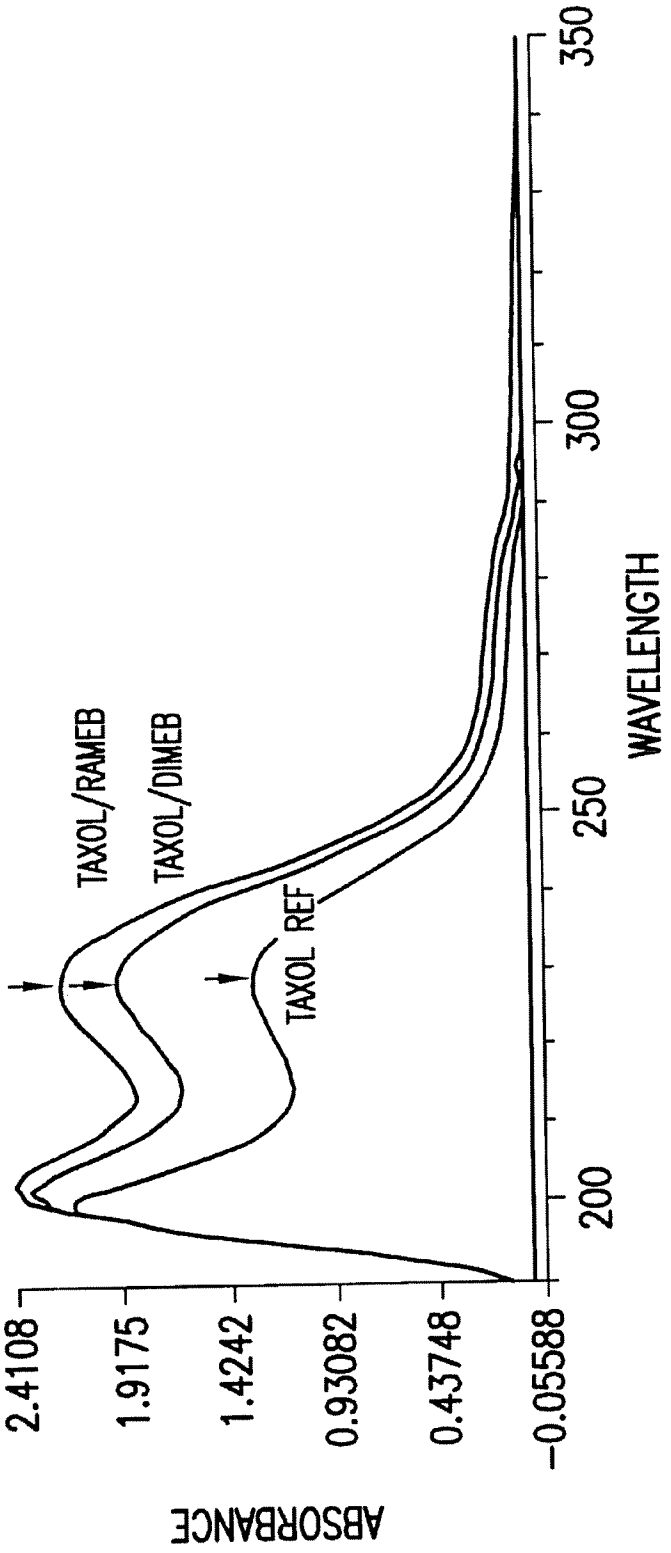

ABSORBANCE
2.4108
1.9175
1.4242
0.93082
0.43748
−0.05588
200
250
300
350
WAVELENGTH
TAXOL/RAMEB
TAXOL/DIMEB
TAXOL REF

FIG.2

COMPLEXES AND THEIR COMPOSITIONS

The invention relates to the inclusion complexes or mixtures of Taxol {[2aR-[2aα,4β,4aβ,6β,9α(αR*, βS*a11α,12α,12aα,12bα]]-β-(benzoylamino)-α-hydroxybenzene-propanoic acid 6,12-b-bis(acetyloxy)-12-(benzoyloxy)-2a,3-4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetra-methyl-5-oxo-7,11-methano-1H-cyklodeca[3,4]-benz-[1,2-b]-oxeth-9-yl-ester]} or Taxotere (butoxycarbonyl-10-desacetyl-N-debenzoyl-Taxol) or Taxus extracts (containing other diterpene Taxane derivatives besides Taxolon like cephalomannin 10-desacetyltaxol, desacetyl-baccatine III, baccatine III, baccatine III, cinnamoyl taxines, taxusine) formed with a cyclodextrin derivative and a co-solvent, process for their preparation and pharmaceutical compositions containing them, further their pharmaceutical application.

Although Taxol shows promising biological effect and significant anti-tumor activity, its pharmaceutical use is accompanied by several difficulties:

- the solubility of taxanes is rather poor, e.g. taxol dissolves in water at 25° C. by 0.55–0.59 μg/ml (determined by Cyclolab Kft. Budapest);
- taxol is very sensitive to light and pH, during its decomposition biologically inactive products are formed;
- the pharmacological results relating to taxol are questionable because the solvents used (Cremophor EL) are themselves cytotoxic [J. N. Denis; J. Am Chem. Soc. 110, 5917 (1988); M. I. Fjaellskog et al: Lancet. 342–873 (1993); and L. Webster et al: J. Natl. Cancel Inst. 85, 1685 (1993)].

Several processes are known for eliminating the disadvantageous features described above:

- use of solubilizing agents [1:1 mixture of Cremophor EI and anhydrous ethanol (Natl. Cancer Institute, Paclitaxel Documentation)];
- forming of chemically modified micromicelles by using phosphatidylethanolamines (Lipis Specialities, Inc., European patent specification No. 118.316);
- use of ethanol polysorbate mixtures for increasing solubility (Rhone-Poulenc Rorer, European patent specifications Nos. 522.936 and 522.937);
- use of liposomic taxol formulations [e.g. R. Aquilar and R. Rafaelloff: published patent specification No. WO 93/18751; A. Sharma et al: Pharm. Res. 11, 889–896 (1994); and M. H. Alkan et al: J. Liposome Research 3.42 (1993)]: a Taxol concentration of about 1 mg/ml was obtained in unstable (four days at room temperature) compositions.

Attempts have been made for increasing the water-solubility of taxol also by forming synthetic derivatives [Zhao et al: J. Nat Prod. 54, 6, 1607 (1991); D. I. Kingston and Y. Y. Xang: European patent specification No. 537.905 and H. M. Deutsch et al: U.S. Pat. No. 5,157,0049]. The biological effectiveness of the chemically modified taxol derivatives having increased water-solubility was, however, modified disadvantageously, the multidrug resistance showed generally an increasing tendency while cytotoxicity, i.e. the biological effect, decreased.

To overcome the difficulties connected with the parenteral administration of taxol, taxol prodrugs with increased water-solubility have also been synthetized [A. Matthew et al: J. Med. Chem. 35, 1, 145 (1992)].

Bartoli et al tried to improve the generally weak stability of taxol by its microencapsulation [H. Bartoli et al: J. Microencapsulation, 7, 2, 191, (1991)].

Especially the preparation of liquid taxol-containing pharmaceutical compositions for parenteral administration is difficult as the diterpenoid-type, very lipophilic taxane derivatives cannot be converted into suitable storable solutions in the desired concentration even by using significant amounts of detergents and mixtures containing aqueous-organic solvents [D. Tarr et al: Pharm. Res. 4, 162–165 (1987)]. The taxol composition described contains soybean oil, lecithin, egg-yolk, phosphilipids and glycerol, its taxol-content is, however, only 0.3 mg/ml due to the low solubility. A taxol emulsion with a taxol content of 20 mg/ml has also been developed; this composition contains 50% of triacetine (1,2,3-triacetyl-glycerol) but this triacetine has also been proved toxic (in mouse experiments LD_{50}=1.2 mg/ml, a 50% triacetine emulsion).

The registered parenteral taxol compositions are formulated in emulsions in a concentration of 6 mg/ml containing a 1:1 by volume mixture of polyoxyethylated castor oil (Cremophor-EL): alcohol and are diluted to ten-fold volume when administered. The use of these parenteral compositions is accompanied by several disadvantageous side effects such as a heavy allergy due to the Cremophor EL administered intravenously. Further, the taxol formulations prepared in an ethanolic solvent mixture are not clear solutions but are slightly opalescent [L. A. Trissel: Am. J. Hosp. Pharm. 50, 300 (1993)], thus they can precipitate when diluted or administered simultaneously with other medicines.

The only commercially available Taxol composition, i.e. PACLITAXEL (prepared by the firm Bristol-Myers-Squibb), contains 6 mg/ml of Taxol together with 527 mg/ml Cremophor EL and 47% by weight of anhydrous ethanol. Before administration it is to be diluted by 0.9% physiologic sodium chloride solution of 5% dextrose to a concentration of 0.03 mg/ml. The physical and chemical stability of the diluted solution is indicated between 12 and 24 hours. The diluted solution must be filtered through a 0.2μmembrane filter before its administration by infusion as the solution may be opalescent due to the non-ionic surfactants, such as Cremophor EL.

Although the Cremophor EL generally used in Taxol derivatives is well soluble and is a solvent generally used in the preparation of other pharmaceutical compositions, it is not a biologically inert agent. It causes sensitivity reactions accompanied by different vasodilating, air-thirst causing and hypotensive effects. According to literature references [e.g; Pharmacology and Toxicology of Cremophor EL diluent: The Annals of Pharmacotheraphy, 1994 May, Vol. 28, S11–S115; Pharmaceutical Research, Vol. II., No. 6, 889–895; and Vol. II, No. 2, 206–212, (1994)] Cremophor EL is toxic and causes allergic reactions. Its toxic effect has been proved also by our own biological pharmacological tests. The Journal of the National Cancer Institute (Vol. 85, No. 20, Oct. 20, 1993) describes that Cremophor EL is not only toxic but in case of Taxol compounds inhibits the active ingredients to exert their effect in the intracellular field.

A mixed-miceller proliposomal Taxol composition suitable for parenteral administration is described by H. A. Onynksel et al (Pharm. Res. Vol. 11, No. 2, 206–212). Taxol is dissolved in a mixed micelle system containing bile acid salt and phospholipide and the spontaneously formed liposomes are diluted. The solubility of Taxol can be increased only to 0.8 mg/ml even by using various bile acid salts (sodium desoxycholate, sodium cholate, sodium taurocholate, sodium taurodesoxycholate).

According to the authors the large-scale production is connected with plenty of problems and the stability of the composition is limited as Taxol is precipitated upon stand-

ing. A slight precipitation is declared in case of a composition containing 0.4 mg/ml of Taxol stored at a temperature of 7 to 24° C. The composition is diluted directly before administration. Mouse tests prove that bile acid salts are less toxic than Cremophor EL.

In patent specification No. WO 94/07484 published recently (Research Corporation Technologies Inc., USA) Taxol-containing solutions and emulsions are disclosed. Taxol is dissolved in alcohol, then in oil and oil-in-water type emulsions containing 0.5–5 mg/ml of Taxol and having a drop size of 2–10 μm are prepared. These compositions are, however, unsuitable for administration by injection or infusion.

In patent specifications Nos. WO 94/12030 and WO 94/12198 injectable Taxol compositions are disclosed. In order to increase their stability, the pH-value of the Taxol and Cremophor EL containing compositions is adjusted to a value below 8.1, preferably between 5 and 7.5 by citric acid (the pH-value of the know Paclitaxel is 9.1) to obtain a solution with a stability of 7 days at 40° C.

In Australian patent specification No. 645,927 (Ensuiko Sugar Refining Co. Ltd. Yokohama-Shi, Japan) the inclusion complexes of Taxol formed with α- and γ-cyclodextrin further with maltosyl derivatives of cyclodextrins are disclosed, 1 mole of Taxol is reacted with 1–20 moles of cyclodextrin or a derivative thereof. The authors describe that the solubility of Taxol is increasing. The solubility increasing effect of γ-cyclodextrin proved to be the best at an increasing extent by increasing the concentration, however, only a solubility of 0.16 mg/ml could be achieved at a molar ratio of 1:20.

The interaction between 23 anticancer agents, Taxol included, and hydroxypropyl-β-cyclodextrin has been studied by T. Cserháti et al (Int. J. Pharm., 1994, 108,1, 69–75) and it was found very low in case of Taxol.

As disclosed in our Hungarian patent application No. P93 01373 we aimed at increasing the solubility of Taxol and Taxol derivatives by using cyclodextrins and derivatives thereof. A solubility of about 1 mg/ml could be achieved by using in each case 250–350 moles of a methylated cyclodextrin derivative related to 1 mole of Taxol. A complex has also been prepared from 1 mole of Taxol by using 2.3 moles of DIMEB in solid phase.

From the aforesaid it follows that according to literature references a Taxol concentration of up to about 1 mg/ml can be achieved by the various methods, except for the compositions prepared by using Cremophor EL (e.g. PACLITAXEL, 6 mg/ml). These are, however, not acceptable due to the toxic character of Cremophor EL.

The present inventors had the aim to increase the water-solubility of Taxol, Taxotere and Taxus extracts to a Taxol concentration of about 3–6 mg/ml without using Cremophor EL, which is a toxic auxiliary generally used in Taxol compositions. Further, we set the aim to prepare stable pharmaceutical compositions which can be diluted and formulated according to the different administration methods.

According to our invention the solubility of Taxol, Taxotere and Taxane derivatives is increased by using cyclodextrins and/or cyclodextrin derivatives and/or mixtures thereof and co-solvents without forming a real chemical bond between the Taxol type compounds and cyclodextrins. Depending on the mole ratios used and reaction conditions, solubility increasing interactions arise or complexes are formed with increased solubility. The formed inclusion complexes may optionally be recovered. The increase of the solubility achieved may be further increased by using a co-solvent and due to the use of co-solvents even compositions of such a concentration may be obtained which can be diluted by water without risking precipitation or decomposition.

The solubility-increasing effect of co-solvents is a surprising recognition as according to B. W. Müller and E. Albers (Journal of Pharmaceutical Sciences, Vol. 80, No. 6, June 1991) co-solvents disadvantageously influence the solubility-increasing effect of cyclodextrin derivatives. They examined and found disadvantageous the effect of the usual solubilizing agents, such as 1,2-propyleneglycol, sodium desoxycholate, exerted on different active ingredients (e.g. cholesterol) and hydroxypropyl-β-cyclodextrin.

The positive and synergistic effect of ethanol for increasing the solubility of Taxol with the simultaneous use of cyclodextrin was surprising as several earlier publications declared that the solubilizing effect of the chemically modified cyclodextrins is decreased by ethanol even in low concentrations

M. Otagiri et al described [Acta Farm. Suec. 1984, 21(6), p. 357–366] that the value of the stability constant and thereby the achievable solubility-increasing effect in the case of β-cyclodextrin and methylated derivatives is linearly decreased by methanol. In case of flufenamic acid the measurements indicated that the "aqueous" stability constant decreased from 1300 M^{-1} to about 400 $M^{31\ 1}$ in the presence of 25% by volume methanol.

J. Pitha and T. Hoshino [Int. J. Pharm., 80,243 (1992)] and T. Loftsson et al [7th Int. Symp. on Cyclodextrin (1994), Tokyo] also report that the drug-cyclodextrin complex formation decreases on the effect of different adjuvants, such as organic solvents. For example, in aqueous medium the solubility-increasing effect of cyclodextrin testosterone is decreased by ethanol even in low concentration, it acts as a competitive "guest" molecule.

In our experiments we have found that although a similar decrease was expected from ethanol, an increase of activity and an improvement of absorption could be observed.

Although Taxol itself dissolves well in ethanol and in a 1:1 mixture of ethanol and water, it immediately precipitates when diluted.

In our experiments we have found in case of a higher concentration, i.e. 4–6 mg/ml of Taxol and 150–200 mg/ml DIMEB or RAMEB (molar ratio of 1:10–1:20) that a clear solvent is obtained in a 1:1 or 2:1 co-solvent mixture of ethanol and distilled water. This mixture became cloudy during storage, then the Taxol precipitated and the solvent turned to white and gelatinous. However, on adding either an alcohol or a cyclodextrin derivative or mixtures thereof, the stable solution state could be reinstated.

We have further recognized that the best solubility could be observed at a Taxol:cyclodextrin molar ratio of about 1:30–1:40, when cyclodextrin presumably induces not only the interaction necessary for the complex-formation but further, e.g. hydrotropic interactions.

The compositions which contain Taxol and a cyclodextrin derivative and are prepared with a co-solvent, are clear solutions without opalescence and can be stored at room temperature by normal light for three months and can be, if necessary, further diluted. Thus, they can be used also in the form of injections and infusions.

Thus, the present invention relates to inclusion complexes of Taxol {[2aR-[2aα,4β,4aβ,6β,9α(αR*,βS*),11α-12α, 12aα,12bα]] β-(benzoylamino)-α-hydroxy-benzene-propanoic acid 6,12-b-bis(acetyloxy)-12-(benzoyloxy)-2a,3, 4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclo-deca

[3,4]-benz-[1,2-b]-oxeth-9-yl-ester]} or Taxotere (butoxycarbonyl-10-desacetyl-N-debenzoyll-Taxol) or Taxus extracts formed with a cyclodextrin derivative and a co-solvent.

Further, the present invention relates to compositions of increased water-solubility and stability, containing 0.01–0.6% by volume of a Taxol or Taxotere or Taxus extract, 10–65% by volume of cyclodextrin derivative, 10–90% by volume of a co-solvent and water in an amount necessary to 100% by volume.

The inclusion complexes of the invention can be prepared by

a) reacting a Taxol or Taxotere or Taxus extract in an aqueous co-solvent mixture with a cyclodextrin derivative, then separating the complex from the mixture by a method known per se;

b) reacting a Taxol or Taxotere or Taxus extract with a co-solvent and a cyclodextrin derivative in solid phase;

c) subjecting a Taxol or Taxotere or Taxus extract, a cyclodextrin derivative and a co-solvent to "high energy milling" treatment.

The complex can be separated from the mixture e.g. by filtration, centrifuging, lyophilization, drying by pulverization or drying in vacuo.

The "high energy milling" treatment of a Taxol or Taxotere or Taxus extract with a cyclodextrin derivative is disclosed in the published Hungarian patent specification No. T/52.366.

As preferred cyclodextrin derivatives the following compounds may be used:

heptakis-2,6-0-dimethyl-β-cyclodextrin (DIMEB);

random methylated β-cyclodextrin (RAMEB);

succinyl-methyl-β-cyclodextrin (SUMEB);

2-hydroxypropyl-β-cyclodextrin (HO-P-βCD); and

soluble anionic β-cyclodextrin polymer (CDPSI).

As co-solvent ethanol or a mixture of ethanol and water, preferably a (1–10):1, more preferably (1–3):1 mixture of ethanol and water can be used. The Taxol, Taxotere or Taxus extract and cyclodextrin were used in a molar ratio of 1:(10–65), preferably 1:(30–40).

The solubility-increase of Taxol was examined in the presence of cyclodextrins and derivatives thereof by the Higuchi-Connor method (Advances in Analytical Chemical Chemistry and Instrumentation, Vol. 4, New York, Willey-Interscience 1965, p. 117–212).

Aqueous solutions containing cyclodextrins in different, increasing concentrations, aqueous co-solvents-containing mixtures and Taxol in an amount higher than can be dissolved, were stirred at 22° C. for 24 hours (this time proved to be enough for complete dissolution). The suspension was filtered through a membrane filter with a pore size of 0.2–0.4 μm, and by diluting the clear filtrate the Taxol concentrations were measured by high pressure liquid chromatography method [HPLC, J. Leslie et al: J. Pharm. and Biomed. Anal 11, 1349 (1993)].

The water-solubility of Taxol was measured without cyclodextrin in the presence of different cyclodextrin derivatives by using co-solvents. The results are summarized in Table 1. The solubility data show that the solubility already increased due to the presence of cyclodextrins was further increased by the co-solvent.

TABLE 1

CD	solubility mg/ml	molar ratio TAXOl:CD	co-solvent	remark
—	0.0059		water	
—	4		2:1 ethanol:water	clear solution. opalescening. then white precipitate
γ-CD	4	1:63	2:1 ethanol:water	white suspension
DIMEB	~1	1:250	water	
	4	1:30	2:1 ethanol:water	
RAMEB	0.0044	1:1500	water	
	0.0425	1:750	water	
	0.2317	1.300	water	
	0.8599	1:278	water	
	4	1:33.8	2:1 ethanol-water	
	4	1;35	ethanol-water	
OH-P-βCD	0.1	1:28#5	water	

When preparing pharmaceutical compositions for the treatment of human cancer we selected, on the basis of the measured solubility data, solutions with relatively high Taxol that are stable and can be diluted by water without opalescence.

The effect of the Taxol-cyclodextrin compositions was examined on two human cancer cell cultures (PC 3 and K 562) in Taxol concentrations corresponding to a Taxol content of 10^{-4}, 10^{-5} and $10^{31\ 6}$ moles.

The examined compositions were the diluted solutions of Taxol-DIMEB according to Example 1, Taxol-RAMEB according to Example 2 and Taxol-γ-cyclodextrin according to Example 4. As control solutions containing similar amounts of cyclodextrins and no Taxol, further the Taxol-Cremophor EL composition. Cremophor EL solution and the untreated cell cultures were examined.

The experiments were carried out and evaluated on both cell lines according to the examination methods of F. Skehan et al [New Colorimetric Assay of Anticancer Drug Screening, J. Natl. Canc. Inst. 82, 1107–1113 (1990) and A. Martin and M. Clynes (Comparison of 5 Microplate Colorimetric Assays for in Vitro Cytotoxicity Testing and Cell Proliferation Assays, Cytotechnology 11, 49–58 (1993)] in the Pathological and Experimental Cancer Research Institute No. 1 of the Semmelweis Medical University, Budapest.

The cells were exposed in a RPMI 1640 medium containing 10% of Foetal Calf Serum (FCS) medium on a microplate of 96 wells, by placing 5000 cells in 100 μl of medium.

The cell cultures were treated after 24 hours with a solution containing the test substances in 100 μl of a FCS-free RPMI medium, thus the final concentration of FCS became 5%. Every evaluation point is the averaged result of 8 parallels, the control was present in 8 parallels on each plate, thus the evaluation point was obtained by averaging 24 parallels. The eight test compositions were examined simultaneously, in one test on each cell line.

After 72 and 96 hours the cell growth was measured by SRB-assay (the determining method is SRB-painting of the total protein, the total protein is proportional to the cell growth, the extinction was read by a Microplate reader at a wave length of 540 nm).

During the tests both cell lines were in growing phase even in the last 24 hours. The test results are summarized in Tables 2 and 3. From the data obtained it follows that:

Cremophor EF proved to be toxic per se for both tested cell lines;

cyclodextrins in a concentration of 0.1 mM without taxol (highest concentration used) caused practically a total cell destruction;

in case of the most diluted concentration (0.001 mM) the cyclodextrin "carriers" proved to be ineffective, they did not hinder proliferation. The Taxol-γ-cyclodextrin showed some effect in case of cell line PC 3, while the Taxol-DIMEB and Taxol-RAMEB compositions showed a higher cytotoxicity both on cell lines K 562 and PC 3 than the corresponding cyclodextrin derivative alone;

in case of cell line PC 3 the cytotoxic effect of Taxol-cyclodextrin was at least as high as that of Taxol dissolved in Cremophor EL.

TABLE 2

The effect of 10^{-6}M of Taxol and cyclodextrin on cell line PC 3

	Incubation Time	
Cell line PC 3	72 hours	96 hours
control	0.757 ± 0.204 (100%)	1.320 ± 0.298 (100%)
Cremophor EL	0.544 ± 0.134 (72%)	0.911 ± 0.280 (69%)
Taxol-Cremophor EL	0.189 ± 0.079 (25%)	0.279 ± 0.080 (21%)
γ-CD	0.582 ± 0.126 (77%)	0.937 ± 0,214 (71%)
Taxol-γ-CD	0.254 ± 0.069 (34%)	0.255 ± 0.063 (19%)
DIMEB	0.725 ± 0.200 (96%)	1.345 ± 0:269 (102%)
Taxol-DIMEB	0.404 ± 0.097 (53%)	0.228 ± 0.038 (17%)
RAMEB	0.701 ± 0.174 (93%)	1.496 ± 0.217 (113%)
Taxol-RAMEB	0.196 ± 0.054 (26%)	0,154 ± 0.032 (12%)

Cremophor is slightly toxic in the tested concentration.

Taxol-Cremophor is more toxic than Cremophor.

DIMEB and RAMEB are not toxic in the tested concentrations.

In Taxol-DIMEB and Taxol-RAMEB mixtures the cytotoxic effect of Taxol previal.

γ-CD is slightly toxic to the cells per se, the toxic effect of the Taxol-γ CD mixture is higher than that of γ-CD.

TABLE 3

The effect of 10−6M of Taxol and cyclodextrin on cell line K562

	Incubation Time	
Cell line K562	72 hours	96 hours
control	1.109 ± 0.235 (100%)	1.571 ± 0.336 (100%)
Cremophor EL	0.556 ± 0.237 (50%)	0.836 ± 0.158 (50%)
Taxol-Cremophor EL	0.459 ± 0.094 (41%)	0.394 ± 0.058 (25%)
γ-CD	0.555 ± 0.200 (50%)	0.531 ± 0,072 (34%)
Taxol-γ-CD	0.448 ± 0.070 (40%)	0.606 ± 0.107 (39%)
DIMEB	0.819 ± 0.178 (74%)	1.729 ± 0.185 (110%)

TABLE 3-continued

The effect of 10−6M of Taxol and cyclodextrin on cell line K562

	Incubation Time	
Cell line K562	72 hours	96 hours
Taxol-DIMEB	0.383 ± 0.075 (35%)	0.513 ± 0.064 (33%)
RAMEB	0.922 ± 0.239 (83%)	1.696 ± 0.163 (108%)
Taxol-RAMEB	0.196 ± 0.054 (26%)	0,154 ± 0.032 (12%)

Cremophor is toxic in the tested concentration.

Taxol-Cremophor is more toxic than Cremophor.

DIMEB and RAMEB are not toxic in the tested concentrations.

In Taxol-DIMEB and Taxol-RAMEB mixtures the cytotoxic effect of Taxol previal.

γ-CD is very toxic to the cells, the toxic effect of the Taxol-γ-CD mixture is not stronger than that of γ-CD.

The present invention also relates to pharmaceutical compositions which

a) contain an effective amount of an inclusion complex of a Taxol or Taxotere or Taxus brevifolia extract formed with a cyclodextrin derivative, preferably heptakis-2, 6-0-dimethyl-β-cyclodextrin, random methylated β-cyclodextrin, succinylmethyl-β-cyclodextrin and a co-solvent, as active ingredient together with filling, diluting and further auxiliaries generally used in the pharmaceutical industry;

b) contain an effective amount of Taxol or Taxotere or a Taxus brevifolia extract and a cyclodextrin derivative, preferably heptakis-2,6-0-dimethyl-β-cyclodextrin, random methylated β-cyclodextrin, succinylmethyl-β-cyclodextrin and a co-solvent, as active ingredient together with filling, diluting and further auxiliaries generally used in the pharmaceutical industry;

c) contain an inclusion complex of Taxol, Taxotere or Taxus extracts formed with a cyclodextrin or a cyclodextrin derivative as active ingredient, they further contain ethanol or an ethanol-water mixture.

The pharmaceutical compositions described above can be prepared by methods known per se.

The pharmaceutical compositions can be used for treating human cancer by administering an effective amount of a pharmaceutical composition containing an inclusion complex of Taxol or Taxotere or a Taxus extract with a cyclodextrin derivative, preferably heptakis-2,6-0-dimethyl-β-cyclodextrin, random methylated β-cyclodextrin, succinylmethyl-β-cyclodextrin and a co-solvent.

The treatment of human cancer can also be performed by administering an effective amount of a pharmaceutical composition containing as active ingredient Taxol or Taxotere or a Taxus extract and a cyclodextrin derivative, preferably heptakis-2,6-0-dimethyl-β-cyclodextrin, random methylated β-cyclodextrin, succinylmethyl-β-cyclodextrin and a co-solvent.

The advantages of the compositions according to the invention are as follows:

they are pharmaceutical compositions containing an effective amount of a Taxol or Taxotere or Taxus extracts,

they contain besides the Taxol active ingredients less amount of cyclodextrin derivative than expected due to

the effect of the co-solvent, the amount and side-effect of the "carriers" deminished;

the Taxol compositions were prepared without using Cremophor EL;

stable solutions were prepared containing 3–6 mg/ml of Taxol, Taxotere or Taxus extract, which can be diluted by water without limitation, thus they can be used also for injection of infusion purpose;

the solutions containing 3–6 mg/ml of Taxol, Taxotere or Taxus extracts are stable at room temperature at normal daylight for three months and show no opalescence or precipitation within 8 hours even in diluted state.

In another embodiment of the invention, the present invention relates to a pharmaceutical composition with increased water-solubility and stability containing Taxol or Taxotere or a Taxus extract containing

0.01–0.6% by weight of Taxol or Taxotere or a Taxus extract;

10–65% by weight of a cyclodextrin derivative;

10–90% by weight of a co-solvent; and

water in an amount necessary to 100% by weight.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. **1A**, **1B** and **1C** show the comparative HPLC chromatograms of the Taxol-DIMEB and RAMEB formulations prepared according to Examples 1 and 2 after a two-month storage at room temperature by light.

FIG. **2** shows the ultraviolet spectra of the same formulations also after storage.

In both cases the comparative compound is the freshly made Taxol reference solution.

the compositions containing the Taxol, Taxotere or Taxus extract showed cytotoxicity on the PC 3 and K 562 human cancer cell lines.

The details of the invention are illustrated by the following non-limiting examples.

EXAMPLE 1

A Taxol-DIMEB composition containing 4 mg/ml of Taxol

8.7 mg of Taxol (prepared by SIGMA, St. Luise, USA) are dissolved in 1.3 ml of 95% ethanol by ultrasonic stirring, then 400 mg of DIMEB and 0.6 ml of water are added. The solution is homogenized and stirred by ultrasound till the solution becomes clear. A stable, dilutable solution is obtained.

EXAMPLE 2

A Taxol-DIMEB composition containing 4 mg/ml of Taxol

8.6 mg of Taxol are dissolved in 1.3 ml of 95% ethanol, 400 mg of RAMEB (prepared by Wacker Chemie GmbH. München, Germany) and 0.6 ml of distilled water are added. The solution is homogenized by ultrasonic stirring and clear solution is obtained.

EXAMPLE 3

A Taxol-DIMEB composition is prepared by dissolving 3.7 mg of Taxol and 200 mg of RAMEB simultaneously in 0.7 ml of 95% of ethanol. After stirring and complete dissolution also a clear solution is obtained, the Taxol content of which is 5.1 mg/ml.

EXAMPLE 4

4.0 mg/ml of Taxol and 100 mg/ml γ-cyclodextrin are dissolved in a 2:1 mixture of ethanol and water. A white suspension is obtained after homogenization and ultrasonic stirring.

EXAMPLE 5

A solution containing 3 mg/ml of Taxotere

2.5 mg of Taxotere was dissolved in 0.5 ml of 95% ethanol. 175 mg of DIMEB and 0.3 ml of water are added. After ultrasonic stirring a clear solution is obtained.

EXAMPLE 6

A composition containing 5 mg/ml of Taxol

2.7 mg of Taxol are dissolved in 0.35 ml of 95% ethanol. 250 mg of RAMEB and 0.15 ml of water are added. After stirring a clear solution is obtained.

EXAMPLE 7

The Taxol-DIMEB composition according to Example 1 is stored in ampoules at room temperature for 3 months. An infusion solution is prepared for treating human cancer by diluting the content of each ampoule to its 100fold with distilled water, 1.9% isotonic saline solution and 5% dextrose solution. A clear solution is obtained in the case of all the three dilutions which did not change according to visual observation in 6 hours after dilution (no opalescence, no precipitation). According to HPLC control the active ingredient content of the solutions did not change during storage.

EXAMPLE 8

The Taxol-DIMEB solution according to Example 1 is diluted to its 100fold volume by 0.9% physiologic saline solution containing 5 mg/ml of DIMEB. A diluted solution is obtained which can be stored for 48 hours without opalescence.

EXAMPLE 9

The Taxol-RAMEB solution according to Example 2 is diluted to its 100fold volume with 5% dextrose solution containing 5 mg/ml of RAMEB. A stable, clear solution is obtained which can be stored for 48 hours.

What is claimed is:

1. An inclusion complex of Taxol or Taxotere with increased water-solubility and stability formed with a heptakis-2,6-0-dimethyl-β-cyclodextrin and either ethanol or a mixture of ethanol and water.

2. An inclusion complex of Taxol or Taxotere with increased water-solubility and stability formed with random methylated β-cyclodextrin and either ethanol or a mixture of ethanol and water.

3. An inclusion complex of Taxol or Taxotere with succinylmethyl-β-cyclodextrin and either ethanol or a mixture of ethanol and water and having increased water-solubility and stability.

4. Inclusion complexes of Taxol ((2aR-(aα,4β,4aβ,6β,9α(αR*,βS*)11α-12α,12aα.12bα))-β-(benzoylamino)-α-hydroxy-benzene-propanoic acid 6,12-b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca(3,4)-benz-(1,2-b)-oxeth-9-yl-ester)) or Taxotere (butoxycarbonyl-10-desacetyl-N-debenzoyl-Taxol) formed with ethanol or a mixture of ethanol and water and with a cyclodextrin derivative selected from the group consisting of heptakis-2,6,O-dimethyl-β-cyclodextrin (DIMEB), random methylated β-cyclodextrin (RAMEB), and succinylmethyl-β-cyclodextrin (SUMEB).

5. An inclusion complex according to claim **4**, which comprises a 1:1–10:1 mixture of ethanol and water.

6. An inclusion complex according to claim **4**, which comprises a 1:1–3:1 mixture of ethanol and water.

7. An inclusion complex according to claim **4**, wherein the molar ratio of Taxol or Taxotere to cyclodextrin is 1:10–1:65.

8. An inclusion complex according to claim **4**, wherein the molar ratio of Taxol or Taxotere to cyclodextrin is 1:30–1:40.

9. A pharmaceutical composition containing as an active ingredient an effective amount for increasing water solubility and stability of an inclusion complex of Taxol or Taxotere formed with a cyclodextrin derivative selected from the group consisting of heptakis-2,6,0-dimethyl-β-cyclodextrin, random methylated β-cyclodextrin, and succinylmethyl-β-cyclodextrin, and a co-solvent of ethanol or a mixture of ethanol and water.

10. A pharmaceutical composition with increased water-solubility and stability containing Taxol or Taxotere comprising:

0.01–0.6% by weight of Taxol or Taxotere;

10–65% by weight of a cyclodextrin derivative selected from the group consisting of heptakis-2,6-O-dimethyl-β-cyclodextrin (DIMEB), random methylated β-cyclodextrin (RAMEB), and succinylmethyl-β-cyclodextrin (SUMEB);

10–90% by weight of ethanol or a mixture of ethanol and water; and

optionally water or a suitable carrier in an amount necessary to obtain 100% by weight.

11. The composition according to claim **10**, wherein the molar ratio of Taxol or Taxotere to cyclodextrin is 1:10–1:65.

12. The pharmaceutical composition according to claim **10**, which comprises a 1:1–10:1 mixture of ethanol and water.

13. The pharmaceutical composition according to claim **10**, which comprises a 1:1–3:1 mixture of ethanol and water.

14. The pharmaceutical composition according to claim **10**, wherein the molar ratio of Taxol or Taxotere to cyclodextrin is 1:30–1:40.

15. The pharmaceutical composition of claim **10**, which comprises about 3–6 mg/ml of Taxol or Taxotere.

16. A process for inhibiting the division of cancer cells, which comprises treating a patient with an effective amount of the composition according to claim **10** for inhibiting division of said cancer cells.

17. A process for inhibiting the division of cancer cells, which comprises treating a patient with an effective amount of an inclusion complex of Taxol or Taxotere formed with ethanol or a mixture of ethanol and water and with a cyclodextrin derivative selected from the group consisting of heptakis-2,6,O-dimethyl-β-cyclodextrin (DIMEB), random methylated β-cyclodextrin (RAMEB), and succinylmethyl-β-cyclodextrin (SUMEB), for inhibiting division of said cancer cells.

18. A process according to claim **17**, wherein the treatment is orally or parenterally.

19. The process of claim **17**, wherein the effective amount is 3–6 mg/ml.

20. A process for inhibiting the division of cancer cells, which comprises treating said cancer cells with an effective amount of an inclusion complex of Taxol or Taxotere formed with ethanol or a mixture of ethanol and water with a cyclodextrin derivative selected from the group consisting of heptakis-2,6,O-dimethyl-β-cyclodextrin (DIMEB), random methylated β-cyclodextrin (RAMEB), and succinylmethyl-β-cyclodextrin (SUMEB), for inhibiting division of said cancer cells.

21. The process of claim **20**, wherein the effective amount is 3–6 mg/ml.

22. A process for the preparation of an inclusion complex of Taxol or Taxotere formed with either ethanol or a mixture of ethanol and water and with a cyclodextrin derivative, which comprises reacting Taxol or Taxotere with a cyclodextrin derivative selected from the group consisting of heptakis-2,6,O-dimethyl-β-cyclodextrin (DIMEB), random methylated β-cyclodextrin (RAMEB), and succinylmethyl-β-cyclodextrin (SUMEB), and ethanol or a mixture of ethanol and water.

* * * * *

EXHIBIT 2

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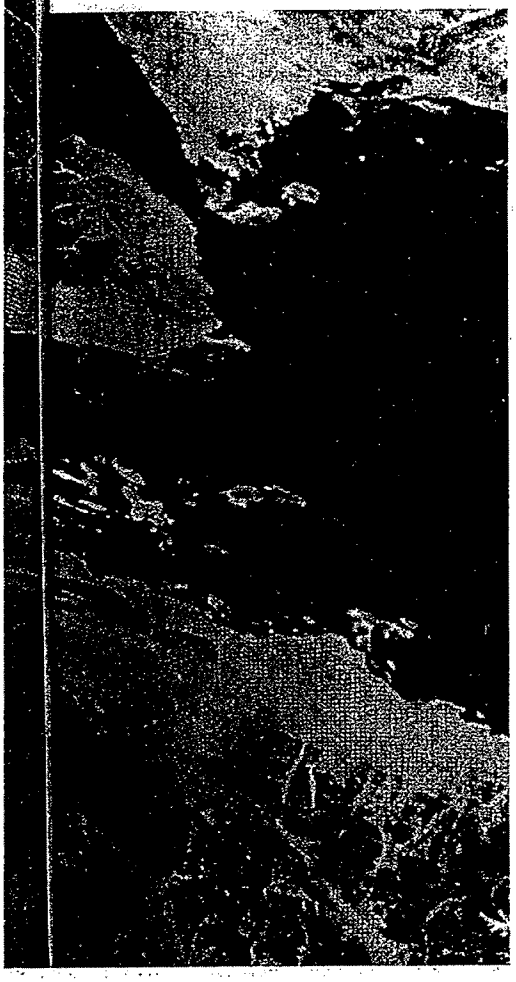

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On the cover: Pattern produced from white light by a computer-generated diffraction plate containing 529 square apertures arranged in a 23 × 23 array. (R. B. Hoover, Marshall Space Flight Center)

On the title pages: Aerial photograph of the Sinai Peninsula made by Gemini spacecraft. (NASA)

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In addition, material has been drawn from the following references: R. E. Huschke, *Glossary of Meteorology*, American Meteorological Society, 1959; *U.S. Air Force Glossary of Standardized Terms*, AF Manual 11-1, vol. 1, 1972; *Communications-Electronics Terminology*, AF Manual 11-1, vol. 3, 1970; W. H. Allen, ed., *Dictionary of Technical Terms for Aerospace Use*, 1st ed., National Aeronautics and Space Administration, 1965; J. M. Gilliland, *Solar-Terrestrial Physics: A Glossary of Terms and Abbreviations*, Royal Aircraft Establishment Technical Report 67158, 1967; *Glossary of Air Traffic Control Terms*, Federal Aviation Agency; *A Glossary of Range Terminology, White Sands Missile Range, New Mexico*, National Bureau of Standards, AD 467-424; *A DOD Glossary of Mapping, Charting and Geodetic Terms*, 1st ed., Department of Defense, 1967; P. W. Thrush, comp. and ed., *A Dictionary of Mining, Mineral, and Related Terms*, Bureau of Mines, 1968; *Nuclear Terms: A Glossary*, 2d ed., Atomic Energy Commission; F. Casey, ed., *Compilation of Terms in Information Sciences Technology*, Federal Council for Science and Technology, 1970; *Glossary of Stinfo Terminology*, Office of Aerospace Research, U.S. Air Force, 1963; *Naval Dictionary of Electronic, Technical, and Imperative Terms*, Bureau of Naval Personnel, 1962; *ADP Glossary*, Department of the Navy, NAVSO P-3097.

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dicular or oblique to the axis of another fold. Also known as subsequent fold; superimposed fold; transverse fold. { 'krȯs ˌfōld }

crossfoot [COMPUT SCI] To add numbers in several different ways in a computer, for checking purposes. { 'krȯsˌfůt }

cross furring ceiling [BUILD] A ceiling in which furring members are attached perpendicular to the main runners or other structural members. { 'krȯs ˌfər·iŋ ˌsēl·iŋ }

cross gateway *See* cross heading. { 'krȯs 'gātˌwā }

cross hair [ENG] An inscribed line or a strand of hair, wire, silk, or the like used in an optical sight, transit, or similar instrument for accurate sighting. { 'krȯs ˌher }

crosshatch generator [ELECTR] A signal generator that generates a crosshatch pattern for adjusting color television receiver circuits. { 'krȯsˌhach ˌjen·əˌrād·ər }

crosshaul [MECH ENG] A device for loading objects onto vehicles, consisting of a chain that is hooked on opposite sides of a vehicle, looped under the object, and connected to a power source and that rolls the object onto the vehicle. { 'krȯsˌhȯl }

crosshead [MECH ENG] A block sliding between guides and containing a wrist pin for the conversion of reciprocating to rotary motion, as in an engine or compressor. [MET] A device generally employed in wire coating which is attached to the discharge end of the extruder cylinder; designed to facilitate extruding material at an angle. [MIN ENG] A runner or guide positioned just above a sinking bucket to restrict excessive swinging. { 'krȯsˌhed }

cross heading [MIN ENG] Mine passage driven for ventilation from the airway to the gangway, or from one breast through the pillar to the adjoining working. Also known as cross gateway; cross hole; headway. { 'krȯs ˌhed·iŋ }

cross hole *See* cross heading. { 'krȯs ˌhōl }

crossing angle [NAV] The angle at which two lines of position intersect. Also known as angle of cut. { 'krȯs·iŋ ˌaŋ·gəl }

crossing over [GEN] The exchange of genetic material between paired homologous chromosomes during meiosis. Also known as crossover. { ˈkrȯs·iŋ ˈō·vər }

crossing plates [CIV ENG] Plates placed between a crossing and the ties to support the crossing and protect the ties. { 'krȯs·iŋ ˌplāts }

crossing symmetry [PARTIC PHYS] The amplitude for a process that involves creation of a particle with four-momentum P_μ is equal to the amplitude for a process which is the same except it involves destruction of the antiparticle with four-momentum $-P_\mu$. { 'krȯs·iŋ ˌsim·ə·trē }

cross joint [GEOL] A fracture in igneous rock perpendicular to the lineation caused by flow magma. Also known as transverse joint. { 'krȯs ˌjȯint }

cross-lamination *See* cross-bedding. { ˌkrȯs lam·əˈnā·shən }

cross-level [ENG] To level at an angle perpendicular to the principal line of sight. { 'krȯs ˌlev·əl }

crossline screen [GRAPHICS] In halftone photography, a grid that has opaque lines intersecting at right angles, forming transparent squares (screen apertures). Also known as a glass screen. { 'krȯsˌlīn ˌskrēn }

cross-linking [ORG CHEM] The setting up of chemical links between the molecular chains of polymers. { 'krȯs ˌliŋk·iŋ }

cross-magnetizing effect [ELECTROMAG] The distortion in the flux-density distribution in the air gap of an electric rotating machine caused by armature reaction. { ˌkrȯs 'mag·nəˌtīz·iŋ iˈfekt }

crossmarks [GRAPHICS] Register marks used for the exact positioning of images in step-and-repeat, double, or multicolor printing; also used for superimposing overlays onto a base or onto each other. { 'krȯsˌmärks }

cross matching [IMMUNOL] Determination of blood compatibility for transfusion by mixing donor cells with recipient serum, and recipient cells with donor serum, and examining for an agglutination reaction. { 'krȯs ˌmach·iŋ }

cross modulation [COMMUN] A type of interference in which the carrier of a desired signal becomes modulated by the program of an undesired signal on a different carrier frequency; the program of the undesired station is then heard in the background of the desired program. { ˌkrȯs ˌmäj·əˈlā·shən }

cross multiplication [MATH] Multiplication of the numerator of each of two fractions by the denominator of the other, as when eliminating fractions from an equation. { ˌkrȯs ˌməl·tə·pləˈkā·shən }

cross-neutralization [ELECTR] Method of neutralization used in push-pull amplifiers, whereby a portion of the plate-cathode alternating-current voltage of each vacuum tube is applied to the grid-cathode circuit of the other vacuum tube through a neutralizing capacitor. { ˌkrȯs ˌnü·trə·ləˈzā·shən }

cross office switching time [COMMUN] Time required to connect any input through the switching center to any selected output. { 'krȯs ˌȯf·əs 'swich·iŋ ˌtīm }

Crossopterygii [PALEON] A subclass of the class Osteichthyes comprising the extinct lobefins or choanate fishes and represented by one extant species; distinguished by two separate dorsal fins. { krāˌsäp·təˈrij·ēˌī }

Crossosomataceae [BOT] A monogeneric family of xerophytic shrubs in the order Dilleniales characterized by perigynous flowers, seeds with thin endosperm, and small, entire leaves. { ˌkrä·səˌsō·məˌtās·ēˌē }

crossover [CIV ENG] An S-shaped section of railroad track joining two parallel tracks. [ELEC] A point at which two conductors cross, with appropriate insulation between them to prevent contact. [ENG] The portion of a draw works' drum containing grooves for angle control so the wire rope can cross over to begin a new wrap. [GEN] *See* crossing over. { 'krȯsˌō·vər }

crossover distortion [ELECTR] Amplitude distortion in a class B transistor power amplifier which occurs at low values of current, when input impedance becomes appreciable compared with driver impedance. { 'krȯsˌō·vər disˈtȯr·shən }

crossover experiment [MED] An experiment or clinical investigation in which subjects are divided randomly into at least as many groups as there are kinds of treatment to be given, and then the groups are interchanged until every subject has received each treatment. { 'krȯsˌō·vər ikˈsper·ə·mənt }

crossover flange [ENG] Intermediate pipe flange used to connect flanges of different working pressures. { 'krȯsˌō·vər ˌflanj }

crossover frequency [ENG ACOUS] **1.** The frequency at which a dividing network delivers equal power to the upper and lower frequency channels when both are terminated in specified loads. **2.** *See* transition frequency. { 'krȯsˌō·vər ˌfrē·kwən·sē }

crossover joint [PETRO ENG] A casing length with different threads at either end to permit a change from one thread to another in a casing string. { 'krȯsˌō·vər ˌjȯint }

crossover length [MATH] A length characteristic of a fractal network such that at scales which are small compared with this length the fractal nature of the structure is manifest in its dynamics, whereas at scales which are large compared with this length the dynamics resemble those of a crystalline structure. { 'krȯsˌō·vər ˌleŋkth }

crossover network [ENG ACOUS] A selective network used to divide the audio-frequency output of an amplifier into two or more bands of frequencies. Also known as dividing network; loudspeaker dividing network. { 'krȯsˌō·vərˌnetˌwərk }

crossover spiral *See* lead-over groove. { 'krȯsˌō·vər ˌspī·rəl }

crossover voltage [ELECTR] In a cathode-ray storage tube, the voltage of a secondary writing surface, with respect to cathode voltage, on which the secondary emission is unity. { 'krȯsˌō·vər ˌvōl·tij }

cross-peen hammer [ENG] A hammer with a wedge-shaped surface at one end of the head. { 'krȯs ˌpēn 'ham·ər }

cross-pointer indicator [NAV] A flight instrument having two needles which cross in the center when the aircraft is on course; the vertical needle indicates the position of the aircraft with respect to the localizer course, and the horizontal needle serves a similar purpose for the glide slope of an instrument landing system. { 'krȯs ˌpȯint·ər ˌin·dəˌkād·ər }

cross-polarization [ELECTROMAG] The component of the electric field vector normal to the desired polarization component. { ˌkrȯs ˌpō·lə·rə·zāˈshən }

cross-pollination [BOT] Transfer of pollen from the anthers of one plant to the stigmata of another plant. { ˌkrȯs ˌpä·laˌnā·shən }

cross product [MATH] An anticommutative multiplication on the vectors of euclidean three-dimensional space. Also known as vector product. { 'krȯs ˌprä·dəkt }

cross-reaction [IMMUNOL] Reaction between an antibody and a closely related, but not complementary, antigen. { 'krȯs rēˈak·shən }

cross-referencing program [COMPUT SCI] A computer pro-

EXHIBIT 3

US005145684A

United States Patent [19]

Liversidge et al.

[11] Patent Number: 5,145,684

[45] Date of Patent: Sep. 8, 1992

[54] SURFACE MODIFIED DRUG NANOPARTICLES

[75] Inventors: Gary G. Liversidge, West Chester; Kenneth C. Cundy, Pottstown, both of Pa.; John F. Bishop, Rochester; David A. Czekai, Honeoye Falls, both of N.Y.

[73] Assignee: Sterling Drug Inc., New York, N.Y.

[21] Appl. No.: 647,105

[22] Filed: Jan. 25, 1991

[51] Int. Cl.[5] A61K 9/14

[52] U.S. Cl. 424/489; 424/495; 424/499

[58] Field of Search 424/495, 489, 499

[56] References Cited

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Primary Examiner—Thurman K. Page

Assistant Examiner—William E. Benston, Jr.

Attorney, Agent, or Firm—Arthur H. Rosenstein; William J. Davis

[57] ABSTRACT

Dispersible particles consisting essentially of a crystalline drug substance having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 400 nm, methods for the preparation of such particles and dispersions containing the particles. Pharmaceutical compositions containing the particles exhibit unexpected bioavailability and are useful in methods of treating mammals.

20 Claims, No Drawings

SURFACE MODIFIED DRUG NANOPARTICLES

FIELD OF THE INVENTION

This invention relates to drug particles, methods for the preparation thereof and dispersions containing the particles. This invention further relates to the use of such particles in pharmaceutical compositions and methods of treating mammals.

BACKGROUND OF THE INVENTION

Bioavailability is the degree to which a drug becomes available to the target tissue after administration. Many factors can affect bioavailability including the dosage form and various properties, e.g., dissolution rate of the drug. Poor bioavailability is a significant problem encountered in the development of pharmaceutical compositions, particularly those containing an active ingredient that is poorly soluble in water. Poorly water soluble drugs, i.e., those having a solubility less than about 10 mg/ml, tend to be eliminated from the gastrointestinal tract before being absorbed into the circulation. Moreover, poorly water soluble drugs tend to be unsafe for intravenous administration techniques, which are used primarily in conjunction with fully soluble drug substances.

It is known that the rate of dissolution of a particulate drug can increase with increasing surface area, i.e., decreasing particle size. Consequently, methods of making finely divided drugs have been studied and efforts have been made to control the size and size range of drug particles in pharmaceutical compositions. For example, dry milling techniques have been used to reduce particle size and hence influence drug absorption. However, in conventional dry milling, as discussed by Lachman, et al., *The Theory and Practice of Industrial Pharmacy*, Chapter 2, "Milling", p. 45, (1986), the limit of fineness is reached in the region of 100 microns (100,000 nm) when material cakes on the milling chamber. Lachman, et al. note that wet grinding is beneficial in further reducing particle size, but that flocculation restricts the lower particle size limit to approximately 10 microns (10,000 nm). However, there tends to be a bias in the pharmaceutical art against wet milling due to concerns associated with contamination. Commercial airjet milling techniques have provided particles ranging in average particle size from as low as about 1 to 50 μm (1,000–50,000 nm).

Other techniques for preparing pharmaceutical compositions include loading drugs into liposomes or polymers, e.g., during emulsion polymerization. However, such techniques have problems and limitations. For example, a lipid soluble drug is often required in preparing suitable liposomes. Further, unacceptably large amounts of the liposome or polymer are often required to prepare unit drug doses. Further still, techniques for preparing such pharmaceutical compositions tend to be complex. A principal technical difficulty encountered with emulsion polymerization is the removal of contaminants, such as unreacted monomer or initiator, which can be toxic, at the end of the manufacturing process.

U.S. Pat. No. 4,540,602 (Motoyama et al.) discloses a solid drug pulverized in an aqueous solution of a water-soluble high molecular substance using a wet grinding machine. However, Motoyama et al. teach that as a result of such wet grinding, the drug is formed into finely divided particles ranging from 0.5 μm (500 nm) or less to 5 μm (5,000 nm) in diameter.

EPO 275,796 describes the production of colloidally dispersible systems comprising a substance in the form of spherical particles smaller than 500 nm. However, the method involves a precipitation effected by mixing a solution of the substance and a miscible non-solvent for the substance and results in the formation of non-crystalline nanoparticle. Furthermore, precipitation techniques for preparing particles tend to provide particles contaminated with solvents. Such solvents are often toxic and can be very difficult, if not impossible, to adequately remove to pharmaceutically acceptable levels to be practical.

U.S. Pat. No. 4,107,288 describes particles in the size range from 10 to 1,000 nm containing a biologically or pharmacodynamically active material. However, the particles comprise a crosslinked matrix of macromolecules having the active material supported on or incorporated into the matrix.

It would be desirable to provide stable dispersible drug particles in the submicron size range which can be readily prepared and which do not appreciably flocculate or agglomerate due to interparticle attractive forces and do not require the presence of a crosslinked matrix. Moreover, it would be highly desirable to provide pharmaceutical compositions having enhanced bioavailability.

SUMMARY OF THE INVENTION

We have discovered stable, dispersible drug nanoparticles and a method for preparing such particles by wet milling in the presence of grinding media in conjunction with a surface modifier. The particles can be formulated into pharmaceutical compositions exhibiting remarkably high bioavailability.

More specifically, in accordance with this invention, there are provided particles consisting essentially of a crystalline drug substance having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 400 nm.

This invention also provides a stable dispersion consisting essentially of a liquid dispersion medium and the above-described particles dispersed therein.

In another embodiment of the invention, there is provided a method of preparing the above-described particles comprising the steps of dispersing a drug substance in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of the drug substance to an effective average particle size of less than about 400 nm. The particles can be reduced in size in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

In a particularly valuable and important embodiment of the invention, there is provided a pharmaceutical composition comprising the above-described particles and a pharmaceutically acceptable carrier therefor. Such pharmaceutical composition is useful in a method of treating mammals.

It is an advantageous feature that a wide variety of surface modified drug nanoparticles free of unacceptable contamination can be prepared in accordance with this invention.

It is another advantageous feature of this invention that there is provided a simple and convenient method

for preparing drug nanoparticles by wet milling in conjunction with a surface modifier.

Another particularly advantageous feature of this invention is that pharmaceutical compositions are provided exhibiting unexpectedly high bioavailability.

Still another advantageous feature of this invention is that pharmaceutical compositions containing poorly water soluble drug substances are provided which are suitable for intravenous administration techniques.

Other advantageous features will become readily apparent upon reference to the following Description of Preferred Embodiments.

DESCRIPTION OF PREFERRED EMBODIMENTS

This invention is based partly on the discovery that drug particles having an extremely small effective average particle size can be prepared by wet milling in the presence of grinding media in conjunction with a surface modifier, and that such particles are stable and do not appreciably flocculate or agglomerate due to interparticle attractive forces and can be formulated into pharmaceutical compositions exhibiting unexpectedly high bioavailability. While the invention is described herein primarily in connection with its preferred utility, i.e., with respect to nanoparticulate drug substances for use in pharmaceutical compositions, it is also believed to be useful in other applications such as the formulation of particulate cosmetic compositions and the preparation of particulate dispersions for use in image and magnetic recording elements.

The particles of this invention comprise a drug substance. The drug substance exists as a discrete, crystalline phase. The crystalline phase differs from a noncrystalline or amorphous phase which results from precipitation techniques, such as described in EPO 275,796 cited above.

The invention can be practiced with a wide variety of drug substances. The drug substance preferably is present in an essentially pure form. The drug substance must be poorly soluble and dispersible in at least one liquid medium. By "poorly soluble" it is meant that the drug substance has a solubility in the liquid dispersion medium of less than about 10 mg/ml, and preferably of less than about 1 mg/ml. A preferred liquid dispersion medium is water. However, the invention can be practiced with other liquid media in which a drug substance is poorly soluble and dispersible including, for example, aqueous salt solutions, safflower oil and solvents such as ethanol, t-butanol, hexane and glycol. The pH of the aqueous dispersion media can be adjusted by techniques known in the art.

Suitable drug substances can be selected from a variety of known classes of drugs including, for example, analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics (including penicillins), anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytic sedatives (hypnotics and neuroleptics), astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants (expectorants and mucolytics), diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics (antiparkinsonian agents), haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones (including steroids), anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators and xanthines. Preferred drug substances include those intended for oral administration and intravenous administration. A description of these classes of drugs and a listing of species within each class can be found in Martindale, The Extra Pharmacopoeia, Twenty-ninth Edition, The Pharmaceutical Press, London, 1989, the disclosure of which is hereby incorporated by reference in its entirety. The drug substances are commercially available and/or can be prepared by techniques known in the art.

Representative illustrative species of drug substances useful in the practice of this invention include:

17-α-pregno-2,4-dien-20-yno-[2,3-d]-isoxazol-17-ol (Danazol);

5α,17α,-1'-(methylsulfonyl)-1'H-pregn-20-yno[3,2-c]-pyrazol-17-ol (Steroid A);

piposulfam;

piposulfan;

camptothecin; and

ethyl-3,5-diacetoamido-2,4,6-triiodobenzoate

In particularly preferred embodiments of the invention, the drug substance is a steriod such as danazol or Steroid A or an antiviral agent.

The particles of this invention contain a discrete phase of a drug substance as described above having a surface modifier adsorbed on the surface thereof. Useful surface modifiers are believed to include those which physically adhere to the surface of the drug substance but do not chemically bond to the drug.

Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants. Representative examples of excipients include gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, e.g., macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, e.g., the commercially available Tweens, polyethylene glycols, polyoxyethylene stearates, colloidol silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethycellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, and polyvinylpyrrolidone (PVP). Most of these excipients are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986, the disclosure of which is hereby incorporated by reference in its entirety. The surface modifiers are commercially available and/or can be prepared by techniques known in the art.

Particularly preferred surface modifiers include polyvinyl pyrrolidone, Pluronic F68 and F108, which are block copolymers of ethylene oxide and propylene oxide, Tetronic 908, which is a tetrafunctional block copolymer derived from sequential addition of ethylene

oxide and propylene oxide to ethylenediamine, dextran, lecithin, Aerosol OT, which is a dioctyl ester of sodium sulfosuccinic acid, available from American Cyanamid, Duponol P, which is a sodium lauryl sulfate, available from DuPont, Triton X-200, which is an alkyl aryl polyether sulfonate, available from Rohm and Haas, Tween 80, which is a polyoxyethylene sorbitan fatty acid ester, available from ICI Specialty Chemicals, and Carbowax 3350 and 934, which are polyethylene glycols available from Union Carbide. Surface modifiers which have found to be particularly useful include polyvinylpyrrolidone, Pluronic F-68, and lecithin.

The surface modifier is adsorbed on the surface of the drug substance in an amount sufficient to maintain an effective average particle size of less than about 400 nm. The surface modifier does not chemically react with the drug substance or itself. Furthermore, the individually adsorbed molecules of the surface modifier are essentially free of intermolecular crosslinkages.

As used herein, particle size refers to a number average particle size as measured by conventional particle size measuring techniques well known to those skilled in the art, such as sedimentation field flow fractionation, photon correlation spectroscopy, or disk centrifugation. By "an effective average particle size of less than about 400 nm" it is meant that at least 90% of the particles have a weight average particle size of less than about 400 nm when measured by the above-noted techniques. In preferred embodiments of the invention, the effective average particle size is less than about 250 nm. In some embodiments of the invention, an effective average particle size of less than about 100 nm has been achieved. With reference to the effective average particle size, it is preferred that at least 95% and, more preferably, at least 99% of the particles have a particle size less than the effective average, e.g., 400 nm. In particularly preferred embodiments, essentially all of the particles have a size less than 400 nm. In some embodiments, essentially all of the particles have a size less than 250 nm.

The particles of this invention can be prepared in a method comprising the steps of dispersing a drug substance in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of the drug substance to an effective average particle size of less than about 400 nm. The particles can be reduced in size in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

A general procedure for preparing the particles of this invention is set forth below. The drug substance selected is obtained commercially and/or prepared by techniques known in the art in a conventional coarse form. It is preferred, but not essential, that the particle size of the coarse drug substance selected be less than about 100 μm as determined by sieve analysis. If the coarse particle size of the drug substance is greater than about 100 μm, then it is preferred that the particles of the drug substance be reduced in size to less than 100 μm using a conventional milling method such as airjet or fragmentation milling.

The coarse drug substance selected can then be added to a liquid medium in which it is essentially insoluble to form a premix. The concentration of the drug substance in the liquid medium can vary from about 0.1–60%, and preferably is from 5–30% (w/w). It is preferred, but not essential, that the surface modifier be present in the premix. The concentration of the surface modifier can vary from about 0.1 to about 90%, and preferably is 1–75%, more preferably 20–60%, by weight based on the total combined weight of the drug substance and surface modifier. The apparent viscosity of the premix suspension is preferably less than about 1000 centipoise

The premix can be used directly by subjecting it to mechanical means to reduce the average particle size in the dispersion to less than 400 nm. It is preferred that the premix be used directly when a ball mill is used for attrition. Alternatively, the drug substance and, optionally, the surface modifier, can be dispersed in the liquid medium using suitable agitation, e.g., a roller mill or a Cowles type mixer, until a homogeneous dispersion is observed in which there are no large agglomerates visible to the naked eye. It is preferred that the premix be subjected to such a premilling dispersion step when a recirculating media mill is used for attrition.

The mechanical means applied to reduce the particle size of the drug substance conveniently can take the form of a dispersion mill. Suitable dispersion mills include a ball mill, an attritor mill, a vibratory mill, and media mills such as a sand mill and a bead mill. A media mill is preferred due to the relatively shorter milling time required to provide the intended result, i.e., the desired reduction in particle size. For media milling, the apparent viscosity of the premix preferably is from about 100 to about 1000 centipoise. For ball milling, the apparent viscosity of the premix preferably is from about 1 up to about 100 centipoise. Such ranges tend to afford an optimal balance between efficient particle fragmentation and media erosion.

The grinding media for the particle size reduction step can be selected from rigid media preferably spherical or particulate in form having an average size less than about 3 mm and, more preferably, less than about 1 mm. Such media desirably can provide the particles of the invention with shorter processing times and impart less wear to the milling equipment. The selection of material for the grinding media is not believed to be critical. We have found that zirconium oxide, such as 95% ZrO stabilized with magnesia, zirconium silicate, and glass grinding media provide particles having levels of contamination which are believed to be acceptable for the preparation of pharmaceutical compositions. However, other media, such as stainless steel, titania, alumina, and 95% ZrO stabilized with yttrium, are expected to be useful. Preferred media have a density greater than about 3 g/cm^3.

The attrition time can vary widely and depends primarily upon the particular mechanical means and processing conditions selected. For ball mills, processing times of up to five days or longer may be required. On the other hand, processing times of less than 1 day (residence times of one minute up to several hours) have provided the desired results using a high shear media mill.

The particles must be reduced in size at a temperature which does not significantly degrade the drug substance. Processing temperatures of less than about 30°–40° C. are ordinarily preferred. If desired, the processing equipment can be cooled with conventional cooling equipment. The method is conveniently carried out under conditions of ambient temperature and at processing pressures which are safe and effective for the milling process. For example, ambient processing pressures are typical of ball mills, attritor mills and vibratory mills. Processing pressures up to about 20 psi (1.4 kg/cm^2) are typical of media milling.

The surface modifier, if it was not present in the premix, must be added to the dispersion after attrition in an amount as described for the premix above. Thereafter, the dispersion can be mixed, e.g., by shaking vigorously. Optionally, the dispersion can be subjected to a sonication step, e.g., using an ultrasonic power supply. For example, the dispersion can be subjected to ultrasonic energy having a frequency of 20–80 kHz for a time of about 1 to 120 seconds.

The relative amount of drug substance and surface modifier can vary widely and the optimal amount of the surface modifier can depend, for example, upon the particular drug substance and surface modifier selected, the critical micelle concentration of the surface modifier if it forms micelles, etc. The surface modifier preferably is present in an amount of about 0.1–10 mg per square meter surface area of the drug substance. The surface modifier can be present in an amount of 0.1–90%, preferably 20–60% by weight based on the total weight of the dry particle.

As indicated by the following examples, not every combination of surface modifier and drug substance provides the desired results. Consequently, the applicants have developed a simple screening process whereby compatible surface modifiers and drug substances can be selected which provide stable dispersions of the desired particles. First, coarse particles of a selected drug substance of interest are dispersed in a liquid in which the drug is essentially insoluble, e.g., water at 5% (w/w) and milled for 60 minutes in a DYNO-MILL under the standard milling conditions which are set forth in Example 1 which follows. The milled material is then divided into aliquots and surface modifiers are added at concentrations of 2, 10 and 50% by weight based on the total combined weight of the drug substance and surface modifier. The dispersions are then sonicated (1 minute, 20 kHz) to disperse agglomerates and subjected to particle size analysis by examination under an optical microscope (1000×magnification). If a stable dispersion is observed, then the process for preparing the particular drug substance surface modifier combination can be optimized in accordance with the teachings above. By stable it is meant that the dispersion exhibits no flocculation or particle agglomeration visible to the naked eye at least 15 minutes, and preferably, at least two days or longer after preparation.

The resulting dispersion of this invention is stable and consists of the liquid dispersion medium and the above-described particles. The dispersion of surface modified drug nanoparticles can be spray coated onto sugar spheres or onto a pharmaceutical excipient in a fluid-bed spray coater by techniques well known in the art.

Pharmaceutical compositions according to this invention include the particles described above and a pharmaceutically acceptable carrier therefor. Suitable pharmaceutically acceptable carriers are well known to those skilled in the art. These include non-toxic physiologically acceptable carriers, adjuvants or vehicles for parenteral injection, for oral administration in solid or liquid form, for rectal administration, and the like. A method of treating a mammal in accordance with this invention comprises the step of administering to the mammal in need of treatment an effective amount of the above-described pharmaceutical composition. The selected dosage level of the drug substance for treatment is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore, depends upon the particular drug substance, the desired therapeutic effect, on the route of administration, on the desired duration of treatment and other factors. As noted, it is a particularly advantageous feature that the pharmaceutical compositions of this invention exhibit unexpectedly high bioavailability as illustrated in the examples which follow. Furthermore, it is contemplated that the drug particles of this invention provide more rapid onset of drug action and decreased gastrointestinal irritancy.

It is contemplated that the pharmaceutical compositions of this invention will be particularly useful in oral and parenteral, including intravenous, administration applications. It is expected that poorly water soluble drug substances, which prior to this invention, could not have been administered intravenously, may be administered safely in accordance with this invention. Additionally, drug substances which could not have been administered orally due to poor bioavailability may be effectively administered in accordance with this invention.

While applicants do not wish to be bound by theoretical mechanisms, it is believed that the surface modifier hinders the flocculation and/or agglomeration of the particles by functioning as a mechanical or steric barrier between the particles, minimizing the close, interparticle approach necessary for agglomeration and flocculation. Alternatively, if the surface modifier has ionic groups, stabilization by electrostatic repulsion may result. It was surprising that stable drug particles of such a small effective average particle size and free of unacceptable contamination could be prepared by the method of this invention.

The following examples further illustrate the invention.

EXAMPLE 1

PVP Modified Danazol Particles Prepared in a Ball Mill

A nanoparticulate dispersion of Danazol was prepared using a DYNO-MILL (Model KDL, manufactured by Willy A. Bachoffen AG Maschinenfabrik). The following ingredients were added to a glass vessel and agitated on a roller for 24 hours to dissolve the polyvinylpyrrolidone surface modifier.

Polyvinylpyrrolidone K-15 (made by GAF)—98 g

High purity water—664 g

Subsequently, 327 grams of dry powdered Danazol was added to the above solution and rolled for one week. This step aided in evenly dispersing the Danazol in the surface modifier solution, thereby reducing the treatment time required in the media mill. The Danazol was purchased in a micronized form (average particle size of about 10 microns) from Sterling Drug Inc. The particles had been prepared by a conventional airjet milling technique. This premix was added to a holding vessel and agitated with a conventional propeller mixer at low speed to maintain a homogeneous mixture for the media milling event. The media mill was prepared accordingly for the media milling process. The mill grinding chamber was partially filled with silica glass spheres and the premix was continuously recirculated through the media mill operating at the following conditions:

Grinding vessel: water jacketed stainless steel chamber

Premix flow rate: 250 ml per minute

Available volume of grinding vessel: 555 ml

Media volume: 472 ml of glass beads

Media type: size range of 0.5–0.75 mm silica glass beads, unleaded (distributed by Glen Mills, Inc.)
Recirculation time: 240 min
Residence time: 60 min
Impeller speed: 3000 RPM, tangential speed 1952 ft/min (595 m/min)
Grinding vessel coolant: water
Coolant temperature: 50° F. (10° C.)

After recirculating the slurry for 240 minutes, a sample of the dispersion was removed and evaluated for particle size distribution using a sedimentation field flow fractionator (made by DuPont). The particles were determined to have a number average diameter of 77.5 nm and a weight average diameter of 139.6 nm. The particle size of the dispersion ranged in size from 3–320 nm.

EXAMPLE 2

PVP Modified Danazol Particles Prepared in a Ball Mill at Low Solids.

A nanoparticulate dispersion of Danazol was prepared using a ball mill process. A 600 ml cylindrical glass vessel (inside diameter=3.0 inches (7.6 cm)) was filled approximately halfway with the following grinding media:

Grinding media: zirconium oxide grinding spheres (made by Zircoa, Inc.)
Media size: 0.85–1.18 mm diameter
Media volume: 300 ml

The following dry ingredients were added directly to this glass vessel:

Danazol (micronized): 10.8 g
Polyvinylpyrrolidone K-15: 3.24 g
High purity water: 201.96 g

Danazol was purchased in the micronized form (average particle size 10 microns) from Sterling Drug Inc. and the polyvinylpyrrolidone was K-15 grade produced by GAF. The cylindrical vessel was rotated horizontally about its axis at 57% of the "critical speed". The critical speed is defined as the rotational speed of the grinding vessel when centrifuging of the grinding media occurs. At this speed the centrifugal force acting on the grinding spheres presses and holds them firmly against the inner wall of the vessel. Conditions that lead to unwanted centrifuging can be computed from simple physical principles.

After 5 days of ball milling, the slurry was separated from the grinding media through a screen and evaluated for particle size with the sedimentation field flow fractionator. The number average particle diameter measured was 84.9 nm and the weight average particle diameter was 169.1 nm. The particles varied in size from 26 to 340 nm. The amount and type of surface modifier was sufficient to provide colloidal stability to agglomeration and to maintain a homogeneous blend of ingredients assuring precise material delivery during subsequent processing steps.

BIOAVAILABILITY TESTING

Bioavailability of Danazol from the nanoparticulate dispersion described above was compared to that from a suspension of unmilled Danazol in fasted male beagle dogs. The unmilled material was prepared as a suspension in the same manner as the dispersion, with the exception of the ball milling process. Both formulations were administered to each of five dogs by oral gavage and plasma obtained via a cannula in the cephalic vein. Plasma Danazol levels were monitored over 24 hours. The relative bioavailability of Danazol from the nanoparticulate dispersion was 15.9 fold higher than from the Danazol suspension containing Danazol particles having an average particle size of about 10 microns prepared by conventional airjet milling. Comparison of oral plasma levels with dose corrected plasma levels following intravenous administration of Danazol gave a mean absolute bioavailability (±SEM) of 82.3±10.1% for the nanoparticulate dispersion and 5.1±1.9% for the unmilled material.

EXAMPLE 3

PVP Modified Danazol Particles Prepared in a Ball Mill at High Solids

A nanoparticle dispersion of Danazol was prepared using 1 mm diameter glass grinding media (0.85–1.18 mm from Potters Industries). A cylindrical glass vessel having a diameter of 2.75 inches (7.0 cm) with a volume of 400 ml was charged with 212 ml of unleaded glass grinding media. The following ingredients were added to this vessel:

30.4 g of micronized Danazol
9.12 g of Polyvinylpyrrolidone K-15
112.48 g of high purity water

This vessel was rotated horizontally on its axis at a controlled rotational speed of 80.4 revolutions per minute (50% of critical speed) for 5 days. The slurry was immediately separated from the grinding media and evaluated for particle size and grinding media attrition using inductively coupled plasma emissions (ICP). The particle size measured with a sedimentation field flow fractionator yielded a number average diameter of 112.7 nm and a weight average diameter of 179.3 nm. The extent of media attrition was measured to establish the purity of the final dispersion using an inductively coupled plasma-atomic emission spectroscopy method. The level of silicon in the final dispersion was less than 10 parts of elemental silicon per million parts of the slurry.

EXAMPLE 4

PVP Modified Danazol Particles

A nanoparticle dispersion of Danazol was prepared for clinical evaluation using a ball milling dispersion method. This dispersion was prepared by milling with glass grinding media. The grinding media used was:

Media type: 0.85–1.18 mm unleaded glass spheres
Media quantity: 6100 ml

The media was added to a 3 gallon porcelain jar. The following ingredients were then added to the jar:

1000 g Danazol (micronized)
300 g Polyvinylpyrrolidone K-15
3700 g high purity water

The vessel was rolled 5 days at a rotational speed of 39.5 revolutions per minute (50% critical speed). The liquid slurry was separated from the grinding media with a screen and used to prepare solid oral doses for clinical studies. The dispersion was assessed for particle size using the sedimentation field flow fractionator and was measured to have a number average diameter of 134.9 nm and a weight average diameter of 222.2 nm. The level of contamination from the grinding media was measured (by ICP) to be 36 parts of silicon per million parts of dispersion. Less than 5 ppm of aluminum was detected. X-ray powder diffraction data of the starting powder was compared with the dispersed Danazol and showed the crystal structure morphology

of the solid dispersed particles was unchanged by the dispersion process.

EXAMPLE 5

PVP Modified Danazol Particles

A nanoparticulate dispersion of Danazol was prepared using a laboratory media mill and glass grinding media. The media mill was equipped with a 50 ml grinding chamber and the mill was a "Mini" Motormill manufactured by Eiger Machinery Inc.

The media mill was operated at the following process conditions:

Bead charge: 42.5 ml glass spheres

Rotor speed: 5000 RPM (2617 feet per minute (798 m/min) tangential speed)

Grinding media: 0.75–1.0 mm unleaded glass beads (distributed by Glens Mills)

The dispersion formula was prepared by dissolving 27 g of polyvinylpyrrolidone in 183 g of water and agitated in a steel vessel with a 50 mm "Cowles" type blade until the solution was clear and free of undissolved PVP polymer. The rotational speed of the mixer was maintained at 5000 RPM. 90 g of micronized Danazol was slowly added to this blend with the same mixing for 30 min. 200 cc of the premix was added to the holding tank of the mill and recirculated for 5 hours and 51 minutes. The final residence time in the grinding zone was 40 minutes.

The final average particle size was measured and determined to have a number average diameter of 79.9 nm and a weight average diameter of 161.2 nm. The particles varied in size from 30–415 nm. The level of attrition from erosion of the grinding media and grinding vessel were measured (by ICP) to be 170 ppm of iron and 71 ppm silicon. The crystal structure was determined by X-ray diffraction to be unchanged by the dispersion process.

EXAMPLE 6

Lecithin Modified Steroid A Particles

A nanoparticulate dispersion of Steroid A was prepared by ball milling with zirconium oxide grinding beads. The dispersion was prepared in the absence of a surface modifier and a post addition of Lecithin and a sonication step were required to stablize the dispersed phase of Steroid A and prevent agglomeration and rapid sedimentation. A fine particle dispersion of Steroid A was prepared by ball milling the following ingredients:

5 g Steroid A

95 g high purity water

Steroid A was in the form of unmilled coarse grains having a particle size of about 100 μm and ranging in size up to about 400 μm.

The following process conditions were used:

Media: 135 ml

Vessel volume: 240 ml

Media type: 0.85–1.18 mm Zirbeads (manufactured by Zircoa Inc.)

Milling time: 4 days

Milling speed: 86 RPM (50% critical speed)

After four days of ball milling the slurry was separated from the grinding media through a screen. One gram of this unstabilized slurry was added to 10 g of an aqueous solution of Lecithin (1% Centrolex "P" by weight in high purity water, Lecithin manufactured by Central Soya Company, Inc.) and mixed by vigorous shaking, followed by a sonication step for 20 seconds using an ultrasonic horn (Model 350 Branson Ultrasonic Power Supply, Horn Diameter=0.5 inch (1.27 cm), Power setting=2). The slurry was sized under a microscope. An Olympus BH-2 optical microscope equipped with phase contrast illumination was used to observe the size and condition of the dispersion.

A drop of the above dilute slurry was placed between a microscope slide and glass cover slip and observed microscopically at high magnification (1,000 times) and compared to the slurry similarly diluted with water only (no surface modifier). The unmodified dispersion exhibited extensive particle agglomeration. The particle size of the unmodified dispersion was more than 10 microns and the unmodified dispersion exhibited no Brownian Motion. Brownian motion is the oscillatory or jiggling motion exhibited by particles in a liquid that fall in the size range of less than about 1 micron. The Lecithin modified particles exhibited rapid Brownian motion. The thus observed dispersion had the characteristics and appearance consistent with a number average particle size of less than 400 nm. Furthermore, it is expected that additional milling would lead to further particle size reduction.

EXAMPLE 7

Alkyl Aryl Polyether Sulfonate Modified Steroid A

Example 6 was repeated except that the Lecithin was replaced with Triton X-200 (manufactured by Rohm and Haas). Similar results were observed.

EXAMPLE 8

Gum Acacia Modified Steroid A

Example 6 was repeated except that the Lecithin was replaced with gum acacia (available from Eastman Kodak Co.) Similar results were observed.

EXAMPLE 9

Sodium Lauryl Sulfate Modified Steroid A

Example 6 was repeated except that the Lecithin was replaced with sodium lauryl sulfate (available as Duponol ME from DuPont, Inc.). Similar results were observed.

EXAMPLE 10

Steroid A Modified with a Dioctylester of Sodium Sulfosuccinic Acid

Example 6 was repeated except that the Lecithin was replaced with Aerosol OT (available from American Cyanamid Chemical Products, Inc.). Similar results were observed.

EXAMPLE 11

Steroid A Modified with a Block Copolymer of Ethylene Oxide and Propylene Oxide

Example 6 was repeated except that the Lecithin was replaced with Pluronic F68 (available from BASF Corp.). Similar results were observed.

EXAMPLE 12

Steroid A Modified with a Block Copolymer of Ethylene Oxide and Propylene Oxide

A nanoparticulate dispersion of Steroid A was prepared by ball milling with zirconium oxide grinding

media for 5 days. 70 cc of grinding media were added to a 115 cc vessel followed by:

2.5 g Steroid A
0.75 g of Pluronic F68
46.75 g high purity water

The resulting mixture was ball milled for 5 days at 50% of the critical rotational speed. The final dispersion was separated from the grinding media and microscopically evaluated for particle size as in Example 6. The dispersion exhibited rapid Brownian Motion and no particles were larger than 1 micron. Most particles were less than 400 nm.

EXAMPLE 13

Lecithin Modified Steroid A Particles

Example 12 was repeated except that the Pluronic F68 was replaced with Centrolex P. No particles larger than 1 micron were observed microscopically and most were less than 400 nm.

EXAMPLE 14

Steroid A Particles Modified with a Block Copolymer of Ethylene Oxide and Propylene Oxide

A nanoparticulate dispersion of Steroid A was prepared by a ball milling process. The following ingredients were added to a cylindrical 0.95 l vessel. The vessel was filled approximately halfway with the following grinding media:

Grinding media: 0.85–1.18 mm diameter zirconium oxide spheres (made by Zircoa)

The following dispersion ingredients were added directly to the glass vessel:

18 g Steroid A
4.5 g Pluronic F68 (purchased from BASF Corp.)
336.6 g high purity water

Steroid A was purchased from Sterling Drug Inc. in the form of unmilled tabular crystals having an average particle size of approximately 100 μm.

The vessel was rotated concentrically on its axis at 50% critical speed for 5 days. After this time 4.45 g of Pluronic F68 was added to the slurry and rolled for 5 more days at the same conditions. The slurry was then discharged and separated from the grinding media and evaluated for particle size using the sedimentation field flow fractionator. The number average particle size measured was 204.6 nm and the weight average particle size was 310.6 nm. The particle size distribution ranged from approximately 68–520 nm. The dispersion was examined with an optical microscope. It exhibited excellent particle integrity, free flocculation and agglomeration. The dispersion particles exhibited rapid Brownian motion.

BIOAVAILABILITY TESTING

Bioavailability of Steroid A from the nanoparticulate dispersion described above was compared to that from a suspension of unmilled Steroid A (having an average particle size of about 100 μm) in male beagle dogs. The unmilled material was prepared as a suspension in the same manner as the dispersion, with the exception of the ball milling process. Both formulations were administered to each of five dogs by oral gavage and plasma obtained via a cannula in the cephalic vein. Plasma Steroid A levels were monitored over 24 hours. The relative bioavailability of Steroid A from the nanoparticulate dispersion was 7.1 fold higher than from the unmilled Steroid A suspension. Comparison of oral plasma levels with dose corrected plasma levels following intravenous administration of Steroid A gave a mean absolute bioavailability (±SEM) of 14.8±3.5% for the nanoparticulate dipersion and 2.1±1.0% for the unmilled material.

COMPARATIVE EXAMPLE A

A dispersion of Steroid A was prepared using a ball milling process with zirconium oxide grinding beads. The dispersion was prepared in the absence of a surface modifier and a post-sonication step was used to minimize flocculation and reaggregation.

A fine particle dispersion was prepared by ball milling the following ingredients:

5 g Steroid A
95 g high purity water

The following process conditions were used:

Grinding media: 135 ml
Vessel volume: 240 ml
Grinding media: 0.85–1.18 mm Zirbeads XR
Milling time: 4 days
Milling speed: 86 RPM (50% critical speed)

After four days of ball milling, the slurry was separated from the grinding media through a screen. One gram of the unstablized slurry was blended with 10 grams of high purity water and mixed by vigorous shaking, followed by a sonication step for 20 seconds using an ultrasonic horn (Model 350 Branson Ultrasonic Power Supply, Horn diameter=0.5 inch, Power setting=2). The slurry was sized under a microscope. An optical microscope equipped with phase contrast illumination was used to observe the condition of the dispersion.

A drop of the dilute slurry was placed between a microscope slide and a glass cover slip and observed at high magnification (400×). The dispersion exhibited severe particle aggregation. The aggregate size was greater than 10 microns and exhibited no Brownian particle movement.

COMPARATIVE EXAMPLE B

Comparative Example A was repeated except that 1 gram of the slurry was added to 10 grams of a dilute solution (1% by weight) of PVP K-15. The resultant dispersion after 6 days was aggregated. The aggregate size was at least 5 microns. After 6 days of holding, the dispersion settled completely leaving a clear supernatant and a layer of Steroid A sediment.

COMPARATIVE EXAMPLE C

Comparative Example B was repeated except that the 1% PVP solution was replaced with a 1% solution of purified sodium methyl oleoyl taurate (available from GAF as Igepon T and subsequently purified at Eastman Kodak). After 6 days the dilute dispersion was partially flocculated and had many aggregates larger than 1 micron.

COMPARATIVE EXAMPLE D

Comparative Example B was repeated except that 1 gram of slurry was added to 10 grams of a 1% aqueous solution of polyethylene glycol (available from Union Carbide as PEG 3350). The dispersion after sonification was flocculated with particles larger than 35 microns.

COMPARATIVE EXAMPLE E

Comparative Example B was repeated except that the dispersion was diluted with an aqueous 1% solution of

gum tragacanth (available from Eastman Kodak). This freshly prepared dispersion exhibited flocculation with particles 10 microns and larger.

COMPARATIVE EXAMPLE F

A dispersion of Danazol was prepared by ball milling with zirconium oxide grinding spheres. A cylindrical glass vessel was filled about halfway with the following ingredients:

Grinding media: 135 ml 0.85–1.18 mm Zirbeads XR
5 g Danazol
1 g PVP K-15
94 g high purity water

This vessel was rotated horizontally on its axis at a controlled speed of 50% critical speed (85 RPM) for 4 days. The slurry was discharged and separated from the grinding media through a screen and examined for particle size with an optical microscope. The slurry was examined for particle size after holding it for 4 days at room temperature (23° C.). A drop of undiluted slurry was placed between a glass microscope slide and a glass cover slip and observed optically at high magnification (400X). The slurry was partially aggregated with particles up to 10 microns in diameter. Unlike Examples 1–5, the amount of PVP present was insufficient to hinder particle agglomeration.

The invention has been described in detail with particular reference to preferred embodiments thereof, but it will be understood that variations and modifications can be effected within the spirit and scope of the invention.

What is claimed is:

1. Particles consisting essentially of 99.9–10% by weight of a crystalline drug substance having a solubility in water of less than 10 mg/ml, said drug substance having a non-crosslinked surface modifier adsorbed on the surface thereof in an amount of 0.1–90% by weight and sufficient to maintain an effective average particle size of less than about 400 nm.

2. The particles of claim **1** having an effective average particle size of less than 250 nm.

3. The particles of claim **1** having an effective average particle size of less than 100 nm.

4. The particles of claim **1** wherein said drug substance is selected from analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytic sedatives, astringents, beta-adrenoceptor blocking agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immuriological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, sympathomimetics, thyroid agents, vasodilators and xanthines.

5. The particles of claim **1** wherein said drug substance is a steroid.

6. Particles consisting essentially of 99.9–10% by weight of a crystalline drug substance having a solubility in water of less than 10 mg/ml, said drug substance having a non-crosslinked surface modifier absorbed on the surface thereof in an amount of 0.1–90% by weight and sufficient to maintain an effective average particle size of less than about 400 nm, wherein said drug substance is selected from the group consisting of Danazol, 5α,17α,-1'-(methylsulfonyl)-1'H-pregn-20-yno-[3,2-c]-pyrazol-17-ol, piposulfam, piposulfan, camptothecin, and ethyl-3,5-diacetamido-2,4,6-triiodobenzoate.

7. The particles of claim **1** wherein said surface modifier is selected from the group consisting of gelatin, casein, lecithin, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene caster oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidol silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethycellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, and polyvinylpyrrolidone.

8. The particles of claim **1** wherein said surface modifier is selected from the group consisting of polyvinylpyrrolidone, an ethylene oxide-propylene oxide block copolymer, lecithin, an alkyl aryl polyether sulfonate, gum acacia, sodium dodecylsulfate, and a dioctylester of sodium sulfosuccinic acid.

9. Particles consisitng essentially of 80–40% by weight of crystalline danazol having polyvinyl pyrrolidone adsorbed on the surface thereof in an amount of 20–60% by weight and sufficient to maintain an effective average particle size of less than about 100 nm.

10. Particles consisting essentially of 99.9–10% by weight of crystalline 5α, 17α,-1'-(methylsulfonyl)-1'H-pregn-20-yno-pyrazol-17-ol having an ethylene oxide propylene-oxide block copolymer adsorbed on the surface thereof in an amount of 0.1–90% by weight and sufficient to maintain an effective average particle size of less than about 400 nm.

11. A stable dispersion consisting essentially of a liquid dispersion medium and the particles of claim **1**.

12. The dispersion of claim **11** wherein said dispersion medium is water.

13. The dispersion of claim **11** wherein said dispersion medium is selected from the group consisting of safflower oil, ethanol, t-butanol, hexane and glycol.

14. A pharmaceutical composition comprising the particles of claim **1** and a pharmaceutically acceptable carrier therefor.

15. A method of treating a mammal comprising the step of administering to the mammal an effective amount of the pharmaceutical composition of claim **14**.

16. A method of preparing the particles of claim **1** comprising the steps of dispersing a drug substance in a liquid dispersion medium and wet grinding said drug substance in the presence of rigid grinding media having an average particle size of less than 3 mm and a surface modifier to reduce the particle size of said drug substance to an effective average particle size of less than about 400 nm.

17. A method of preparing the particles of claim **1** comprising the steps of dispersing a drug substance in a liquid dispersion medium, wet grinding said drug substance in the presence of rigid grinding media having an average particle size of less than 3 mm, thereafter contacting said drug substance with a surface modifier by mixing said surface modifier with said dispersion me-

dium to form particles having an effective average particle size of less than about 400 nm.

18. The method of claim 17 further including the step of subjecting the dispersion medium containing said drug substance and said surface modifier to ultrasonic energy.

19. The method of claim 16 wherein said grinding media have an average particle size of less than 1 mm.

20. The method of claim 16 wherein said grinding media have a density greater than 3 g/cm^3.

* * * * *

EXHIBIT 4

Version: May 2007

Rx Only

ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound)

(Patient Information Enclosed)

WARNING

ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

ABRAXANE therapy should not be administered to patients with metastatic breast cancer who have baseline neutrophil counts of less than 1,500 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE.

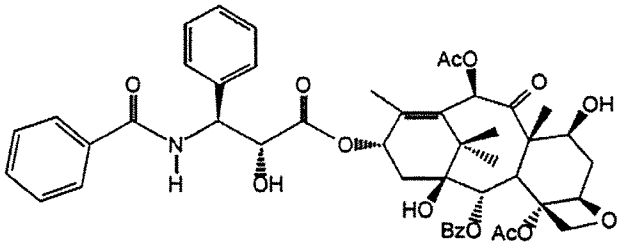
Note: An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS.

DESCRIPTION

ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. ABRAXANE is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. ABRAXANE is free of solvents.

The active agent in ABRAXANE® is paclitaxel, a natural product with antitumor activity. Paclitaxel is obtained from *Taxus media*. The chemical name for paclitaxel is 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine.

Paclitaxel has the following structural formula:



Paclitaxel is a white to off-white crystalline powder with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.91. It is highly lipophilic, insoluble in water, and melts at approximately 216°C to 217°C.

CLINICAL PHARMACOLOGY

Mechanism of Action

ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Human Pharmacokinetics

The pharmacokinetics of total paclitaxel following 30 and 180-minute infusions of ABRAXANE at dose levels of 80 to 375 mg/m^2 were determined in clinical studies. Dose levels of mg/m^2 refer to mg of paclitaxel in ABRAXANE. Following intravenous administration of ABRAXANE, paclitaxel plasma concentrations declined in a biphasic manner, the initial rapid decline

representing distribution to the peripheral compartment and the slower second phase representing drug elimination. The terminal half-life was about 27 hours.

The drug exposure (AUCs) was dose proportional over 80 to 375 mg/m^2 and the pharmacokinetics of paclitaxel for ABRAXANE® were independent of the duration of administration. At the recommended ABRAXANE clinical dose, 260 mg/m^2, the mean maximum concentration of paclitaxel, which occurred at the end of the infusion, was 18,741 ng/mL. The mean total clearance was 15 L/hr/m^2. The mean volume of distribution was 632 L/m^2; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

The pharmacokinetic data of 260 mg/m^2 ABRAXANE administered over 30 minutes was compared to the pharmacokinetics of 175 mg/m^2 paclitaxel injection over 3 hours. The clearance of ABRAXANE was larger (43%) than for the clearance of paclitaxel injection and the volume of distribution of ABRAXANE was also higher (53%). Differences in C_{max} and C_{max} corrected for dose reflected differences in total dose and rate of infusion. There were no differences in terminal half-lives.

In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicate that between 89% to 98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

After a 30-minute infusion of 260 mg/m^2 doses of ABRAXANE, the mean values for cumulative urinary recovery of unchanged drug (4%) indicated extensive non-renal clearance. Less than 1% of the total administered dose was excreted in urine as the metabolites 6α-hydroxypaclitaxel and 3'-*p*-hydroxypaclitaxel. Fecal excretion was approximately 20% of the total dose administered.

In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by CYP2C8; and to two minor metabolites, 3'-*p*-hydroxypaclitaxel and 6α, 3'-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole,

verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4 (see **PRECAUTIONS: Drug Interactions**). The effect of renal or hepatic dysfunction on the disposition of ABRAXANE® has not been investigated.

Possible interactions of paclitaxel with concomitantly administered medications have not been formally investigated.

CLINICAL STUDIES

Metastatic Breast Carcinoma:

Data from 106 patients accrued in two single arm open label studies and from 460 patients enrolled in a randomized comparative study were available to support the use of ABRAXANE in metastatic breast cancer.

Single Arm Open Label Studies- In one study, ABRAXANE was administered as a 30-minute infusion at a dose of 175 mg/m^2 to 43 patients with metastatic breast cancer. The second trial utilized a dose of 300 mg/m^2 as a 30 minute infusion in 63 patients with metastatic breast cancer. Cycles were administered at 3 week intervals. Objective responses were observed in both studies.

Randomized Comparative Study- This multicenter trial was conducted in 460 patients with metastatic breast cancer. Patients were randomized to receive ABRAXANE at a dose of 260 mg/m^2 given as a 30-minute infusion, or paclitaxel injection at 175 mg/m^2 given as a 3-hour infusion. Sixty-four percent of patients had impaired performance status (ECOG 1 or 2) at study entry; 79% had visceral metastases; and 76% had > 3 sites of metastases. Fourteen percent of the patients had not received prior chemotherapy; 27% had received chemotherapy in the adjuvant setting, 40% in the metastatic setting and 19% in both metastatic and adjuvant settings. Fifty-

nine percent received study drug as second or greater than second-line therapy. Seventy-seven percent of the patients had been previously exposed to anthracyclines.

In this trial, patients in the ABRAXANE® treatment arm had a statistically significantly higher reconciled target lesion response rate (the trial primary endpoint) of 21.5% (95% CI: 16.2% to 26.7%), compared to 11.1% (95% CI: 6.9% to 15.1%) for patients in the paclitaxel injection treatment arm. See Table 1. There was no statistically significant difference in overall survival between the two study arms.

Table 1: Efficacy Results from Randomized Trial

		ABRAXANE 260 mg/m²	Paclitaxel Injection 175 mg/m²
Reconciled Target Lesion Response Rate (primary endpoint) [a]			
All randomized patients	Response Rate [95% CI]	50/233 (21.5%) [16.19% – 26.73%]	25/227 (11.1%) [6.94% – 15.09%]
	P-value [b]	0.003	
Patients who had failed combination chemotherapy or relapsed within 6 months of adjuvant chemotherapy[c]	Response Rate [95% CI]	20/129 (15.5%) [9.26% – 21.75%]	12/143 (8.4%) [3.85% – 12.94%]

[a] Reconciled Target Lesion Response Rate (TLRR) was the prospectively defined protocol specific endpoint, based on independent radiologic assessment of tumor responses reconciled with investigator responses (which also included clinical information) for the first 6 cycles of therapy. The reconciled TLRR was lower than the investigator Reported Response Rates, which are based on all cycles of therapy.

[b] From Cochran-Mantel-Haenszel test stratified by 1st line vs. > 1st line therapy.

[c] Prior therapy included an anthracycline unless clinically contraindicated.

INDICATION

ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

CONTRAINDICATIONS

ABRAXANE should not be used in patients who have baseline neutrophil counts of < 1,500 cells/mm^3.

WARNINGS

Bone marrow suppression (primarily neutropenia) is dose dependent and a dose limiting toxicity. ABRAXANE should not be administered to patients with baseline neutrophil counts of < 1,500 cells/mm^3. Frequent monitoring of blood counts should be instituted during ABRAXANE treatment. Patients should not be retreated with subsequent cycles of ABRAXANE until neutrophils recover to a level >1,500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3.

The use of ABRAXANE has not been studied in patients with hepatic or renal dysfunction. In the randomized controlled trial, patients were excluded for baseline serum bilirubin >1.5 mg/dL or baseline serum creatinine >2 mg/dL.

Pregnancy – Teratogenic Effects: Pregnancy Category D: ABRAXANE can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel protein-bound particles to rats on gestation days 7 to 17 at doses of 6 mg/m^2 (approximately 2% of the daily maximum recommended human dose on a mg/m^2 basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions (up to 5-fold), reduced numbers of litters and live fetuses, reduction in fetal body weight and increase in fetal anomalies. Fetal anomalies included soft tissue and skeletal malformations, such as eye bulge, folded retina, microphthalmia, and dilation of brain ventricles. A lower incidence of soft tissue and skeletal

malformations were also exhibited at 3 mg/m^2 (approximately 1% of the daily maximum recommended human dose on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women using ABRAXANE®. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with ABRAXANE.

Use in Males: Men should be advised to not father a child while receiving treatment with ABRAXANE (see **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility** for discussion of effects of ABRAXANE exposure on male fertility and embryonic viability).

Albumin (Human): ABRAXANE contains albumin (human), a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob Disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS

Drug Interactions: No drug interaction studies have been conducted with ABRAXANE.

The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering ABRAXANE (paclitaxel protein-bound particles for injectable suspension) concomitantly with known substrates or inhibitors of CYP2C8 and CYP3A4 (see **CLINICAL PHARMACOLOGY**).

Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (such as ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.

Hematology: ABRAXANE® therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE. Patients should not be retreated with subsequent cycles of ABRAXANE until neutrophils recover to a level >1,500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3. In the case of severe neutropenia (<500 cells/mm^3 for seven days or more) during a course of ABRAXANE therapy, a dose reduction for subsequent courses of therapy is recommended (see **DOSAGE and ADMINISTRATION**).

Nervous System: Sensory neuropathy occurs frequently with ABRAXANE. The occurrence of grade 1 or 2 sensory neuropathy does not generally require dose modification. If grade 3 sensory neuropathy develops, treatment should be withheld until resolution to grade 1 or 2 followed by a dose reduction for all subsequent courses of ABRAXANE (see **DOSAGE and ADMINISTRATION**).

Injection Site Reaction: Injection site reactions occur infrequently with ABRAXANE and were mild in the randomized clinical trial. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenic potential of ABRAXANE has not been studied.

Paclitaxel has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). ABRAXANE was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.

Administration of paclitaxel protein-bound particles to male rats at 42 mg/m^2 on a weekly basis (approximately 16% of the daily maximum recommended human exposure on a mg/m^2 basis) for 11 weeks prior to mating with untreated female rats resulted in significantly reduced fertility accompanied by decreased pregnancy rates and increased loss of embryos in mated females. A low incidence of skeletal and soft tissue fetal anomalies was also observed at doses of 3 and 12

mg/m^2/week in this study (approximately 1 to 5% of the daily maximum recommended human exposure on a mg/m^2 basis). Testicular atrophy/degeneration has also been observed in single-dose toxicology studies in rodents administered paclitaxel protein-bound particles at 54 mg/m^2 and dogs administered 175 mg/m^2 (see **WARNINGS**).

Pregnancy: Teratogenic Effects: Pregnancy Category D: (See **WARNINGS** section).

Nursing Mothers: It is not known whether paclitaxel is excreted in human milk. Following intravenous administration of carbon-14 labeled paclitaxel to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving ABRAXANE® therapy.

Pediatric Use: The safety and effectiveness of ABRAXANE in pediatric patients have not been evaluated.

Geriatric use: Of the 229 patients in the randomized study who received ABRAXANE, 11% were at least 65 years of age and < 2% were 75 years or older. No toxicities occurred notably more frequently among elderly patients who received ABRAXANE.

Information for Patients: (See **Patient Information Leaflet**).

ADVERSE REACTIONS:

The following table shows the frequency of important adverse events in the randomized comparative trial for the patients who received either single-agent ABRAXANE® or paclitaxel injection for the treatment of metastatic breast cancer.

Table 2: Frequency[a] of Important Treatment Emergent Adverse Events in the Randomized Study on an Every-3-Weeks Schedule

	Percent of Patients	
	ABRAXANE® 260/30min[b] (n=229)	**Paclitaxel Injection 175/3h[c,d] (n=225)**
Bone Marrow		
Neutropenia		
< 2.0 x 10^9/L	80	82
< 0.5 x 10^9/L	9	22
Thrombocytopenia		
< 100 x 10^9/L	2	3
< 50 x 10^9/L	<1	<1
Anemia		
< 11 g/dL	33	25
< 8 g/dL	1	<1
Infections	24	20
Febrile Neutropenia	2	1
Bleeding	2	2
Hypersensitivity Reaction[e]		
All	4	12
Severe[f]	0	2
Cardiovascular		
Vital Sign Changes[g]		
Bradycardia	<1	<1
Hypotension	5	5
Severe Cardiovascular Events[f]	3	4
Abnormal ECG		
All patients	60	52
Patients with Normal Baseline	35	30
Respiratory		
Cough	7	6
Dyspnea	12	9
Sensory Neuropathy		
Any Symptoms	71	56
Severe Symptoms[f]	10	2
Myalgia / Arthralgia		
Any Symptoms	44	49
Severe Symptoms[f]	8	4

Table 2: Frequency[a] of Important Treatment Emergent Adverse Events in the Randomized Study on an Every-3-Weeks Schedule, Continued

	Percent of Patients	
	ABRAXANE® 260/30min[b] (n=229)	**Paclitaxel Injection 175/3h[c,d] (n=225)**
Asthenia		
Any Symptoms	47	39
Severe Symptoms[f]	8	3
Fluid Retention/Edema		
Any Symptoms	10	8
Severe Symptoms[f]	0	<1
Gastrointestinal		
Nausea		
Any symptoms	30	22
Severe symptoms[f]	3	<1
Vomiting		
Any symptoms	18	10
Severe Symptoms[f]	4	1
Diarrhea		
Any Symptoms	27	15
Severe Symptoms[f]	<1	1
Mucositis		
Any Symptoms	7	6
Severe Symptoms[f]	<1	0
Alopecia	90	94
Hepatic (Patients with Normal Baseline)		
Bilirubin Elevations	7	7
Alkaline Phosphatase Elevations	36	31
AST (SGOT) Elevations	39	32
Injection Site Reaction	<1	1

[a] Based on worst grade.
[b] ABRAXANE dose in mg/m^2/duration in minutes.
[c] paclitaxel injection dose in mg/m^2/duration in hours.
[d] paclitaxel injection pts received premedication.
[e] Includes treatment-related events related to hypersensitivity (e.g., flushing, dyspnea, chest pain, hypotension) that began on a day of dosing.
[f] Severe events are defined as at least grade 3 toxicity.
[g] During study drug dosing.

Myelosuppression and sensory neuropathy were dose related.

Adverse Event Experiences by Body System: Unless otherwise noted, the following discussion refers to the primary safety database of 229 patients with metastatic breast cancer treated with single-agent ABRAXANE® in the randomized controlled trial. The frequency and severity of important adverse events for the study are presented above in tabular form. In some instances, rare severe events observed with paclitaxel injection may be expected to occur with ABRAXANE.

Hematologic: Neutropenia, the most important hematologic toxicity, was dose dependent and reversible. Among patients with metastatic breast cancer in the randomized trial, neutrophil counts declined below 500 cells/mm^3 (Grade 4) in 9% of the patients treated with a dose of 260 mg/m^2 compared to 22% in patients receiving paclitaxel injection at a dose of 175 mg/m^2.

In the randomized metastatic breast cancer study, infectious episodes were reported in 24% of the patients treated with a dose of 260 mg/m^2 given as a 30-minute infusion. Oral candidiasis, respiratory tract infections and pneumonia were the most frequently reported infectious complications. Febrile neutropenia was reported in 2% of patients in the ABRAXANE arm and 1% of patients in the paclitaxel injection arm.

Thrombocytopenia was uncommon. In the randomized metastatic breast cancer study, bleeding episodes were reported in 2% of the patients in each treatment arm.

Anemia (Hb <11 g/dL) was observed in 33% of patients treated with ABRAXANE in the randomized trial and was severe (Hb <8 g/dL) in 1% of the cases. Among all patients with normal baseline hemoglobin, 31% became anemic on study and 1% had severe anemia.

Hypersensitivity Reactions (HSRs): In the randomized controlled metastatic breast cancer study, Grade 1 or 2 HSRs occurred on the day of ABRAXANE administration and consisted of dyspnea (1%) and flushing, hypotension, chest pain, and arrhythmia (all <1%). The use of

ABRAXANE® in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

During postmarketing surveillance, rare occurrences of severe hypersensitivity reactions have been reported with ABRAXANE. The use of ABRAXANE in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied. Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be rechallenged with the drug.

Cardiovascular: Hypotension, during the 30-minute infusion, occurred in 5% of patients in the randomized metastatic breast cancer trial. Bradycardia during the 30-minute infusion, occurred in <1% of patients. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation.

Severe cardiovascular events possibly related to single-agent ABRAXANE occurred in approximately 3% of patients in the randomized trial. These events included chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension. Cases of cerebrovascular attacks (strokes) and transient ischemic attacks have been reported rarely.

Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 60% of patients in the metastatic breast cancer randomized trial. Among patients with a normal ECG prior to study entry, 35% of all patients developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, and sinus tachycardia.

Respiratory: Reports of dyspnea (12%) and cough (6%) were reported after treatment with ABRAXANE in the randomized trial. Rare reports (<1%) of pneumothorax were reported after treatment with ABRAXANE. Rare reports of interstitial pneumonia, lung fibrosis, and

pulmonary embolism have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment. Rare reports of radiation pneumonitis have been received in paclitaxel injection patients receiving concurrent radiotherapy. There is no experience with the use of ABRAXANE with concurrent radiotherapy.

Neurologic: The frequency and severity of neurologic manifestations were influenced by prior and/or concomitant therapy with neurotoxic agents.

In general, the frequency and severity of neurologic manifestations were dose-dependent in patients receiving single-agent ABRAXANE®. In the randomized trial, sensory neuropathy was observed in 71% of patients (10% severe) in the ABRAXANE arm and in 56% of patients (2% severe) in the paclitaxel injection arm. The frequency of sensory neuropathy increased with cumulative dose. Sensory neuropathy was the cause of ABRAXANE discontinuation in 7/229 (3%) patients in the randomized trial. In the randomized comparative study, 24 patients (10%) treated with ABRAXANE developed Grade 3 peripheral neuropathy; of these patients, 14 had documented improvement after a median of 22 days; 10 patients resumed treatment at a reduced dose of ABRAXANE and 2 discontinued due to peripheral neuropathy. Of the 10 patients without documented improvement, 4 discontinued the study due to peripheral neuropathy.

No incidences of grade 4 sensory neuropathies were reported in the clinical trial. Only one incident of motor neuropathy (grade 2) was observed in either arm of the controlled trial.

Cranial nerve palsies have been reported during postmarketing surveillance of ABRAXANE. Because these events have been reported during clinical practice, true estimates of frequency cannot be made and a causal relationship to the events has not been established.

Reports of autonomic neuropathy resulting in paralytic ileus have been received as part of the continuing surveillance of paclitaxel injection safety.

Ocular/visual disturbances occurred in 13% of all patients (n=366) treated with ABRAXANE in single arm and randomized trials and 1% were severe. The severe cases (keratitis and blurred

vision) were reported in patients in a single arm study who received higher doses than those recommended (300 or 375 mg/m^2). These effects generally have been reversible. However, rare reports in the literature of abnormal visual evoked potentials in patients treated with paclitaxel injection have suggested persistent optic nerve damage.

Arthralgia/Myalgia: Forty-four percent of patients treated in the randomized trial experienced arthralgia/myalgia; 8% experienced severe symptoms. The symptoms were usually transient, occurred two or three days after ABRAXANE® administration, and resolved within a few days.

Hepatic: Among patients with normal baseline liver function treated with ABRAXANE in the randomized trial, 7%, 36%, and 39% had elevations in bilirubin, alkaline phosphatase, and AST (SGOT), respectively. Grade 3 or 4 elevations in GGT were reported for 14% of patients treated with ABRAXANE and 10% of patients treated with paclitaxel injection in the randomized trial.

Rare reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment.

Renal: Overall 11% of patients experienced creatinine elevation, 1% severe. No discontinuations, dose reductions, or dose delays were caused by renal toxicities.

Gastrointestinal (GI): Nausea/vomiting, diarrhea, and mucositis were reported by 33%, 27%, and 7% of ABRAXANE treated patients in the randomized trial.

Rare reports of intestinal obstruction, intestinal perforation, pancreatitis, and ischemic colitis have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment. Rare reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, were observed in patients treated with paclitaxel injection alone and in combination with other chemotherapeutic agents.

Injection Site Reaction: Injection site reactions have occurred infrequently with ABRAXANE and were mild in the randomized clinical trial. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel injection at a different site, i.e., "recall", has been reported rarely.

Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been received as part of the continuing surveillance of paclitaxel injection safety. In some cases the onset of the injection site reaction in paclitaxel injection patients either occurred during a prolonged infusion or was delayed by a week to ten days.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Asthenia: Asthenia was reported in 47% of patients (8% severe) treated with ABRAXANE® in the randomized trial. Asthenia included reports of asthenia, fatigue, weakness, lethargy and malaise.

Other Clinical Events: Rare cases of cardiac ischemia/infarction and thrombosis/embolism possibly related to ABRAXANE treatment have been reported. Alopecia was observed in almost all of the patients. Nail changes (changes in pigmentation or discoloration of nail bed) were uncommon. Edema (fluid retention) was infrequent (10% of randomized trial patients); no patients had severe edema.

The following rare adverse events have been reported as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment: skin abnormalities related to radiation recall as well as reports of Stevens-Johnson syndrome, toxic epidermal necrolysis, conjunctivitis, and increased lacrimation. As part of the continuing surveillance of ABRAXANE, skin reactions including generalized or maculo-papular rash, erythema, and pruritis have been observed. Additionally, there have been case reports of photosensitivity reactions, radiation recall phenomenon, and in some patients previously exposed to capecitabine, reports of palmar-plantar erythrodysaesthesiae. Because these events have been reported during

clinical practice, true estimates of frequency cannot be made and a causal relationship to the events has not been established.

Accidental Exposure: No reports of accidental exposure to ABRAXANE® have been received. However, upon inhalation of paclitaxel, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported. Following topical exposure, events have included tingling, burning, and redness.

OVERDOSAGE

There is no known antidote for ABRAXANE overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, sensory neurotoxicity, and mucositis.

DOSAGE AND ADMINISTRATION

After failure of combination chemotherapy for metastatic breast cancer or relapse within 6 months of adjuvant chemotherapy, the recommended regimen for ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks.

Hepatic Impairment: The appropriate dose of ABRAXANE for patients with bilirubin greater than 1.5 mg/dL is not known.

Dose Reduction: Patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer) or severe sensory neuropathy during ABRAXANE therapy should have dosage reduced to 220 mg/m^2 for subsequent courses of ABRAXANE. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m^2. For grade 3 sensory neuropathy hold treatment until resolution to grade 1 or 2, followed by a dose reduction for all subsequent courses of ABRAXANE.

Preparation and Administration Precautions: ABRAXANE is a cytotoxic anticancer drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in

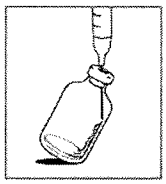
handling ABRAXANE. The use of gloves is recommended. If ABRAXANE (lyophilized cake or reconstituted suspension) contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure to paclitaxel, events may include tingling, burning and redness. If ABRAXANE® contacts mucous membranes, the membranes should be flushed thoroughly with water.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. Limiting the infusion of ABRAXANE to 30 minutes, as directed, reduces the likelihood of infusion-related reactions (see **PRECAUTIONS: Injection Site Reaction**).

No premedication to prevent hypersensitivity reactions is required prior to administration of ABRAXANE.

Preparation for Intravenous Administration: ABRAXANE is supplied as a sterile lyophilized powder for reconstitution before use. **AVOID ERRORS, READ ENTIRE PREPARATION INSTRUCTIONS PRIOR TO RECONSTITUTION.**

1. Aseptically, reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.
2. Slowly inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the INSIDE WALL OF THE VIAL.



3. DO NOT INJECT the 0.9% Sodium Chloride Injection, USP, directly onto the lyophilized cake as this will result in foaming.
4. Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder.
5. Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam.
6. If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.

Each mL of the reconstituted formulation will contain 5 mg/mL paclitaxel.

Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient: Dosing volume (mL) = Total dose (mg)/5 (mg/mL)

The reconstituted suspension should be milky and homogenous without visible particulates. If particulates or settling are visible, the vial should be **gently** inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed. Discard any unused portion.

Inject the appropriate amount of reconstituted ABRAXANE® into an empty, sterile IV bag (plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type IV bag). The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer ABRAXANE infusions. The use of an in-line filter is not recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Stability: Unopened vials of ABRAXANE are stable until the date indicated on the package when stored between 20°C to 25°C (68°F to 77°F), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product.

Stability of Reconstituted Suspension in the Vial

Reconstituted ABRAXANE should be used immediately, but may be refrigerated at 2°C to 8°C (36°F to 46°F) for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

Stability of Reconstituted Suspension in the Infusion Bag

The suspension for infusion prepared as recommended in an infusion bag should be used immediately, but may be stored at ambient temperature (approximately 25° C) and lighting conditions for up to 8 hours.

HOW SUPPLIED

Product No. 103450

NDC No. 68817-134-50 100 mg of paclitaxel in a single use vial, individually packaged in a carton.

Storage: Store the vials in original cartons at 20° C to 25° C (68° F to 77°F). Retain in the original package to protect from bright light.

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

U.S. Patent Numbers: 5,439,686; 5,498,421; 6,096,331; 6,506,405; 6,537,579; 6,749,868; 6,753,006

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Issued: May 2007

ABRAXIS
ONCOLOGY
A Division of Abraxis BioScience, Inc.
Los Angeles, CA 90049

PATIENT INFORMATION

ABRAXANE® for Injectable Suspension

[generic name = (paclitaxel protein-bound particles for injectable suspension) (albumin-bound)]

WHAT IS ABRAXANE?

ABRAXANE is a prescription cancer medicine. It is injected into a vein and it is used to treat advanced breast cancer.

WHAT IS CANCER?

Under normal conditions, the cells in your body divide and grow in an orderly, controlled way. Cell division and growth are necessary for the human body to perform its functions and to repair itself, when necessary. Cancer cells are different from normal cells because they are not able to control their own growth. The reasons for this abnormal growth are not yet fully understood. A tumor is a mass of unhealthy cells that are dividing and growing fast and in an uncontrolled way. When a tumor invades surrounding healthy body tissue it is known as a malignant tumor. A malignant tumor can spread (metastasize) from its original site to other parts of the body if not found and treated early.

HOW DOES ABRAXANE WORK?

ABRAXANE is a type of medical treatment called chemotherapy. The purpose of chemotherapy is to kill cancer cells or prevent their growth.

All cells, whether they are healthy cells or cancer cells, go through several stages of growth. During one of the stages, the cell starts to divide. ABRAXANE may stop the cells from dividing and growing, so they eventually die. In addition, normal cells may also be affected by ABRAXANE causing some of the side effects. (see **WHAT ARE THE POSSIBLE SIDE EFFECTS OF ABRAXANE?** below).

WHO SHOULD NOT TAKE ABRAXANE?

ABRAXANE should not be given to patients with dangerously low white blood cell counts.

HOW IS ABRAXANE® GIVEN?

ABRAXANE is injected into a vein [intravenous (I.V.) infusion] over 30 minutes.

WHAT PREMEDICATION IS REQUIRED WITH ABRAXANE?

While reactions can occur to any medication, severe allergic reactions to ABRAXANE are uncommon and premedication is not required. However, you should make your doctor aware of any allergies you may have so he/she can determine the course of action required.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF ABRAXANE?

Most patients taking ABRAXANE will experience side effects, although it is not always possible to tell whether such effects are caused by ABRAXANE, another medicine they may be taking, or the cancer itself. Important side effects are described below; however, some patients may experience other side effects that are less common. *Report any unusual symptoms to your doctor.*

Important side effects observed in studies of patients taking ABRAXANE were as follows:

Hair Loss: Complete hair loss, or alopecia, almost always occurs with ABRAXANE. This usually involves the loss of eyebrows, eyelashes, and pubic hair, as well as scalp hair. It can occur suddenly after treatment has begun, but usually happens 14 to 21 days after treatment. *Hair generally grows back after you've finished your ABRAXANE treatment.*

Infections Due to Low White Blood Cell Count: Among the body's defenses against bacterial infections are white blood cells. Between your ABRAXANE treatment cycles, you will often have blood tests to check your white blood cell counts. ABRAXANE usually causes a brief drop in white blood cells. *If you have a fever (temperature above 100.4°F) or other sign of infection, tell your doctor right away. Sometimes serious infections develop that require treatment in the hospital with antibiotics. Serious illness or death could result if such infections are not treated when white blood cell counts are low.*

Numbness, Tingling, or Burning in the Hands and/or Feet (Neuropathy): These symptoms occur often with ABRAXANE® and usually get better or go away without medication within three weeks of interrupting treatment. Be sure to tell your doctor about any numbness, tingling or burning that you have in your hands or feet so that he/she can decide the best approach for relief of your symptoms. Sometimes it is necessary to interrupt treatment with ABRAXANE until these symptoms improve. After improvement, treatment can be restarted at a lower dose.

Fatigue and Weakness: ABRAXANE may cause asthenia, fatigue, weakness, lethargy and malaise. These side effects are usually self-limited and do not require dose modification or interruption.

Low Red Blood Cell Count: Red blood cells deliver oxygen to tissues throughout all parts of the body and take carbon dioxide from the tissues by using a protein called hemoglobin. A lowering of the volume of red blood cells may occur following ABRAXANE treatment causing anemia. Some patients may need a blood transfusion to treat the anemia. Patients can feel tired, tire easily, appear pale, and become short of breath. Contact your doctor if you experience any of these symptoms following ABRAXANE treatment.

Mouth or Lip Sores (Mucositis): Some patients develop redness and/or sores in the mouth or on the lips. These symptoms might occur a few days after the ABRAXANE treatment and usually decrease or disappear within one week. Talk with your doctor about proper mouth care and other ways to prevent or reduce your chances of developing mucositis.

Joint and Muscle Pain: You may get joint and muscle pain a few days after your ABRAXANE treatment. These symptoms usually disappear in a few days. Although pain medicine may not be necessary, tell your doctor if you are uncomfortable.

Stomach Upset and Diarrhea: Some patients experience nausea, vomiting, and/or diarrhea following ABRAXANE use. If you experience nausea or stomach upset, tell your doctor because medicines can be given that almost always reduce or eliminate these symptoms.

Diarrhea will usually disappear without treatment; however, *if you experience severe abdominal or stomach area pain and/or severe diarrhea, tell your doctor right away.*

Heart and Blood Vessel (Cardiovascular) Effects: ABRAXANE® may cause a drop in heart rate (bradycardia) and low blood pressure (hypotension). The patient usually does not notice these changes. These changes usually do not require treatment. You should notify your doctor if you have a history of heart disease.

Irritation at the Injection Site: ABRAXANE may cause irritation at the site where it enters the vein. Reactions may include discomfort, redness, swelling, inflammation (of the surrounding skin or of the vein itself), and ulceration (open sores). These reactions are usually caused by the I.V. (intravenous) fluid leaking into the surrounding area. *If you notice anything unusual at the site of the injection (needle), either during or after treatment, tell your doctor right away.*

Talk with your doctor or other healthcare professional to discuss ways to prevent or reduce some of these side effects. Because this leaflet does not include all possible side effects that can occur with ABRAXANE, it is important to talk with your doctor about other possible side effects.

CAN I TAKE ABRAXANE IF I AM PREGNANT OR NURSING A BABY?

ABRAXANE could harm the fetus when given to a pregnant woman. Women should avoid becoming pregnant while they are undergoing treatment with ABRAXANE. *Tell your doctor if you become pregnant or plan to become pregnant while taking ABRAXANE.*

Men should be advised not to father a child while receiving treatment with ABRAXANE.

Because studies have shown the active agent (paclitaxel) in ABRAXANE to be present in the breast milk of animals receiving the active agent, it may be present in human breast milk as well. Therefore, nursing a baby while taking ABRAXANE is NOT recommended. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving ABRAXANE therapy.

This medicine was prescribed for your particular condition. This summary does not include everything there is to know about ABRAXANE®. Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. If you have questions or concerns, or want more information about ABRAXANE, your doctor and pharmacist have the complete prescribing information upon which this guide is based. You may want to read it and discuss it with your doctor. Remember, no written summary can replace careful discussion with your doctor.

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This Patient Information Leaflet has been approved by the U.S. Food and Drug Administration.
Based on: ABRAXANE Package Insert issued: May 2007
Revised: May 2007

EXHIBIT 5

REDACTED

EXHIBIT 6

- Unlike other taxane formulations, ABRAXANE is free of solvents. ABRAXANE can be administered at a dose of 260 mg/m² over a shortened infusion time. ABRAXANE is the only taxane that does not require steroid premedication to prevent hypersensitivity reactions.

WARNING:

- ABRAXANE should be administered under the supervision of an experienced physician.
- ABRAXANE should not be administered to patients with neutrophil counts <1,500 cells/mm³.
- Administration of Taxol® (paclitaxel) Injection has resulted in fatal reactions despite premedication. Taxol is typically administered at 175 mg/m² over 3 hours. Thus, inadvertent administration of Taxol using the ABRAXANE dose and schedule and without steroid premedication may result in severe, life-threatening, or fatal adverse events. Therefore, for the safety of your patients, it is extremely important that you **DO NOT SUBSTITUTE ABRAXANE** for or with other paclitaxel formulations.
- ABRAXANE does not contain a warning for hypersensitivity reactions.

DESCRIPTION:

- ABRAXANE, the first "protein-bound particle" in the taxane class of chemotherapeutics, is a next-generation albumin-bound paclitaxel, and is free of solvents.
- ABRAXANE consists only of albumin-bound paclitaxel particles with a mean size of approximately 130 nanometers.
- The proprietary albumin-bound technology utilized by ABRAXANE eliminates the need for toxic solvents.

Abraxane
for Injectable Suspension
(paclitaxel protein-bound particles for injectable suspension)
(albumin-bound)

Rx Only

WARNING

ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

ABRAXANE therapy should not be administered to patients with metastatic breast cancer who have baseline neutrophil counts of less than 1,500 cells/mm³. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE.

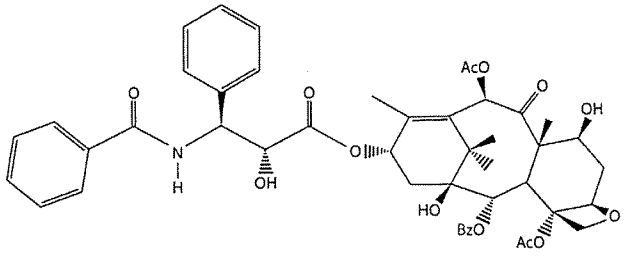
Note: An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS.

DESCRIPTION:

ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. ABRAXANE is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. ABRAXANE is free of solvents.

The active agent in ABRAXANE is paclitaxel, a natural product with antitumor activity. Paclitaxel is obtained from *Taxus media*. The chemical name for paclitaxel is 5ß,20-Epoxy-1,2α,4,7ß,10ß,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine.

Paclitaxel has the following structural formula:



Paclitaxel is a white to off-white crystalline powder with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.91. It is highly lipophilic, insoluble in water, and melts at approximately 216°C to 217°C.

EXHIBIT 7

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EXHIBIT 8

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EXHIBIT 9

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EXHIBIT 10

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