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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#10/A  
3/14/97  
Amend

In re Application of: Lindberg et al.  
 Serial No.: 08/376,512  
 Filed: January 23, 1995  
 For: NEW COMPOUNDS  
 Examiner: J. Fan  
 Group Art Unit: 1203

I hereby certify that this paper is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner of Patents Washington, D.C. 20231

Marg-Peter G. Hoffmann 37,382  
 Name Reg. No.  
 Signature Date 2/12/97

Assistant Commissioner of Patents  
Washington, D.C. 20231

AMENDMENT AND RESPONSE

Sir:

This communication is submitted in response to the Office Action dated August 12, 1996.

Please consider the amendment and remarks set forth below.

A

IN THE CLAIMS:

Please cancel claims 1-34 without prejudice.

Please add the following new claims:

- 35.<sup>1</sup> A pharmaceutical formulation for oral administration comprising a pure solid state alkaline salt of the (-)-enantiomer of 5-methoxy-2[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and a pharmaceutically acceptable carrier. --
- 36.<sup>2</sup> The pharmaceutical formulation according to claim 35 wherein the solid state salt is optically pure. --
- 37.<sup>3</sup> The pharmaceutical formulation according to claim 35, wherein the alkaline salt is a Na<sup>+</sup>, Mg<sup>2+</sup>, Li<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup> or N<sup>+</sup>(R)<sub>4</sub> salt. --
- 38.<sup>4</sup> The pharmaceutical formulation according to claim 35, wherein the solid state salt is in substantially crystalline form. --
- 39.<sup>5</sup> The pharmaceutical formulation according to claim 35 wherein the alkaline salt is a sodium or magnesium salt. --
- 40.<sup>6</sup> A method of inhibiting gastric acid secretion comprising the oral administration of a pharmaceutical formulation comprising a therapeutically effective amount of a pure solid state alkaline salt of the (-)-enantiomer of 5-methoxy-2[[4-methoxy-3,5-dimethyl-2-

pyridinyl)methyl]sulfinyl]-1H-benzimidazole and a pharmaceutically acceptable carrier. --

-7 41. A method for the treatment of gastrointestinal inflammatory disease comprising the oral administration to a mammal including man in need of such treatment of a pharmaceutical formulation comprising a therapeutically effective amount of a pure solid state alkaline salt of the (-)-enantiomer of 5-methoxy-2[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and a pharmaceutically acceptable carrier. --

B -- 42.<sup>6</sup> A method for the treatment of gastrointestinal inflammatory diseases comprising the oral administration to a mammal including man in need of such treatment<sup>a</sup> composition comprising an effective amount of the pure (-)-enantiomer of 5-methoxy-2[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and a pharmaceutically acceptable carrier. --

A1  
C. 43.<sup>9</sup> A method of inhibiting gastric acid secretion comprising the oral administration of a pharmaceutical composition comprising an effective amount of the pure (-)-enantiomer of 5-methoxy-2[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and a pharmaceutically acceptable carrier. --

--44.<sup>10</sup> The method of claim 40 or 41 wherein the alkaline salt is a Na<sup>+</sup>, Mg<sup>2+</sup>, Li<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup> or N<sup>+</sup>(R)<sub>4</sub> salt.

REMARKS

Applicants acknowledge with gratitude the opportunity of the interview with the Examiner on January 21, 1997.

Claims 1-11, 19, 21-22, 24-31 and 34 are pending. Claims 1-34 have been cancelled without prejudice. Applicants reserve the right to prosecute the subject matter of these claims in a continuation application. Cancelled claims 12-18, 20, 23, 32 and 33 are drawn to nonelected subject matter pursuant to the previous restriction requirement.

Claims 35-39 directed to pharmaceutical compositions for oral administration have been added. The new claims reflect the patentable distinctions discussed during the interview and are drawn to a pharmaceutical formulation comprising a pure solid state alkaline salt of the (-)-enantiomer of omeprazole and a pharmaceutical carrier. Claims 40-44 have been added to further define the present invention in terms of methods of treatment using compositions containing the (-)-enantiomer of omeprazole. No new matter has been introduced by the amendment adding new claims.

The Declaration of Dr. Tommy Andersson is submitted herewith and sets out in Declaration form the unexpected pharmacokinetic properties of the preferred

(-)-enantiomer of omeprazole disclosed in the Specification on page 2, lines 10-15 and p. 16, and summarized at the interview by co-inventor Dr. Per Lindberg. The Andersson Declaration discusses clinical studies which involved both the monovalent sodium salt and the divalent magnesium salt of the (-)-enantiomer of omeprazole, thus supporting the full scope of the genus of alkaline salts disclosed in the application and as claimed herein, as suggested by the Examiner at the interview.

The subject matter of the new claims is fully supported by the Specification as discussed at the interview, and the patentability of the claimed subject matter is further supported by the evidence of unexpected properties set forth in the Andersson Declaration.

As shown in the Andersson Declaration the (-)-omeprazole enantiomer, as administered in the form of its alkaline salts, unexpectedly exhibits a different and more advantageous pharmacokinetic profile than the racemic mixture or the (+)-enantiomer of omeprazole. This is contrary to the prior art teaching on the pharmacodynamic effect which was previously demonstrated in gastric glands to be the same for the two enantiomers as would be expected since the active form has a non-chiral structure (see Andersson Declaration, p. 3).

Although a safe and effective drug with no dose related side effects, omeprazole racemate has been found to

exhibit polymorphic metabolism. The slow metabolizers of the drug are a minority (3% of Caucasians and 15% of Asians) as compared to the majority of the "normal" rapid metabolizers (97% of Caucasians and 85% of Asians). The slow metabolizers lack the activity of the main omeprazole-metabolizing enzyme. This results in a certain degree of interindividual variation in plasma levels of omeprazole within the total population during treatment with the drug. (See Andersson Declaration, p. 5). The objective of the clinical pharmacologist is to achieve as low a degree of interindividual variation in the treated population as possible.

The Declaration by Dr. Andersson discusses the results of two clinical studies, Study A and Study B. Study A of the Declaration compares the pharmacokinetic profile with respect to interindividual variation of the sodium salt of (-)-omeprazole, the sodium salt of (+)-omeprazole and the sodium salt of racemic omeprazole in slow and rapid metabolizers. Study B compares the effect of pharmaceutical formulations of the magnesium salt of the (-)-enantiomer of omeprazole on gastric acid secretion with that of a formulation of the current marketed drug, the omeprazole racemate. The results of both studies described in the Declaration demonstrate the advantageous *in vivo* effects of the alkaline salts, e.g., Na<sup>+</sup> or Mg<sup>+2</sup>, of (-)-omeprazole.

Since the inhibition of gastric acid secretion is related to the area under the plasma concentration versus time curve (AUC), the pharmacokinetic profile of the different pure enantiomers of omeprazole and the racemic omeprazole is compared by reference to AUC. It is desirable to obtain and administer a pharmaceutical formulation which has a smaller interindividual variation in plasma levels as measured by the comparison of AUC in the slow and rapid metabolizers and also within the group of rapid metabolizers. Moreover, higher average plasma levels as measured by AUC would result in greater dose efficiency in patients and might provide additional therapeutic advantages.

As set forth in Study A of the Andersson Declaration, using the sodium salts of the enantiomers and the racemate, the difference in AUC between the slow and rapid metabolizers, after adjusting for different dose levels, was approximately 30-fold for (+)-omeprazole enantiomer, almost 10-fold for racemic omeprazole, but only 3-fold for (-)-omeprazole enantiomer. Study A, as well as Study B, further established that the average AUC in the majority of the population (rapid metabolizers) is two-fold higher for the (-)-enantiomer of omeprazole than for omeprazole racemate following the administration of the same dose.

Thus, the clinical results presented in the Andersson Declaration demonstrate that the alkaline salts of the (-)-enantiomer of omeprazole exhibit pharmacokinetic advantages compared to the racemic form of omeprazole or alkaline salt of racemic omeprazole or the alkaline salts of (+)-omeprazole by virtue of higher dose efficiency and significantly less interindividual variation between patients in the treatment of gastric acid-related diseases.

In addition as can be recognized from the data of Study B in the Declaration of Andersson, the (-)-omeprazole affords a longer time, 53% of the 24 hour period post dose, with gastric pH above 4 in reflux patients compared to 44% for racemic omeprazole (i.e., about two additional hours) which means a more pronounced acid inhibitory effect.

Consequently, the advantageous pharmacokinetic properties of the pure (-)-enantiomer of omeprazole allow for the preparation of novel pharmaceutical formulations which can be administered to patients in need of the treatment with a resulting lower interindividual variation while achieving higher average plasma levels of the drug at the same dosage level as that in the prior art. This was not known at the time the presently claimed invention was made and is not reasonably predicted or even remotely suggested by the references cited in the Office Action. The outstanding rejections of the previously pending claims

as discussed below are therefore overcome by the amendments and the supporting Declaration evidence.

The rejections of Claims 7-11 and 34 under 35 U.S.C. § 112 are rendered moot by cancellation of these claims.

Claims 1-6, 19, 21-22, 24-31 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kohl et al. DE 4035455 ("DE '455") (English translation enclosed) and Erlandsson et al. J. Chromatography (1990) 532:305 ("Erlandsson").

As discussed at the interview, the pharmaceutical formulations for oral administration comprising pure solid state alkaline salts of the (-)-enantiomer of omeprazole to which the new claims are directed, are patentable over the prior art and the cited references. In the first instance, the cited DE '455 does not exemplify the (-)-enantiomer, does not disclose the pure solid state salt form of the (-)-enantiomer of omeprazole and most importantly, does not even contemplate that the (-)-enantiomer of omeprazole could have any properties which differ from those of the (+)-enantiomer or the racemate.

The pure solid state salt form of the (-)-enantiomer of omeprazole of this invention provides advantages of purity, long term chemical stability, and chiral stability. This results in the preparation of more effective pharmaceutical formulations and provides new

methods of treatment with these novel formulations which result in improved therapeutic profiles. None of these properties or advantages are disclosed in the cited prior art.

Most significantly the DE '455 reference neither discloses nor even suggests the unexpected preferred pharmacokinetic profile with respect to interindividual variation and high dose-efficiency of the (-)-enantiomer of omeprazole as set forth in the Specification at p.1, lines 19-21, p. 2, line 10-15, and Example 6, and the Andersson Declaration. The unexpected pharmacokinetic properties of the (-)-enantiomers of omeprazole coupled with the ability to prepare the (-)-enantiomer in a pure solid state form allow for the present invention of a more efficacious pharmaceutical formulation for gastrointestinal disorders.

The cited Erlandsson reference, instead of anticipating the invention as presently claimed, actually supports its patentability. The cited Erlandsson reference, which concerns *in vitro* studies of the omeprazole enantiomers, suggests that there is no significant difference in effect between the single enantiomers of omeprazole. Erlandsson teaches that the omeprazole racemate is equal in potency to the (-)-enantiomer, (Erlandsson, p. 318). The present application and the Andersson Declaration prove otherwise. Applicants also direct the Examiner's attention to the disclosure of

Cairns et al. J. of Chromatography 666 (1995) 323-328 discussed during the interview. As pointed out at the interview the Cairns et al. authors at p. 327 concluded that the concentrations of (+)-omeprazole and (-)-omeprazole were essentially equal in plasma samples assayed. The Cairns et al. publication which was published after the filing of the present application further demonstrates the unexpected results and advantages of administering the pure alkaline salts of the (-)-enantiomer of omeprazole of the present invention.

Claims 1-6, 19, 21-22 and 24-31 are rejected under 35 U.S.C. § 103 as obvious over EP 124,495 or CA 117:90292 which allegedly encompass the claimed enantiomers. The individual isomers, in the opinion of the Examiner, are obvious variants over the corresponding racemate because of their presence in the racemate.

Applicants respectfully disagree. As discussed on page 5, lines 19-27 and Examples 12 and 13 of the Specification, prior to the present invention the neutral (-)-enantiomer of omeprazole had only been obtained as syrups or oils. On the contrary, neither of the cited references discloses or even suggests the presently claimed pharmaceutical formulation comprising the salts of the single (-)-enantiomer of omeprazole. The EP reference discloses racemic forms of benzimidazoles but is silent on how to prepare single enantiomers or on any of their

distinct properties. The CA reference discloses a method for preparing various alkali metal salts of omeprazole racemate but not the separate enantiomers, much less pure solid state salts of single enantiomers of omeprazole.

In further support of the patentability of the pending claims, the Examiner is requested to note the recently published results of *in vivo* experiments with lansoprazole and pantoprazole, benzimidazole proton pump inhibitor analogues of omeprazole.

It has been reported that analysis of the enantiomers following oral administration of racemic lansoprazole in rats and dogs found a higher AUC of the (+)-enantiomer than that of the (-)-enantiomer of lansoprazole (Miwa, et al. Jpn. Pharmacol. Ther. (1990) 18 173-175, copy enclosed). More recently this has been supported by the publication of studies in humans which confirm that the (+)-enantiomer of lansoprazole has a higher AUC. (Katsuki, et al. Pharmaceutical Research, 13, (1996) 611-615, see p. 614, copy enclosed). In contrast, analyses of the two separate enantiomers of pantoprazole after a single peroral administration of 80 mg of racemic pantoprazole to a healthy volunteer found only a very small difference in the serum concentration-time profiles of the single enantiomers where the (-)-enantiomer was slightly higher than the (+)-enantiomer (Tanaka, et al. Anal Chem. (1996) 1513-1516, see p. 1516, copy enclosed). Thus, the

determination of which enantiomer of any benzimidazole type compound analogous to omeprazole has advantageous properties, if at all, is entirely unpredictable.

It is requested that the rejections under 35 U.S.C. § 102 and § 103 are improper and should be withdrawn.

Claims 1-11, 24-31 and 34 are provisionally rejected under 35 U.S.C. § 101 as claiming the same claims as copending Serial No. 08/256,174 ("174"). The cancellation of these claims renders this rejection moot.

A form PTO-1449 listing the publications cited in this response is attached. The Declaration (37 C.F.R. § 1.132) has been signed by the Declarant, Tommy Andersson, on February 12, 1997; a facsimile copy of the pertinent page is enclosed.

In view of the foregoing amendment and remarks as well as submission of the Rule 132 Declaration, Applicants believe the application to be in condition for allowance and therefore solicit early favorable action.

The Commissioner is authorized to charge any fee  
which may be due in connection with this response to  
Deposit Account No. 23-1703.

Respectfully submitted,



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Enclosure