EXHIBIT 10

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Tadashi MAKINO et al. Group Art Unit: 125

Serial No. 014,303 Examiner: Waddell

Filed: February 13, 1987

For: STABILIZED PHARMACEUTICAL COMPOSITION AND ITS PRODUCTION

AMENDMENT SUBMITTED UNDER 37 CFR 1.115

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

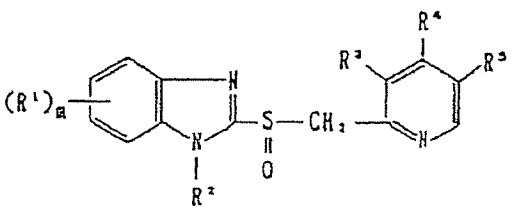
Sir:

This amendment responds to the Official Action dated June 28, 1988.

IN THE CLAIMS

Cancel claims and 1 and 18, replacing them with claims 19 and 20, respectively.

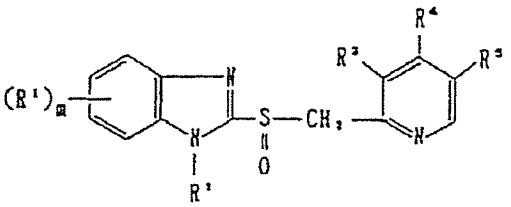
--19. A pharmaceutical composition which comprises an effective amount of anti-ulcer compound of the formula:



wherein R^1 is hydrogen, C_{1-7} alkyl, halogen, cyano, carboxy, carbo-C_{1-4}alkoxy, carbo-C_{1-4}alkoxy-C_{1-4}alkyl, carbamoyl, carbamoyl-C_{1-4}alkyl, hydroxy, C_{1-5}alkoxy, hydroxy-C_{1-7}alkyl, trifluoromethyl, C_{1-4}alkanoyl, carbamoyloxy, nitro, C_{1-4}alkanoyl-oxy, phenyl, phenyloxy, C_{1-6}alkylthio or C_{1-6}alkylsulfinyl, R^2 is hydrogen, C_{1-5}alkyl, C_{1-4}alkanoyl, carbo-C_{1-4} alkoxy, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)-carbamoyl, C_{1-4}alkylcarbonylmethyl, C_{1-4}alkoxycarbonylmethyl or C_{1-4}alkylsulfonyl, R^3 and R^5 are the same or different and each is hydrogen, C_{1-4}alkyl, C_{1-8}alkoxy or C_{1-4}alkoxy-C_{1-4}alkoxy, R^4 is hydrogen, C_{1-4}alkyl, C_{1-8}alkoxy which may optionally be fluorinated, or C_{1-4}alkoxy-C_{1-4}alkoxy, and m is an integer of 0 through 4, and at least one of the basic inorganic salts of magnesium and calcium selected from heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite, aluminum magnesium hydroxide, precipitated calcium carbonate and calcium hydroxide; the amount of the basic inorganic salt relative to parts by weight of the benzimidazole compound being about 0.3-20 parts by weight; the benzimidazole compound being in contact with the basic inorganic salt evenly.

20. A method of producing a stabilized pharmaceutical anti-ulcer composition which comprises incorporating at least one of the basic inorganic salts of magnesium and calcium selected from heavy magnesium carbonate, magnesium carbonate, magnesium oxide,

magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite, aluminum magnesium hydroxide, precipitated calcium carbonate and calcium hydroxide in a pharmaceutical composition containing an effective amount of an anti-ulcer compound of the formula:



wherein R^1 is hydrogen, C_{1-7} alkyl, halogen, cyano, carboxy, carbo-C_{1-4} alkoxy, carbo-C_{1-4} alkoxy-C_{1-4} alkyl, carbamoyl, carbamoyl-C_{1-4} alkyl, hydroxy, C_{1-5} alkoxy, hydroxy-C_{1-7} alkyl, trifluoromethyl, C_{1-4} alkanoyl, carbamoyloxy, nitro, C_{1-4} alkanoyl-oxy, phenyl, phenyloxy, C_{1-6} alkylthio or C_{1-6} alkylsulfinyl, R^2 is hydrogen, C_{1-5} alkyl, C_{1-4} alkanoyl, carbo-C_{1-4} alkoxy, carbamoyl, C_{1-4} alkylcarbamoyl, di(C_{1-4} alkyl)-carbamoyl, C_{1-4} alkylcarbonylmethyl, C_{1-4} alkoxycarbonylmethyl or C_{1-4} alkylsulfonyl, R^3 and R^5 are the same or different and each is hydrogen, C_{1-4} alkyl, C_{1-8} alkoxy or C_{1-4} alkoxy-C_{1-4} alkoxy, R^4 is hydrogen, C_{1-4} alkyl, C_{1-8} alkoxy which may optionally be fluorinated, or C_{1-4} alkoxy-C_{1-4} alkoxy, and m is an integer of 0 through 4; the amount of the basic inorganic salt relative to part by weight of the benzimidazole compound being about 0.3-20

parts by weight; the benzimidazole compound being in contact with the basic inorganic salt evenly.--

Claims 2-17, line 1, change "1" to --19--.

REMARKS

The claims are 2-17, 19 and 20. A favorable reconsideration is courteously requested in view of the foregoing amendments and the following remarks.

In the two generic claims, the substituents R^1 to R^5 have been redefined based on disclosure on page 5, line 16 to page 6, line 14 of the specification. The basic inorganic salts of magnesium and calcium are limited to those specifically disclosed in lines 13-25. Also, the relative amounts of the anti-ulcer benzimidazole compound and the basic inorganic salts of magnesium and calcium stated based on the support of page 18, line 25 and page 19, line 3 in the specification.

Also, following the specification of page 20, lines 1-3, it has been specifically stated that the benzimidazole compound is in contact with the basic inorganic salts evenly.

These changes should avoid the rejection under 35 USC 112 demanding full, clear, concise and exact terms of description.

The claims stand rejected under 35 USC 102(a) as anticipated by or, in the alternative, under 35 USC 103 as obvious from Nohara et al. or Rainer.

Regarding the Nohara reference, it should be noted that its filing date is December 2, 1986. Submitted herewith are verified

translations of two Japanese priority applications for the instant application, filed February 13 and 21, 1986, respectively. These applications clearly antedate the Nohara reference. It should be noted that the U.S. parent application in the Nohara reference, serial number 760,568 filed 1985, now U.S. Patent No. 4,689,333, does not contain the disclosure relied upon by the Examiner for this case.

Rainer et al. disclose the combination of the benzimidazole compounds and magnesium aluminate. However, the reference makes no comment or suggestion on stabilization of the benzimidazole compounds by contacting with magnesium aluminate or any other basic inorganic salt of magnesium and calcium evenly. It should be noted that in Rainer et al., magnesium aluminate is contained in the pharmaceutical formulations as an antacid, and in such use as an antacid, the salt need not contact the benzimidazole compounds at all.

The importance of the even distribution of the basic inorganic salt of the present compound is demonstrated by the experimental information presented herewith under 37 CFR 1.132. The experiment follows the procedure of "Content Uniformity" as set forth by the United States Pharmacopeia, 21st revision, January 1, 1985. The criteria set forth in this standard reference demonstrates that an even or homogeneous mixture is defined when each individual unit is within 6 percent of the relative standard deviation. In Table 1 of the declaration, it is shown that when these guidelines are met, each individual unit

will have an even contact between the benzimidazole compound and the included inorganic salt which leads to a stabilization not shown to be expected in the prior art.

Junggren et al. disclose mixing of the benzimidazole with magnesium stearate or calcium stearate as an antifriction agent. (Column 6, lines 12-13). However, magnesium and calcium stearate are not classified as basic inorganic salts of magnesium or calcium.

The Handbook merely discloses certain inorganic salts to be antacids. There is no suggestion of the instant technique of improving stability. The reference neither discloses nor suggests the combination use of the benzimidazole and the basic inorganic salts of magnesium and calcium

Table 1 on page 35 of the specification shows that the benzimidazole compounds can be stabilized by contacting with the specific inorganic salts of this invention, while combinations with other salts shown on page 36 fail.

Ueno et al. disclose that 4-(3-tert.butylamino-2-hydroxy)propoxy-2-methylisocarbostyril or its acid addition salt is useful for treatment of heart disease and may be stabilized by addition of at least one stabilizing agent selected from magnesium silicate, magnesium oxide, hydrotalcite and sodium hydrogen carbonate. However, the active compound is quite different from the benzimidazole compounds both as to chemical structure and pharmaceutical utility.

Thus, the prior art cannot be fairly said to suggest the stabilized pharmaceutical compositions of the present invention or a method of their preparation.

A favorable reconsideration is, therefore, courteously requested.

Respectfully submitted,

Helmuth A. Wegner
Reg. No. 17,033

WEGNER & BRETSCHNEIDER
P.O. Box 18218
Washington, D.C. 20036-8218
(202) 887-0400

Atty. Docket No. P-8700-19861
Date: November 28, 1988
HAW:mwr/lgl.j/bcm

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application :
Tadashi MAKINO et al. :
Serial No. 014,303 :
Filed: February 13, 1987 :
STABILIZED PHARMACEUTICAL
COMPOSITION AND ITS PRODUCTION :

DECLARATION UNDER RULE 132

Honorable Commissioner of Patent and Trademarks,
Washington, D.C.

Sir:

I, Shin-ichiro Hirai, declare:

That I am a citizen of Japan and a resident of 201 Tamamotocho, Aburakojidori Shomensagaru, Shimogyo-ku, Kyoto, Japan;

That I was born on June 14,1941 in Kyoto, Japan and graduated from Faculty of Pharmaceutical Sciences, Kyoto University, Japan in March, 1965;

That I have been an employee of Takeda Chemical Industries, Ltd. since April 1965, and have been engaged in researches in pharmaceutics at the Central Research Division of the said company and have been a Research Head in Pharmaceutics Laboratories since 1983;

That I was given a degree of Doctor of Pharmacy from Kyoto University in 1982 on my dissertation entitled " Improvement of Bioavailability of Drugs by Nasal Administration ";

That I have contributed with other research workers, scientific reports, e.g., in

(a) Nasal Absorption of Insulin in Dogs.
Diabetes, 27, 296 (1978)

(b) Nasal Absorption of Propranolol in Humans.
J. Pharm. Sci., 69, 1240 (1980)

(c) Absorption of Drugs from the Nasal Mucosa of Rat.
Int. J. Pharm., 7, 317 (1981)

(d) Bioavailability of 5-[4-(1-methylcyclohexylmethoxy)-benzyl]thiazolidene-2,4-dione(ADD-3878) in Beagle Dogs.
Int. J. Pharm., 15, 261 (1983);

That I am a member of the Pharmaceutical Society of Japan, and Academy of Pharmaceutical Science and Technology, Japan;

That I am one of the co-inventors of U.S.Serial No. 014,303;

That the following Experiment was conducted under my direction and supervision;

Experiment

1. Materials and methods

Of the components given below, the compound (A) [2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulfinyl]-benzimidazole], magnesium hydroxide, L-cysteine, lactose and a half amount of microcrystalline cellouse, light silicic anhydride and magnesium stearate were mixed together in a tumbling mixer (Showa Chemical and Machine Ltd.) in the mixing time shown in Table 1 and the obtained mixture was compression-molded on a dry granulator (roller compactor;

Freund,Japan). The compressed mass was ground in a mortar, the resultant granular mass was passed through a round sieve (16 mesh). The remaining portions of microcrystalline cellulose, light silicic anhydride and magnesium stearate were added to the sieved mass and, after admixing, the whole mixture was made up into tablets each weighing 250 mg on a rotary tableting machine (Kikusui Seisakusho, Japan).

These tablets were subjected to the content uniformity test described in USP XXI,p.1277-1278 and after storage at 50 C and 75% RH for 1 week, were observed for changes in appearance.

[Composition]

	per tablet	charge in
Compound (A)	50 mg	500 g
Magnesium hydroxide	30 mg	300 g
L-Cysteine	20 mg	200 g
Corn starch	20 mg	200 g
Lactose	65.2 mg	652 g
Microcrystalline cellulose	60 mg	600 g
Light silicic anhydride	1.8 mg	18 g
Magnesium stearate	3.0 mg	30 g
Total	250.0 mg	2500 g

2. Results

The contents, mean contents relative standard deviation(the sample standard deviation expressed as a percentage of the mean, RSD) and changes in appearance after storage at 50°C ,75% RH for a week in the obtained tablets are shown in Table 1.

Table 1

Mixing time (min)	1	3	5	10
Min.~Max. of content (%)	81.6~118.5	90.6~113.5	96.5~104.4	97.6~104.1
Mean content (%)	98.9	101.7	100.5	100.6
RSD (%)	8.7	6.3	3.2	2.8
Changes in appearance	Moderately to violet	Slightly to violet	No changes	No changes

3. Conclusion

The tablet whose content uniformity is suited to that in USP XXI, does not change in appearance and is sufficiently stable, while the one whose content uniformity is not suited to that in USP XXI, changes in appearance and unstable.

I, the undersigned, declare further that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed November 2, 1988

Shin-ichiro Hirai

Shin-ichiro Hirai

EXHIBIT 11

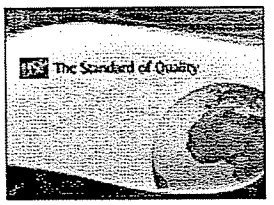
Our impact
Where we're going
ISO certified
Governance
Executive team
History
What's new
Annual report
Newsletters
Press Room
Public access of USP resources
Careers
Contact us
Directions to USP

About USP—An Overview

Who We Are

The United States Pharmacopeia (USP) is the official public standards-setting authority for all prescription and over-the-counter medicines, dietary supplements, and other healthcare products manufactured and sold in the United States. USP sets standards for the quality of these products and works with healthcare providers to help them reach the standards. USP's standards are also recognized and used in more than 130 countries. These standards have been helping to ensure good pharmaceutical care for people throughout the world for more than 185 years.

What's New



Watch USP's new interactive overview
View an online presentation of USP's history and how our programs, products, and services can benefit you.

Resolutions define USP focus areas for 2005–2010.

USP is an independent, science-based public health organization. As a self-sustaining nonprofit organization, USP is funded through revenues from the sale of products and services that help to ensure good pharmaceutical care. USP's contributions to public health are enriched by the participation and oversight of volunteers representing pharmacy, medicine, and other healthcare professions as well as academia, government, the pharmaceutical industry, health plans, and consumer organizations.

Our Mission

USP promotes the public health by developing and disseminating quality standards and information for medicines, healthcare delivery, and related products and practices. Our standards and information help patients and practitioners maintain and improve health.

What We Do

Product Quality—Standards and Verification

USP establishes public standards to help assure good quality medicines, dietary supplements, and related products used to maintain health and treat disease. Prescription and over-the-counter medicines available in the United States must, by federal law, meet USP's public standards, where such standards exist. Many other countries require the use of high-quality standards such as USP's to assure the quality of medicines and related products. USP disseminates its standards to pharmaceutical manufacturers, pharmacists, and other users through its USP-NF

and other publications, official USP Reference Standards materials, and Pharmacopeial Education courses.

USP also conducts verification programs for dietary supplement ingredients and products. These programs involve independent testing and review to verify ingredient and product integrity, purity, and potency for manufacturers who choose to participate.

Patient Safety

USP operates two programs to promote safer care of patients who take medications and stay in hospitals. The Medication Errors Reporting Program allows healthcare professionals to directly report medication errors to USP. MEDMARX®, an Internet-based medication error and adverse drug reaction reporting program, is designed for use in hospitals and health systems. USP also uses its knowledge base to provide information that supports the healthcare community in the research and development of patient safety initiatives.

Healthcare Information

USP develops authoritative, unbiased information relating to various aspects of drug use and disseminates this information to practitioners, pharmacists, and others who make decisions about healthcare around the world. Significant among USP's healthcare information initiatives is the development of a drug classification system that Medicare Prescription Drug Benefit plans may use to develop their formularies. USP also partners with the U.S. Agency for International Development in worldwide projects that help to assure drug quality and proper drug use in many developing countries.

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EXHIBIT 12

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Tadashi MAKINO et al.

Serial No. 014,303 Group Art Unit: 125

Filed: February 13, 1987 Examiner: F. Waddell

For: STABILIZED PHARMACEUTICAL COMPOSITION AND ITS PRODUCTION

APPEAL BRIEF

On Appeal from Group 125

Wegner & Bretschneider
P. O. Box 18218
Washington, DC 20036
Attorneys for Appellants

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APPENDIX A

APPENDIX B

I. STATUS OF CLAIMS

Claims 2-17 and 19-28 are pending in the application. Claims 1 and 18 have been cancelled during the course of prosecution.

Appellants hereby withdraw this appeal without prejudice for active ingredients beyond those of current dependent claims 2 and 6. Appendix A sets forth the claims in their form as finally rejected. Appendix B sets forth a revised version of the independent appealed claims, taking into account the above withdrawal.[1]

II. STATUS OF AMENDMENTS

The Amendment filed May 15, 1989 was denied entry in the May 25, 1989 Advisory Action. A further Amendment filed December 6, 1989 was denied entry in the Advisory Action dated December 26, 1989, as discussed above.

III. SUMMARY OF THE INVENTION

The present invention is directed to anti-ulcer compositions, and method for preparing such compositions, which include as an active ingredient certain benzimidazole compounds. Although these compounds are effective anti-ulcer agents, they suffer difficulties from their poor stability, particularly their

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[1] For a more elegant solution to this question, see the December 6, 1989 Amendment in which claims 2-7, 19, 20 and 23-28 were cancelled and replaced with new claims 29-32. However, the Examiner refused entry of this Amendment in the December 26, 1989 Advisory Action. Regrettably, due to the impending deadline for filing this brief, it was not possible to request reconsideration of this decision.

acid-reactivity. See page 2, line 9 to page 3, line 15 of the specification. In the present invention, stability is provided to the benzimidazole compounds by including basic, inorganic magnesium or calcium salts in a composition containing the benzimidazole compounds. The benzimidazole compounds are evenly contacted with the salts. See page 18, line 10 through page 20, line 10 of the specification. The composition is then coated, for which an enteric coating may be used. See page 20, lines 14-24 of the specification.

IV. ISSUES

The sole issue raised in the February 14, 1989 final rejection is the patentability of the claimed invention over Nohara et al. (U.S. Patent No. 4,689,333), Rainer et al. (U.S. Patent No. 4,686,230), Junggren et al. (U.S. Patent No. 4,255,432), and Handbook of Non Prescription Drugs, Fifth Edition, pg 7-10, in view of Ueno et al. (U.S. Patent No. 4,666,919) and Japanese Patent 19,715/85.

V. GROUPING OF CLAIMS

For the purposes of this appeal only, and noting the withdrawal in part I supra, claims 8-16 and 19-28 are considered to stand or fall together. Claim 17 supports an additional argument for patentability.

VI. ARGUMENT

The presently claimed invention is not suggested by the references cited.

A. Disclosure of the References

Nohara et al. was cited originally in a rejection under 35 USC 102(a) or 103 for disclosing benzimidazoles in conjunction with inorganic magnesium or calcium salts. This rejection was withdrawn following the submission of verified translations of the priority applications, along with a showing that the disclosure upon which the Examiner relied was not supported by a U.S. filing date earlier than the priority date for the present application. It is therefore assumed that this reference is now cited only for teaching compounds similar to the active ingredients of the present claims.

Rainer et al. is directed to certain picoline derivatives useful for gastric acid secretion inhibitors. Column 40, lines 27-28 suggest that the active ingredients can be administered with antacids such as aluminum hydroxide and magnesium aluminate.

Junggren et al. similarly is cited for a showing of compounds related to the active ingredients of the present claims.

The Handbook of Non Prescription Drugs is cited for showing that at least some of the calcium and magnesium salts of the present claims are known antacids.

Ueno et al. and Japanese Publication 19715 teach certain salts, including magnesium silicate, magnesium oxide and hydrotalcite, as stabilizers for isocarbostyril derivatives.

B. The References do not Suggest Benzimidazole Compounds Evenly Contacted with Basic Inorganic Magnesium or Calcium Salts

The present independent composition and method claims require that the benzimidazole derivatives be contacted evenly with a basic inorganic salt of magnesium or calcium. This serves to stabilize the benzimidazole derivatives and is not suggested by the combination of references relied on by the Examiner.

The disclosure of Nohara et al. available as prior art includes no suggestion of any basic inorganic salts to be combined with the benzimidazole derivatives, evenly or otherwise. The same holds true for Junggren et al.

Rainer et al. discloses the combination of certain benzimidazole compounds and certain inorganic salts, such as magnesium aluminate. However, the reference does not attribute any stabilization characteristics to the inorganic salt and makes no mention as to how compositions containing the inorganic salt are to be prepared. There is no disclosure or suggestion in the reference that the benzimidazole compounds and inorganic salt should contact evenly. No evidence of record suggests why one of ordinary skill would infer that the Rainer et al. antacids should be mixed evenly with the benzimidazole derivatives. Nothing in the reference provides any indication whatsoever that contacting

evenly would be necessary to carry out the antacid function ascribed to the inorganic salts.

Therefore, there is nothing in the primary references which suggests that benzimidazole compounds should be evenly contacted with calcium or magnesium basic inorganic salts. This deficiency is not remedied by the secondary references.

The Ueno et al. patent and the Japanese publication appear to include the same disclosure and thus are considered together. The references disclose that certain isocarbostyril derivatives may be stabilized by magnesium silicate, magnesium oxide, hydrotalcite or sodium bicarbonate. The isocarbostyril (i.e. 1-hydroxy isoquinoline) derivatives of the references are unrelated to the benzimidazole compounds of the present invention. Nothing in the references suggests why one of ordinary skill would apply the secondary references' teaching to the far different benzimidazole compounds of the present claims. Moreover, although the references do discuss stabilizing agents, there is nothing in the references suggesting that the isocarbostyril compounds suffer from the problem of acid-lability as do the present benzimidazole compounds. Thus, there would be no reason for one of ordinary skill to expect that the stabilizers for isocarbostyril derivatives could function to overcome the acid-lability problems of the present benzimidazole compounds. Therefore, Ueno et al. and the Japanese reference fail to overcome the deficiencies of the primary references.

The Handbook of Non-Prescription Drugs merely discloses certain compounds as antacid agents. Nothing in this reference suggests that these antacids could be combined with benzimidazole compounds, or that if combined there should be even contact to overcome acid instability problems.

It is therefore submitted that the rejection is a hindsight reconstruction of the claimed invention and should be reversed.

The Declaration of Mr. Hirai, filed with the November 28, 1988 Amendment, further supports the patentability of the present invention. The experimental results reported therein demonstrate the importance of establishing even contact. Inadequate mixing, resulting in uneven contact, yielded unstable products. On the other hand, the products with even contacting showed stability.

In the final rejection, the Examiner stated, with respect to Rainer et al.:

> The remarks regarding contact not being required in Rainer et al. do not obviate the rejection since components are routinely mixed in the art before tableting. Such mixing is adequate to give an even blend or mixture.

However, this reasoning is unsupported by facts in the present record. Rainer et al. fails to indicate that the benzimidazole derivatives should be mixed at all, much less mixed to the extent that even contact is present.

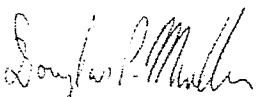
C. The Enteric Coating of Claim 17 is Even Further Removed from the References

Claim 17 requires that the composition be provided with an enteric coating. Such a coating would defeat the antacid function for which Rainer et al. uses the inorganic salts. Thus, Rainer et al. in fact teaches away from the invention of claim 17.

VII. CONCLUSION

The rejection of the present application is untenable and should be reversed.

Respectfully submitted,



Douglas P. Mueller
Reg. No. 30,300

WEGNER & BRETSCHNEIDER
P. O. Box 18218
Washington, DC 20036-8218
(202) 887-0400

Attorney Docket: P8700-19861P
Date: December 29, 1989
DPM:ldc/28

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APPENDIX A

2. A pharmaceutical composition as claimed in claim 23, wherein the compound is 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulfinyl]benzimidazole.

3. A pharmaceutical composition as claimed in claim 19, wherein the compound is 2-[[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-2-pyridyl]methylsulfinyl]benzimidazole.

4. A pharmaceutical composition as claimed in claim 19, wherein the compound is 2-[(4-propoxy-2-pyridyl)methyl-sulfinyl]benzimidazole.

5. A pharmaceutical composition as claimed in claim 19, wherein the compound is 2-[(3-methyl-4-propoxy-2-pyridyl)methylsulfinyl]benzimidazole.

6. A pharmaceutical composition as claimed in claim 23, wherein the compound is 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]benzimidazole.

7. A pharmaceutical composition as claimed in claim 19, wherein the compound is 2-[(2-pyridyl)methylsulfinyl]-benzimidazole.

8. A pharmaceutical composition as claimed in claim 19, wherein the basic inorganic salt of magnesium is magnesium carbonate.

9. A pharmaceutical composition as claimed in claim 19, wherein the basic inorganic salt of magnesium is magnesium hydroxide.

10. A pharmaceutical composition as claimed in claim 19, wherein the basic inorganic salt of magnesium is heavy magnesium carbonate.

11. A pharmaceutical composition as claimed in claim 19, wherein the basic inorganic salt of magnesium is magnesium metasilicate aluminate.

12. A pharmaceutical composition as claimed in claim 19, wherein the basic inorganic salt of magnesium is synthetic hydrotalcite.

13. A pharmaceutical composition as claimed in claim 19, wherein the basic inorganic salt of magnesium is aluminum magnesium hydroxide.

14. A pharmaceutical composition as claimed in claim 19, wherein the basic inorganic salt of magnesium is magnesium silicate.

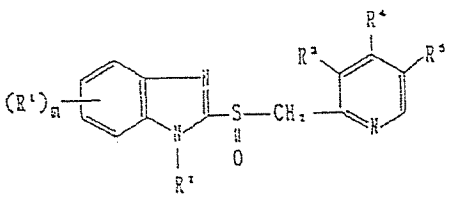
15. A pharmaceutical composition as claimed in claim 19, wherein the basic inorganic salt of calcium is precipitated calcium carbonate.

16. A pharmaceutical composition as claimed in claim 23, wherein the compound is 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulfinyl]benzimidazole and the basic inorganic salt of magnesium is magnesium carbonate.

17. A pharmaceutical composition as claimed in claim 19, wherein the composition is in particle and enteric-coated.

19. A pharmaceutical composition, wherein the composition is made up into tablets or granules and then coated by a coating

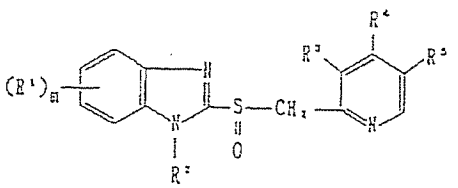
agent, which comprises an effective amount of anti-ulcer compound of the formula:



wherein R^1 is hydrogen, C_{1-7} alkyl, halogen, cyano, carboxy, carbo-C_{1-4}alkoxy, carbo-C_{1-4}alkoxy-C_{1-4}alkyl, carbamoyl, carbamoyl-C_{1-4}alkyl, hydroxy, C_{1-5}alkoxy, hydroxy-C_{1-7}alkyl, trifluoromethyl, C_{1-4}alkanoyl, carbamoyloxy, nitro, C_{1-4}alkanoyloxy, phenyl, phenyloxy, C_{1-6}alkylthio or C_{1-6}alkylsulfinyl, R^2 is hydrogen, C_{1-5}alkyl, C_{1-4}alkanoyl, carbo-C_{1-4}alkoxy, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)-carbamoyl, C_{1-4}alkylcarbonylmethyl, C_{1-4}alkoxycarbonylmethyl or C_{1-4}alkylsulfonyl, R^3 and R^5 are the same or different and each is hydrogen, C_{1-4}alkyl, C_{1-8}alkoxy or C_{1-4}alkoxy-C_{1-4}alkoxy, R^4 is hydrogen, C_{1-4}alkyl, C_{1-8}alkoxy which may optionally be fluorinated or C_{1-4}alkoxy-C_{1-4}alkoxy, and m is an integer of 0 through 4, and at least one of the basic inorganic salts of magnesium and calcium selected from heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite, aluminum magnesium hydroxide, precipitated calcium carbonate and calcium hydroxide; the amount of the basic inorganic salt

relative to parts by weight of the benzimidazole compound being about 0.3-20 parts by weight; the benzimidazole compound being in contact with the basic inorganic salt evenly.

20. A method of producing a stabilized pharmaceutical anti-ulcer composition, wherein the composition is made up into tablets or granules and then coated by a coating agent, which comprises incorporating at least one of the basic inorganic salts of magnesium and calcium selected from heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite, aluminum magnesium hydroxide, precipitated calcium carbonate and calcium hydroxide in a pharmaceutical composition containing an effective amount of an anti-ulcer compound of the formula:



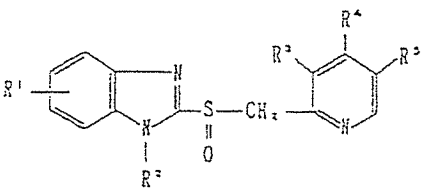
wherein R^1 is hydrogen, C_{1-7} alkyl, halogen, cyano, carboxy, carbo-C_{1-4} alkoxy, carbo-C_{1-4} alkoxy-C_{1-4} alkyl, carbamoyl, carbamoyl-C_{1-4} alkyl, hydroxy, C_{1-5} alkoxy, hydroxy-C_{1-7} alkyl, trifluoromethyl, C_{1-4} alkanoyl, carbamoyloxy, nitro, C_{1-4} alkanoyl-oxy, phenyl, phenyloxy, C_{1-6} alkylthio or C_{1-6} alkylsulfinyl, R^2 is

hydrogen, C_{1-5}alkyl, C_{1-4}alkanoyl, carbo-C_{1-4}alkoxy, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)-carbamoyl, C_{1-4}alkylcarbonylmethyl, C_{1-4}alkoxycarbonylmethyl or C_{1-4}alkylsulfonyl, R^3 and R^5 are the same or different and each is hydrogen, C_{1-4}alkyl, C_{1-8}alkoxy or C_{1-4}alkoxy-C_{1-4}alkoxy, R^4 is hydrogen, C_{1-4}alkyl, C_{1-8}alkoxy which may optionally be fluorinated, or C_{1-4}alkoxy-C_{1-4}alkoxy, and m is an integer of 0 through 4; the amount of the basic inorganic salt relative to part by weight of the benzimidazole compound being about 0.3-20 parts by weight; the benzimidazole compound being in contact with the basic inorganic salt evenly.

21. A pharmaceutical composition as claimed in claim 19, wherein the coating agent is hydroxypropylmethylcellulose, hydroxypropylcellulose, ethyl cellulose, or hydroxymethylcellulose.

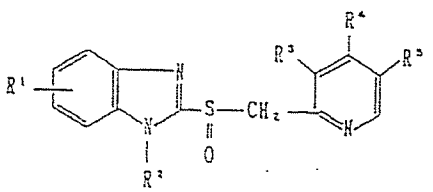
22. A method as claimed in claim 20, wherein the coating agent is hydroxypropylmethylcellulose, hydroxypropylcellulose, ethyl cellulose, or hydroxymethylcellulose.

23. A pharmaceutical composition, wherein the composition is made up into tablets or granules and then coated by a coating agent, which comprises an effective amount of anti-ulcer compound of the formula:



wherein R^1 is hydrogen or methoxy, R^2 is hydrogen, R^3 is methyl, R^4 is methoxy or 2,2,2-trifluoroethoxy, and R^5 is hydrogen or methyl, and at least one of the basic inorganic salts of magnesium and calcium selected from heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite, aluminum magnesium hydroxide, precipitated calcium carbonate and calcium hydroxide; the amount of the basic inorganic salt relative to parts by weight of the benzimidazole compound being about 0.3-20 parts by weight; the benzimidazole compound being in contact with the basic inorganic salt evenly.

24. A method of producing a stabilized pharmaceutical anti-ulcer composition, wherein the composition is made up into tablets or granules and then coated by a coating agent, which comprises incorporating at least one of the basic inorganic salts of magnesium and calcium selected from heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite, aluminum magnesium hydroxide, precipitated calcium carbonate and calcium hydroxide in a pharmaceutical composition containing an effective amount of an anti-ulcer compound of the formula:

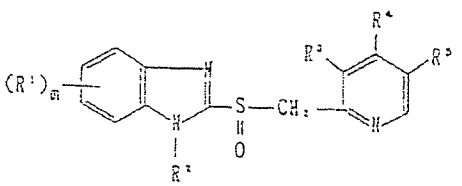


wherein R^1 is hydrogen or methoxy, R^2 is hydrogen, R^3 is methyl, R^4 is methoxy or 2,2,2-trifluoroethoxy, and R^5 is hydrogen or methyl; the amount of the basic inorganic salt relative to part by weight of the benzimidazole compound being about 0.3-20 parts by weight; the benzimidazole compound being in contact with the basic inorganic salt evenly.

25. A method as claimed in claim 24, wherein the compound it 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulfinyl]benzimidazole.

26. A method as claimed in claim 24, wherein the compound is 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]benzimidazole.

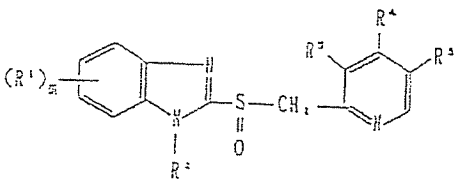
27. A pharmaceutical composition, wherein the composition is made up into tablets or granules and then coated by a coating agent, which comprises an effective amount of anti-ulcer compound of the formula:



wherein R^1 is hydrogen C_{1-7} alkyl, halogen, cyano, carboxy, carbo-C_{1-4} alkoxy, carbo-C_{1-4} alkoxy-C_{1-4} alkyl, carbamoyl, carbamoyl-C_{1-4} alkyl, hydroxy, C_{1-5} alkoxy, hydroxy-C_{1-7} alkyl, trifluoromethyl, C_{1-4} alkanoyl, carbamoyloxy, nitro, C_{1-4} alkanoyl-oxy, phenyl, phenyloxy, C_{1-6} alkylthio or C_{1-6} alkylsulfinyl, R^2 is

hydrogen, C_{1-5}alkyl, C_{1-4}alkanoyl, carbo-C_{1-4}alkoxy, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)-carbamoyl, C_{1-4}alkylcarbonylmethyl, C_{1-4}alkoxycarbonylmethyl or C_{1-4}alkylsulfonyl, R^3 and R^5 are the same or different and each is hydrogen, C_{1-4}alkyl, C_{1-8}alkoxy or C_{1-4}alkoxy-C_{1-4}alkoxy, R^4 is hydrogen, C_{1-4}alkyl, C_{1-8}alkoxy which may optionally be fluorinated, or C_{1-4}alkoxy-C_{1-4}alkoxy, and m is an integer of 0 through 4, and at least one of the basic inorganic salts of magnesium and calcium; the amount of the basic inorganic salt relative to parts by weight of the benzimidazole compound being about 0.3-20 parts by weight; the benzimidazole compound being in contact with the basic inorganic salt evenly.

28. A method of producing a stabilized pharmaceutical anti-ulcer composition, wherein the composition is made up into tablets or granules and then coated by a coating agent, which comprises incorporating at least one of the basic inorganic salts of magnesium and calcium in a pharmaceutical composition containing an effective amount of an anti-ulcer compound of the formula:



wherein R^1 is hydrogen, C_{1-7} alkyl, halogen, cyano, carboxy, carbo-C_{1-4}alkoxy, carbo-C_{1-4}alkoxy-C_{1-4}alkyl, carbamoyl,

carbamoyl-C_{1-4}alkyl, hydroxy, C_{1-5}alkoxy, hydroxy-C_{1-7}alkyl, trifluoromethyl, C_{1-4}alkanoyl, carbamoyloxy, nitro, C_{1-4}alkanoyloxy, phenyl, phenyloxy, C_{1-6}alkylthio or C_{1-6}alkylsulfinyl, R^2 is hydrogen, C_{1-5}alkyl, C_{1-4}alkanoyl, carbo-C_{1-4}alkoxy, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)-carbamoyl, C_{1-4}alkylcarbonylmethyl, C_{1-4}alkoxycarbonylmethyl or C_{1-4}alkylsulfonyl, R^3 and R^5 are the same or different and each is hydrogen, C_{1-4}alkyl, C_{1-8}alkoxy or C_{1-4}alkoxy-C_{1-4}alkoxy, R^4 is hydrogen, C_{1-4}alkyl, C_{1-8}alkoxy which may optionally be fluorinated, or C_{1-4}alkoxy-C_{1-4}alkoxy, and m is an integer of 0 through 4, the amount of the basic inorganic salt relative to parts by weight of the benzimidazole compound being about 0.3-20 parts by weight; the benzimidazole compound being in contact with the basic inorganic salt evenly.



APPENDIX B

Pending Independent Claims Revised in Accordance with the Limitation of this Appeal

19. A pharmaceutical composition, wherein the composition is made up into tablets or granules and then coated by a coating agent, which comprises an effective amount of an anti-ulcer compound selected from the group consisting of 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulfinyl]benzimidazole and 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]benzimidazole, and at least one of the basic inorganic salts of magnesium and calcium selected from heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite, aluminum magnesium hydroxide, precipitated calcium carbonate and calcium hydroxide; the amount of the basic inorganic salt relative to parts by weight of the benzimidazole compound being about 0.3-20 parts by weight; the benzimidazole compound being in contact with the basic inorganic salt evenly.

20. A method of producing a stabilized pharmaceutical anti-ulcer composition, wherein the composition is made up into tablets or granules and then coated by a coating agent, which comprises incorporating at least one of the basic inorganic salts of magnesium and calcium selected from heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate,

magnesium silicate, magnesium aluminate, synthetic hydrotalcite, aluminum magnesium hydroxide, precipitated calcium carbonate and calcium hydroxide in a pharmaceutical composition containing an effective amount of an anti-ulcer compound selected from the group consisting of 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulfinyl]benzimidazole and 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]benzimidazole, the amount of the basic inorganic salt relative to part by weight of the benzimidazole compound being about 0.3-20 parts by weight; the benzimidazole compound being in contact with the basic inorganic salt evenly.

23. A pharmaceutical composition, wherein the composition is made up into tablets or granules and then coated by a coating agent, which comprises an effective amount of anti-ulcer compound selected from the group consisting of 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulfinyl]benzimidazole and 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]benzimidazole, and at least one of the basic inorganic salts of magnesium and calcium selected from heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite, aluminum magnesium hydroxide, precipitated calcium carbonate and calcium hydroxide; the amount of the basic inorganic salt relative to parts by weight of the benzimidazole compound being about 0.3-20 parts by weight; the

benzimidazole compound being in contact with the basic inorganic salt evenly.

24. A method of producing a stabilized pharmaceutical anti-ulcer composition, wherein the composition is made up into tablets or granules and then coated by a coating agent, which comprises incorporating at least one of the basic inorganic salts of magnesium and calcium selected from heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite, aluminum magnesium hydroxide, precipitated calcium carbonate and calcium hydroxide in a pharmaceutical composition containing an effective amount of an anti-ulcer compound selected from the group consisting of 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulfinyl]benzimidazole and 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]benzimidazole, the amount of the basic inorganic salt relative to part by weight of the benzimidazole compound being about 0.3-20 parts by weight; the benzimidazole compound being in contact with the basic inorganic salt evenly.

27. A pharmaceutical composition, wherein the composition is made up into tablets or granules and then coated by a coating agent, which comprises an effective amount of anti-ulcer compound selected from the group consisting of 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulfinyl]benzimidazole and 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-

pyridyl)methylsulfinyl]benzimidazole, and at least one of the basic inorganic salts of magnesium and calcium; the amount of the basic inorganic salt relative to parts by weight of the benzimidazole compound being about 0.3-20 parts by weight; the benzimidazole compound being in contact with the basic inorganic salt evenly.

28. A method of producing a stabilized pharmaceutical anti-ulcer composition, wherein the composition is made up into tablets or granules and then coated by a coating agent, which comprises incorporating at least one of the basic inorganic salts of magnesium and calcium in a pharmaceutical composition containing an effective amount of an anti-ulcer compound selected from the group consisting of 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulfinyl]benzimidazole and 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]benzimidazole, the amount of the basic inorganic salt relative to parts by weight of the benzimidazole compound being about 0.3-20 parts by weight; the benzimidazole compound being in contact with the basic inorganic salt evenly.

EXHIBIT 13

MAIL ROOM SEP 28 1990 PAT. & TRADEMARK OFF

#41
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10/26/90

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Tadashi MAKINO et al.

Serial No. 07/014,303 Examiner: WADDELL

Filed: February 13, 1987 Group Art Unit: 125

For: STABILIZED PHARMACEUTICAL COMPOSITION AND ITS PRODUCTION

REPLY BRIEF TO THIRD SUPPLEMENTAL EXAMINER'S ANSWER

90 OCT 15 PM 3:41

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

This Reply Brief is directed to the new ground of rejection and new points of argument set forth in the outstanding Official Office Action dated August 10, 1990, and styled as an "Examiner's Answer" and "Third Supplemental Examiner's Answer". The request for an oral hearing is reconfirmed, as the $120 fee was paid on March 16, 1990.

DROPPING NOHARA '333

In essence, the Third Supplemental Examiner's Answer drops one reference because it has a bad date and relies upon an earlier reference with a good date. Before the Third Supplemental Examiner's Answer, key reliance was placed in all of the Examiner's preceding actions on matter unique to a Nohara reference having a bad date as to 35 USC §§ 102(e), 103. This reference is now explicitly dropped as to Example 4, the matter that was specifically relied upon in the previous pleadings before this Board. This is admitted in the Third Supplemental Examiner's Answer, page 2, ¶ I):

> Regarding the absence of any "prior art" status under 35 USC 102/103 for one of the references, viz., Nohara 4,689,333, note that Example 4 of the Nohara et al 4,689,333 is no longer relied upon. * * *

NEW GROUND OF REJECTION ON NOHARA '098

Instead of relying upon the Nohara '333 reference, in essence the Examiner now relies on the parent Nohara '098 patent:

> What is relied upon in the reference is the disclosure that is supported in the earlier filed application Serial No. 760,568, filed July 29, 1985, now U.S. Patent No. 4,628,098 (referred to by applicants in Paper No. 7). Such disclosure carries an effective date which is before applicants' effective filing date. This material is prior art under 35 USC 102a/103. * * *

NOHARA '098 DOES NOT LEAD TO APPLICANT'S CONTRIBUTION

As pointed out in the previous pleadings, there is a vital, missing link between the prior art and the claimed contribution that Nohara '333 had previously been relied upon to plug, i.e. the specific disclosure in Nohara '333 Example 4 of a composition containing a benzimidazole active ingredient and magnesium carbonate. The deficiencies of Nohara '098 (i.e. the disclosure of Nohara '333 effective as prior art against the present invention) have been discussed at pages 2-3 of the May 21, 1990 Second Reply Brief (Paper No. 35) and will only be referred to by reference.

On the one hand, the Examiner in his Third Supplemental Examiner's Answer states that:

> * * * The earlier Nohara et al ['098] reference clearly supports the two (2) benzimidazole species of the remaining claims and the inclusion thereof in tablets or granules containing carriers, excipients and/or diluents (compare the disclosure in column 7, lines 3-13 with that of the earlier patent, column 6, lines 53-60). There should be no issue that (1) the compounds and antiulcer activity for the compounds carry the earlier date. See the Abstract of Nohara et al of record and that of the earlier patent. The species are disclosed in column 6 of Nohara et al of record and column 6 of the earlier patent, under "Experimental Results". The remarks regarding basic inorganic salts not being included among the list of excipients, etc., do not obviate the rejection since such excipients are well-known in the art. Moreover, the "Handbook" teaches the inorganic salts to be old antacids, hence, the combination of the claims is obvious for reason set forth in In re Kerkhoven, cited in the Supplemental Examiner's Answer of April 30, 1990. The remarks regarding a "missing link" are not persuasive since impetus to prepare the combination for treating ulcers lies in the individual use of the ingredients for treating ulcers.

But, the question is not whether the salts are known excipients, but rather whether it would have been obvious to mix the salt with the active ingredient so as to provide even contact with the active ingredient, as required by the present claims. Nothing in Nohara '098 suggests any reason for using the presently claimed salts with the active ingredient, much less this claimed feature of even contact.

KERKHOVEN DOES NOT PERMIT HINDSIGHT

The Examiner attempts to excuse the hindsight that permeates the Third Supplemental Examiner's Answer on the basis of:

> II) The [sic-comments] regarding the Examiner's Answer on Remand relying on hindsight to interpret the general disclosure are not well taken and is [sic-are] deemed merely a traveral [sic-traversal] to be resolved

> by the Board. Although a reference can be cited to show that such inorganic salts are excipients in the pharmaceutical art, the same is not deemed necessary since the same is well-known. Moreover, note the rejection as [sic-is] supported by the Kerkhoven decision.
>
> III) With respect to the Rainer reference not disclosing or suggesting the mixing of antacids with the picoline derivatives therein see column 40, lines 27-28 of that reference. As indicated in In re Kerkhoven[, 626 F.2d 846, 205 USPQ 1069 (CCPA 1980)], and taught in the mentioned section of the reference, the combination is clearly obvious. The remarks also are deemed a traversal to be decided by the Board.
>
> IV) The remarks regarding the stabilizers are not convincing since stabilizers are expected to possess their old properties in the absence of evidence to the contrary. Again note In re Kerkhoven, cited supra and the fact that obviousness for one reason, renders the combination obvious for all.

The Examiner's reliance on this one opinion is out of context, wrong and contrary to the body of case law both before and after that opinion. The affirmance in Kerkhoven was based simply on the failure of the applicant to provide comparative data adequately reflecting the scope of the prior art.

The Examiner's attempt to fashion a blanket rule justifying combinations of references is clearly inapt. Seven years after Kerkhoven, the Court reached a contradictory result in In re Geiger, 825 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987) (Archer, J.). The Geiger majority opinion reversed a rejection on the basis that there had been no motivation to make a combination, and hence there was no prima facie obviousness. In a "concurring" opinion (a dissent as to the prima facie case of obviousness) one finds the sole citation of Kerkhoven in any published court opinion in the ten years since that case was decided. Only in this concurring opinion is there any reliance on Kerkhoven, 626 F.2d at 850, 206

USPQ at 1072, cited as authority Geiger (Newman, J., concurring), 815 F.2d at 689, for what is essentially a dissent. Phrased differently, there has not been one single court opinion available on Westlaw that both relies upon Kerkhoven and reaches a result consistent with that case.

As pointed out in Geiger, 815 F.2d at 688 (Archer, J.):

> Appellant argues that the PTO's position represented hindsight reconstruction or, at best, established that it would have been "obvious to try" various combinations of known scale and corrosion prevention agents, including the combination recited in the appealed claims.
>
> We agree with appellant that the PTO has failed to establish a prima facie case of obviousness. Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination. ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed.Cir.1984). We are convinced that the latter are not present here.
>
> Ii does not suggest use of SSMA as its claimed polymeric component and does not require the presence of an organo-phosphorus acid compound or of a zinc compound. Ii notes that it is difficult to maintain a predetermined concentration of polyvalent metal ions, such as the zinc (II) ion, in alkaline cooling water, but states that its claimed polymeric component prevents the "polyvalent metals from becoming insoluble compounds and precipitating...." Although Snyder '733 discloses use of SSMA, it is for the purpose of showing that it, or one of three other specifically recited copolymers, may be used in combination with yet another polymeric component, an acrylic acid/lower alkyl/hydroxy acrylate copolymer, to prevent scale formation. With respect to claims 47 and 49, Hwa does disclose the specifically-recited organo-phosphorus acid compound. It provides, however, no suggestion to add a zinc compound to its disclosed

> combination of SSMA and organo-phosphorus acid compounds, or to use SSMA in combination with an organo-phosphorus acid compound in the treatment of a cooling water system, where the characteristics may significantly differ from those in Hwa's boiler water system. Hwa also provides no suggestion that SSMA could prevent precipitation of the zinc (II) ion in alkaline cooling water in the manner ascribed to the polymeric component of Ii.
>
> At best, in view of these disclosures, one skilled in the art might find it obvious to try various combinations of these known scale and corrosion prevention agents. However, this is not the standard of 35 U.S.C. § 103. In re Goodwin, 576 F.2d 375, 377, 198 USPQ 1, 3 (CCPA 1978); In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977); In re Tomlinson, 363 F.2d 928, 150 USPQ 623 (CCPA 1966).

The Geiger majority view is supported by other members of the court. For example, in In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (Rich, J.), quoted in In re Eli Lilly & Co., 902 F.2d 948, 945, 14 USPQ2d 1741 (Fed. Cir. 1990) (Newman, J.); and Merck & Co., Inc. v. Biocraft Laboratories, Inc., 874 F.2d 804, 807 10 USPQ2d 1843 (Fed. Cir. 1989), it is stated that:

> Appellants * * * argue that the rejection amounts to the application of a standard of "obvious to try" to the field of molecular biology, a standard which this court and its predecessors have repeatedly rejected as improper grounds for a § 103 rejection. E.g., In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988); In re Geiger, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987); In re Merck & Co., Inc., 800 F.2d 1091, 1097, 231 USPQ 375, 379 (Fed. Cir. 1986); In re Antonie, 559 F.2d 618, 620, 195 USPQ 6, 8 (CCPA 1977).

* * *

> The admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. E.g., In re Geiger, 815 F.2d at 688, 2 USPQ2d at 1278; Novo Industri A/S v. Travenol Laboratories, Inc., 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir.1982); In re Yates, 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); In re Antonie, 559 F.2d at 621, 195 USPQ at 8-9. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1986), cert. denied, __ U.S. __ , 107 S.Ct. 1606, 94 L.Ed.2d 792 (1987); In re Tomlinson, 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966). * * *

The Examiner's attempted justification for the rejection is not only legally incorrect, as discussed above, but also factually incorrect. Column 40, lines 27-28 of Rainer merely indicate that antacids can be administered with the active ingredient; no mention is made of mixing at all, much less the establishment of even contact with the active ingredient. Since antacids must be released in the stomach to neutralize stomach acid, mixing to establish even contact is not suggested. With regard to the disclosure of stablilizing properties in Ueno and the Japanese reference, the Examiner still has failed to provide any evidence to support his contention that a stabilizer for one compound would be expected to be useful for different compounds. This is particularly true in view of the differences between the present

benzimidazoles and the isocarbostyril derivatives of the references.

In view of the above, reversal is courteously requested.

Respectfully submitted,

Douglas P. Mueller
Reg. No. 30,300

WEGNER & BRETSCHNEIDER
P.O. Box 18218
Washington, D.C. 20036-8218
(202) 887-0400

Atty. Docket: P-8700-19861P
Date: September 28, 1990
DPM:tm/1.6

EXHIBIT 14

REDACTED

EXHIBIT 15

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of HAND-CARRIED

Tadashi MAKINO et al.

Serial No. 014,303 Group Art Unit: 125

Filed: February 13, 1987 Examiner: Waddell

For: STABILIZED PHARMACEUTICAL COMPOSITION AND ITS PRODUCTION

SUPPLEMENTAL AMENDMENT SUBMITTED UNDER 37 CFR 1.115

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

This is a supplemental to the principal amendment of December 6, 1988.

IN THE CLAIMS

Please amend the claims as follows:

Claim 2, line 1, change "1" to --23--.

Claim 3, line 22, change "1" to --19--.

Claim 4, line 28, change "1" to --19--.

Claim 5, line 31, change "1" to --19--.

Claim 6, line 34, change "1" to --23--.

Claim 7, line 1, change "1" to --19--.

Claim 8, line 4, change "1" to --19--.

Claim 9, line 7, change "1" to --19--.

Claim 10, line 10, change "1" to --19--.

Claim 11, line 13, change "1" to --19--.

Claim 12, line 16, change "1" to --19--.

Claim 13, line 19, change "1" to --19--.

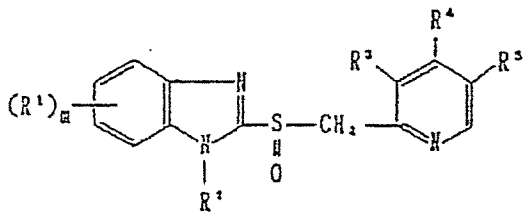
Claim 14, line 22, change "1" to --19--.

Claim 15, line 25, change "1" to --19--.

Claim 16, line 28, change "1" to --23--.

Claim 17, line 33, change "1" to --19--.

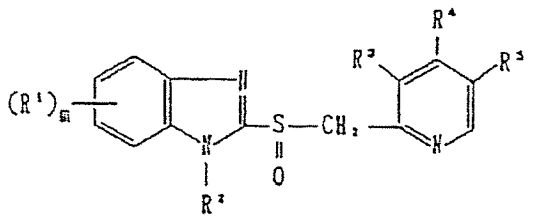
19. (Amended) A pharmaceutical composition, wherein the composition is made up into tablets or granules and then coated by a coating agent, which comprises an effective amount of anti-ulcer compound of the formula:



wherein R^1 is hydrogen, C_{1-7} alkyl, halogen, cyano, carboxy, carbo-C_{1-4} alkoxy, carbo-C_{1-4} alkoxy-C_{1-4} alkyl, carbamoyl, carbamoyl-C_{1-4} alkyl, hydroxy, C_{1-5} alkoxy, hydroxy-C_{1-7} alkyl, trifluoromethyl, C_{1-4} alkanoyl, carbamoyloxy, nitro, C_{1-4} alkanoyl-oxy, phenyl, phenyloxy, C_{1-6} alkylthio or C_{1-6} alkylsulfinyl, R^2 is hydrogen, C_{1-5} alkyl, C_{1-4} alkanoyl, carbo-C_{1-4} alkoxy, carbamoyl, C_{1-4} alkylcarbamoyl, di(C_{1-4} alkyl)-carbamoyl, C_{1-4} alkylcarbonylmethyl, C_{1-4} alkoxycarbonylmethyl or C_{1-4} alkylsulfonyl, R^3 and R^5 are the same or different and each is hydrogen, C_{1-4} alkyl, C_{1-8} alkoxy or C_{1-4} alkoxy-C_{1-4} alkoxy, R^4

is hydrogen, C_{1-4}alkyl, C_{1-8}alkoxy which may optionally be fluorinated, or C_{1-4}alkoxy-C_{1-4}alkoxy, and m is an integer of 0 through 4, and at least one of the basic inorganic salts of magnesium and calcium selected from heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite, aluminum magnesium hydroxide, precipitated calcium carbonate and calcium hydroxide; the amount of the basic inorganic salt relative to parts by weight of the benzimidazole compound being about 0.3-20 parts by weight; the benzimidazole compound being in contact with the basic inorganic salt evenly.

20. (Amended) A method of producing a stabilized pharmaceutical anti-ulcer composition, wherein the composition is made up into tablets or granules and then coated by a coating agent, which comprises incorporating at least one of the basic inorganic salts of magnesium and calcium selected from heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite, aluminum magnesium hydroxide, precipitated calcium carbonate and calcium hydroxide in a pharmaceutical composition containing an effective amount of an anti-ulcer compound of the formula:



wherein R^1 is hydrogen, C_{1-7} alkyl, halogen, cyano, carboxy, carbo-C_{1-4}alkoxy, carbo-C_{1-4}alkoxy-C_{1-4}alkyl, carbamoyl, carbamoyl-C_{1-4}alkyl, hydroxy, C_{1-5}alkoxy, hydroxy-C_{1-7}alkyl, trifluoromethyl, C_{1-4}alkanoyl, carbamoyloxy, nitro, C_{1-4}alkanoyl-oxy, phenyl, phenyloxy, C_{1-6}alkylthio or C_{1-6}alkylsulfinyl, R^2 is hydrogen, C_{1-5}alkyl, C_{1-4}alkanoyl, carbo-C_{1-4} alkoxy, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)-carbamoyl, C_{1-4}alkylcarbonylmethyl, C_{1-4}alkoxycarbonylmethyl or C_{1-4}alkylsulfonyl, R^3 and R^5 are the same or different and each is hydrogen, C_{1-4}alkyl, C_{1-8}alkoxy or C_{1-4}alkoxy-C_{1-4}alkoxy, R^4 is hydrogen, C_{1-4}alkyl, C_{1-8}alkoxy which may optionally be fluorinated, or C_{1-4}alkoxy-C_{1-4}alkoxy, and m is an integer of 0 through 4; the amount of the basic inorganic salt relative to part by weight of the benzimidazole compound being about 0.3-20 parts by weight; the benzimidazole compound being in contact with the basic inorganic salt evenly.

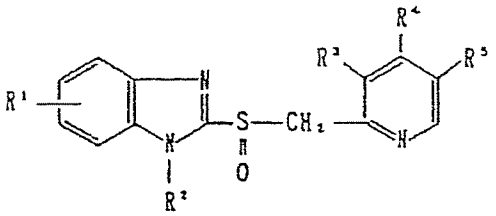
Please add the new claims 21-26 as follows:

--21. A pharmaceutical composition as claimed in claim 19, wherein the coating agent is hydroxypropylmethylcellulose,

hydroxypropylcellulose, ethyl cellulose, or hydroxymethylcellulose.

22. A method as claimed in claim 20, wherein the coating agent is hydroxypropylmethylcellulose, hydroxypropylcellulose, ethyl cellulose, or hydroxymethylcellulose.

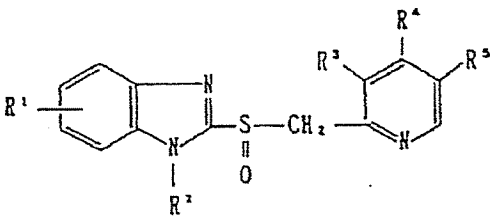
23. A pharmaceutical composition, wherein the composition is made up into tablets or granules and then coated by a coating agent, which comprises an effective amount of anti-ulcer compound of the formula:



wherein R^1 is hydrogen or methoxy, R^2 is hydrogen, R^3 is methyl, R^4 is methoxy or 2,2,2-trifluoroethoxy, and R^5 is hydrogen or methyl, and at least one of the basic inorganic salts of magnesium and calcium selected from heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite, aluminum magnesium hydroxide, precipitated calcium carbonate and calcium hydroxide; the amount of the basic inorganic salt relative to parts by weight of the benzimidazole compound being

about 0.3-20 parts by weight; the benzimidazole compound being in contact with the basic inorganic salt evenly.

24. A method of producing a stabilized pharmaceutical anti-ulcer composition, wherein the composition is made up into tablets or granules and then coated by a coating agent, which comprises incorporating at least one of the basic inorganic salts of magnesium and calcium selected from heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite, aluminum magnesium hydroxide, precipitated calcium carbonate and calcium hydroxide in a pharmaceutical composition containing an effective amount of an anti-ulcer compound of the formula:



wherein R^1 is hydrogen or methoxy, R^2 is hydrogen, R^3 is methyl, R^4 is methoxy or 2,2,2-trifluoroethoxy, and R^5 is hydrogen or methyl; the amount of the basic inorganic salt relative to part by weight of the benzimidazole compound being about 0.3-20 parts by weight; the benzimidazole compound being in contact with the basic inorganic salt evenly.

25. A method as claimed in claim 24, wherein the compound it 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulfinyl] benzimidazole.

26. A method as claimed in claim 24, wherein the compound is 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]benzimidazole.--

REMARKS

Reconsideration of this application is respectfully requested in view of the above supplemental amendment and the following remarks.

The claims are claims 19-26.

Basis for amending claim 19 comes from Applicants' specification on page 20, lines 14-24. The change to claim 20 is taken from page 20, lines 14-24. Concerning claim 21, support is shown at page 20, lines 18 and 19. The addition of claim 22 is supported at page 20, lines 18 and 19. Applicants' original claims 1, 2, and 6 serve as the foundation for new claim 23. Support for Applicants' claim 24 comes from the original claim language of claims 2, 6, and 18. The recitation of claim 25 corresponds to Applicants' original claim 2. Additionally, support for claim 26 is given in Applicants' original claim 6.

Applicants' invention is concerned with an anti-ulcer compound which is made into tablets or granules and then coated by a coating agent. It is submitted that none of the references cited against the claims suggest an anti-ulcer compound which can be made into tablet form and then coated by a coating agent.

Accordingly, withdrawal of the rejections of the claims is respectfully requested. A favorable Action in the form of a Notice of Allowance is solicited.

Respectfully submitted,

WEGNER & BRETSCHNEIDER

Harold C. Wegner
Reg. No. 25,258

WEGNER & BRETSCHNEIDER
P.O. Box 18218
Washington, D.C. 20036-8218
(202) 887-0400

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