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United States Patent [19]

Lindberg et al.

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[54] **METHOD FOR THE TREATMENT OF GASTRIC ACID-RELATED DISEASES AND PRODUCTION OF MEDICATION USING (-) ENANTIOMER OF OMEPRAZOLE**

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[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,714,504.

[21] Appl. No.: **833,962**

[22] Filed: **Apr. 11, 1997**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 376,512, Jan. 23, 1995, Pat. No. 5,714,504, which is a continuation-in-part of Ser. No. 256,174, Jun. 28, 1994, Pat. No. 5,693,818.

[30] **Foreign Application Priority Data**

May 28, 1993 [SE] Sweden 9301830
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[51] **Int. Cl.**[6] **A61K 31/44**

[52] **U.S. Cl.** **514/338**; 514/819; 514/927

[58] **Field of Search** 514/338, 819, 514/927

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,714,504 2/1998 Linberg et al. 514/338

Primary Examiner—Kimberly Jordan
Attorney, Agent, or Firm—White & Case LLP

[57] **ABSTRACT**

A method for treatment of gastric acid related diseases by inhibition of gastric acid secretion comprising administering to a mammal in need of treatment a therapeutically effective amount of the (−)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or a pharmaceutically acceptable salt thereof, so as to effect decreased interindividual variation in plasma levels upon administration. The use of the (−)-enantiomer of omeprazole to receive increased average plasma levels (AUC) upon administration of the same doses of the (−)-enantiomer of omeprazole compared to those of racemic omeprazole is also claimed, as well as an improved anti-secretory effect and a better clinical effect.

23 Claims, 3 Drawing Sheets

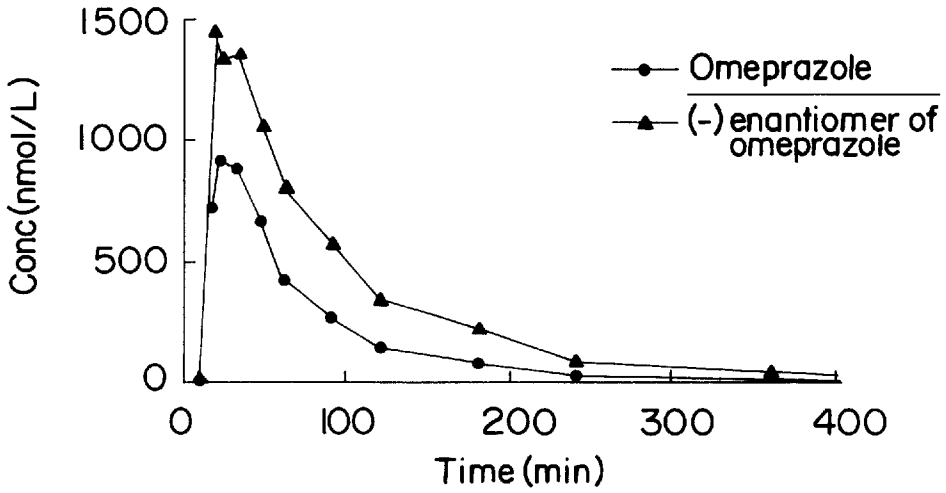

FIG. 1

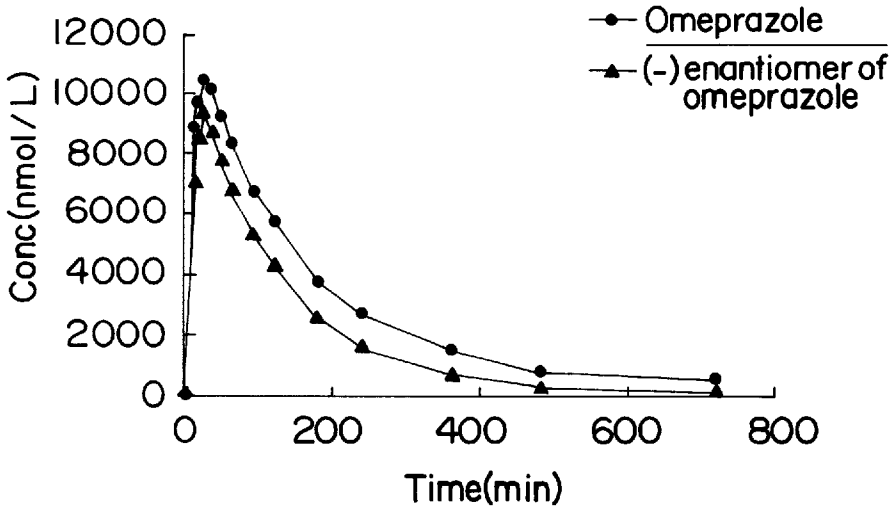

FIG. 2

Mean plasma concentration (day 7)

AUC slow/AUC rapid		
(±)-omeprazole	(−)-omeprazole	(+)-omeprazole
10	3	30

AUC: area under the plasma concentration vs. time curve

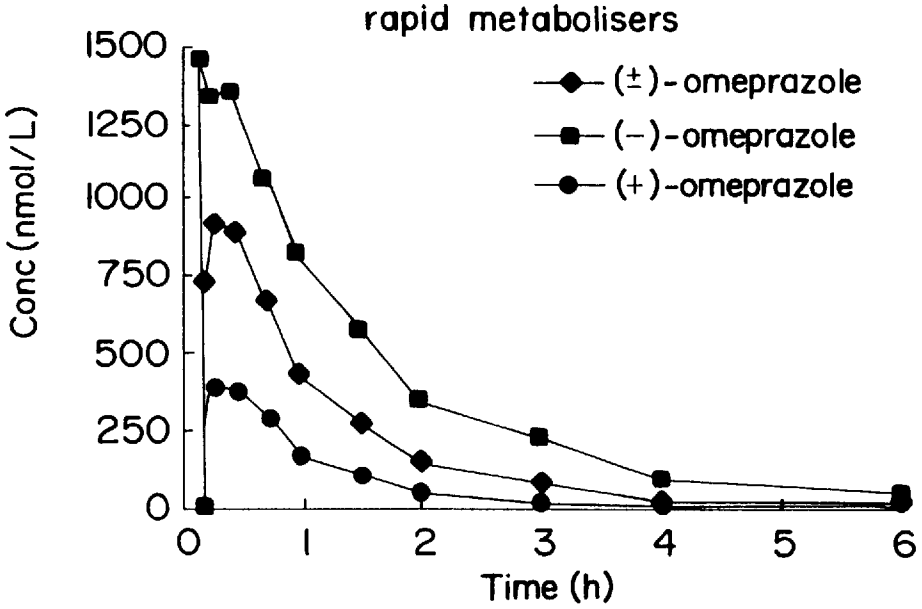

FIG.3A

Mean plasma concentration (day 7)

AUC slow/AUC rapid		
(±)-omeprazole	(−)-omeprazole	(+)-omeprazole
10	3	30

AUC:area under the plasma concentration vs. time curve

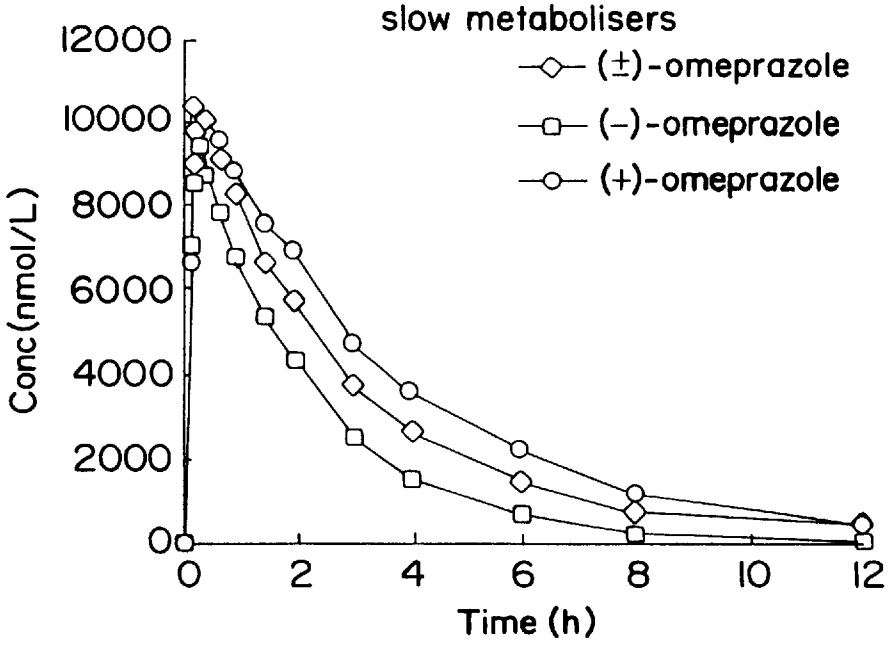

FIG.3B

METHOD FOR THE TREATMENT OF GASTRIC ACID-RELATED DISEASES AND PRODUCTION OF MEDICATION USING (-) ENANTIOMER OF OMEPRAZOLE

This application is a continuation-in-part of Ser. No. 08/376,512 filed on Jan. 23, 1995 now U.S. Pat. No. 5,714,504, which is a continuation-in-part of Ser. No. 08/256,174 filed Jun. 28, 1994, now U.S. Pat. No. 5,693,818.

The description of the salt forms of the single enantiomers of omeprazole and the process of making the same is herein incorporated by reference to copending Ser. No. 08/376,512.

FIELD OF THE INVENTION

The present invention is related to the use of one of the single enantiomers of omeprazole, i.e. the (−)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole or a pharmaceutically acceptable salt thereof, in the treatment of gastric acid related diseases. The expression single enantiomer refers to the fact that the (−)-enantiomer is substantially free from its (+)-enantiomeric contaminant.

BACKGROUND OF THE INVENTION

The compound 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, and therapeutically acceptable salts thereof, are described in EP 5129. The specific alkaline salts of omeprazole are described in EP 124 495. Omeprazole is effective as a gastric acid secretion inhibitor, and is useful as an antiulcer agent. In a more general sense, omeprazole may be used for prevention and treatment of gastric-acid related diseases in mammals and especially in man, including e.g. reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, omeprazole may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease (GERD), and in patients with gastrinomas. Omeprazole may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre-and postoperatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, omeprazole may be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections and diseases related to these.

Omeprazole is a sulfoxide and a chiral compound, wherein the sulfur atom being the stereogenic center. Thus, omeprazole is a racemic mixture of its two single enantiomers, the (+)-enantiomer of omeprazole and the (−)-enantiomer of omeprazole. The absolute configurations of the enantiomers of omeprazole have been determined by an X-ray study of an N-alkylated derivative of the (+)-enantiomer in neutral form. The (+)-enantiomer of the neutral form and the (−)-enantiomer of the neutral form were found to have the R and S configuration, respectively. The conditions for the optical rotation measurement for each of the compounds mentioned above are described in WO 94/27988.

Different salts of the single enantiomers of omeprazole are also described in WO 94/27988. Specific processes for the preparation of the single enantiomers of substituted benzimidazoles are described in WO 96/02535. An oral pharmaceutical dosage form of omeprazole or one of its

single enantiomers is described in WO 96/01623. Other oral dosage forms for the (−)-enantiomer of omeprazole can be found in EP 247 983.

There are few studies on the single enantiomers of omeprazole. One previous in vitro study on inhibition of acid secretion in isolated gastric glands showed no significant difference in effect between the two single enantiomers of omeprazole and the racemic mixture, see Erlandsson P. et al, Journal of Chromatography 1990; 532: 305–319. It has also been shown that, when omeprazole was administered intravenously to one subject, the plasma levels of the two enantiomers were similar, see Cairns A. M. et al, Journal of Chromatography B, 1995; 666: 323–328.

More than 135 million prescriptions by doctors indicate that omeprazole is an effective and safe drug. Notwithstanding, omeprazole exhibits polymorphic metabolism, i.e. a few individuals (3% among the Caucasian populations and 15–20% among Orientals) metabolise omeprazole slowly (slow metabolisers) compared to the rest of the population (rapid metabolisers). Slow metabolisers of omeprazole will obtain higher than the average plasma concentrations of the drug. Since the inhibition of gastric acid secretion is correlated to the area under the plasma concentration versus time curve (AUC), a more pronounced effect from omeprazole is expected in these slow metabolising individuals. A less interindividual variation, i.e. especially slow versus rapid metabolisers, and on the average higher plasma levels, giving higher dose efficiency in patients, could be of therapeutic benefit. Thus, one of the enantiomers of omeprazole, referred to as the (−)-enantiomer of omeprazole, or a pharmaceutically acceptable salt thereof, is hereby claimed to be an improved alternative to omeprazole in the treatment of gastric acid related diseases resulting in higher dose efficiency and in less interindividual variation in plasma levels (AUC), both between rapid and slow metabolisers and within the group of rapid metabolisers.

SUMMARY OF THE INVENTION

The use of the (−)-enantiomer of omeprazole, or a pharmaceutically acceptable salt thereof, in the treatment of gastric acid related diseases as a mean to decrease interindividual variation in plasma levels compared to omeprazole is claimed. The use of the (−)-enantiomer of omeprazole to receive increased average plasma levels (AUC) of the substance compared to those of racemic omeprazole and thereby a higher dose efficiency is also claimed.

DETAILED DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the mean plasma levels of racemic omeprazole and the (−)-enantiomer of omeprazole at steady state (Day 7) in rapid metabolisers following administration of 15 mg doses of each substance.

FIG. **2** shows the mean plasma levels of racemic omeprazole and the (−)-enantiomer of omeprazole at steady state (Day 7) in slow metabolisers following administration of 60 mg doses of each substance.

FIGS. **3***a* and **3***b* show the mean plasma levels of racemic omeprazole, the single (−)-enantiomer of omeprazole and the single (+)-enantiomer of omeprazole at steady state in rapid and slow metabolisers following administration of 15 mg and 60 mg doses of each substance, respectively. The figure sheet also comprises the ratios between the mean AUCs at steady state of slow and rapid metabolisers.

DETAILED DESCRIPTION OF THE INVENTION

Omeprazole is metabolised mainly in the liver by the cytochrome P450 system (CYP). Metabolism can be defined

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