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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ZINC SALT OF (S)-OMEPRAZOLE

(57) Abstract: A zinc salt of the S-enantiomer of omeprazole which is (S)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl]-methyl:sulfanyl]-1H-benzimidazole is provided. Further, processes for preparing the zinc salt, pharmaceutical compositions comprising the salt and a method of treatment or prevention of gastrointestinal ulcers comprising administration of the salt are provided.
ZINC SALT OF (S)-OMEPRAZOLE

Field of the Invention

A zinc salt of the S-enantiomer of omeprazole which is (S)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole is provided.

Further, processes for preparing the zinc salt, pharmaceutical compositions comprising the salt and a method of treatment or prevention of gastrointestinal ulcers comprising administration of the salt are provided.

Background of the Invention

Omeprazole is a gastric acid secretion inhibitor, useful as an anti-ulcer agent.

United States Patent No. 5,714,504 describes alkaline salts of (S)-omeprazole, such as sodium, magnesium, lithium, potassium, calcium or tetraalkylammonium salts. However, only the preparation of sodium and magnesium salts of (S)-omeprazole has been exemplified, besides (S)-omeprazole freebase in this patent. The potassium salt of (S)-omeprazole has been prepared in WO 98/54171 and WO 00/44744. Commercially magnesium salt of (S)-omeprazole is used for treating and preventing peptic ulcers, gastroesophageal reflux disease (GERD or heartburn), erosive esophagitis, other conditions involving excessive stomach acid production, and for treating bacterial infections caused by helicobacter pylori.

Summary of the Invention

Herein is provided the zinc salt of (S)-omeprazole, that is, (S)-omeprazole zinc. Another aspect relates to esomeprazole zinc in an amorphous form.

In yet another aspect, a process for preparing (S)-omeprazole zinc is provided, which comprises contacting (S)-omeprazole freebase or its sodium/potassium salt with zinc salt of an acid in a suitable solvent to form (S)-omeprazole zinc, wherein the process is carried out in the presence of a base whenever (S)-omeprazole freebase is used.

Further aspects include methods for treating or preventing gastrointestinal ulcers which comprise administering (S)-omeprazole zinc, or a pharmaceutical composition that comprises (S)-omeprazole zinc, along with pharmaceutically acceptable excipients.
The term "(S)-omeprazole zinc," as used herein, means any salt comprised of (S)-omeprazole anions and zinc cations. For instance, solid as well as dissolved forms are included, and so are crystalline and amorphous forms. (S)-omeprazole zinc may exist in an anhydrous and/or solvent-free form or as a hydrate and/or a solvate.

The expression "S-omeprazole," as used herein, refers to an omeprazole-containing material which is substantially free of the R-enantiomer of omeprazole, for example, it has an enantiomeric excess of 80%, or for example an enantiomeric excess of 90%. In some particular embodiments, S-omeprazole is in enantiomeric excess of at least about 95%, or at least about 98%, or at least about 99.5%, or at least about 99.8%.

Further, the term "(S)-omeprazole zinc," as used herein, encompasses stoichiometric as well as non-stoichiometric ratios of (S)-omeprazole anion and zinc cation. The ratio of (S)-omeprazole to zinc is not required to be 1:1 in order to be termed (S)-omeprazole zinc. In a particular embodiment (S)-omeprazole zinc is formed as a salt having a 2:1 molar ratio between (S)-omeprazole anion and zinc cation even when an excess of (S)-omeprazole or an excess of zinc salt of an acid is used in the salt formation.

**Brief Description of the Figures**

Figure 1 is an X-Ray diffractogram of (S)-omeprazole zinc.

Figure 2 is an infrared spectrum of (S)-omeprazole zinc.

Figure 3 is a differential scanning calorimetry spectrum of (S)-omeprazole zinc.

Figure 4 is an X-Ray diffractogram of (S)-omeprazole zinc.

Figure 5 is an infrared spectrum of (S)-omeprazole zinc.

Figure 6 is a differential scanning calorimetry spectrum of (S)-omeprazole zinc.

Figure 7 is an X-Ray diffractogram of (S)-omeprazole zinc.

Figure 8 is an infrared spectrum of (S)-omeprazole zinc.

Figure 9 is a differential scanning calorimetry spectrum of (S)-omeprazole zinc.

(S)-omeprazole zinc obtained in amorphous form is non-hygroscopic. Amorphous
form may be advantageous in comparison with the crystalline form as it can be obtained in a finely powdered form with better solubility properties.

Examples of bases which may be used in the process for preparing (S)-omeprazole zinc using (S)-omeprazole freebase include alkali metal hydroxides such as sodium hydroxide or potassium hydroxide, alkali metal carbonates such as sodium carbonate or potassium carbonate, alkali metal bicarbonates such as sodium bicarbonate, and ammonium hydroxide.

The zinc salt of an acid to be used in the process can be the salt of any inorganic or organic acid. Examples of such salts include zinc chloride, zinc nitrate, zinc sulphate, zinc phosphate, zinc carbonate, zinc oxalate, zinc acetate, zinc lactate, zinc succinate, zinc citrate, and zinc tartrate.

Examples of suitable solvents for carrying out the process include water, ketones such as acetone and methyl isobutyl ketone, esters such as ethyl acetate and isopropyl acetate, chlorinated hydrocarbons such as methylene chloride and ethylene dichloride, cyclic ethers such as dioxan and tetrahydrofuran, alcohols such as methanol, ethanol and isopropanol, nitriles such as acetonitrile, dipolar aprotic solvents such as dimethylsulfoxide and dimethylformamide, and mixtures thereof.

In water the reactants are more soluble than the (S)-omeprazole zinc product. In this way, the salt-forming reaction is accompanied by spontaneous precipitation of the produced zinc salt out of the solution.

Alternatively, the precipitation may be facilitated by reducing the volume of the solution and/or by adding an antisolvent, that is, a solvent in which the (S)-omeprazole zinc is insoluble or sparingly soluble. The precipitation can also be induced by reducing the temperature of the solvent, especially if the initial temperature at contact is elevated.

Examples of anti solvents that may be added to precipitate out (S)-omeprazole zinc include lower alkyl ethers such as diethyl ether, and diisopropyl ether; hydrocarbons such as hexane and heptane and mixture(s) thereof.

The (S)-omeprazole freebase or its sodium/potassium salt to be used in the preparation processes can be obtained by methods known in the art including those
described in United States Patent Nos. 5,714,504, 5,948,789, and US 6,162,816, and
International Patent Applications WO 00/44744, WO 98/54171, WO92/08716. The
starting (S)-omeprazole freebase or its sodium/potassium salts may be obtained as a
solution directly from a reaction in which (S)-omeprazole is formed, and used as such.

The precipitated zinc salt may be isolated in a solid state by conventional methods
such as filtration or centrifugation, optionally followed by washing and/or drying.

(S)-omeprazole zinc is a useful proton pump inhibitor and an antibacterial, and
thus can be used to treat any condition that would be benefited by administration of a
gastric acid secretion inhibitor. In particular, (S)-omeprazole zinc can be used for the
treatment or prophylaxis of gastric acid-related diseases and gastrointestinal inflammatory
diseases in mammals and man, such as erosive or ulcerative gastroesophageal reflux
disease (GERD), gastric ulcer, duodenal ulcer, reflux esophagitis, and gastritis.
Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric
antisecretory effect is desirable, for example in patients on NSAID therapy, in patients
with gastrinomas, and in patients with acute upper gastrointestinal bleeding. It may also
be used in patients in intensive care situations, and pre- and postoperatively to prevent acid
aspiration and stress ulceration. Further, (S)-omeprazole zinc may be useful in the
treatment of helicobacter infections and diseases related to these.

The salt can be administered as a component of a pharmaceutical composition.

Accordingly, in a further aspect, there is provided a pharmaceutical composition that
comprises (S)-omeprazole zinc and pharmaceutically acceptable carriers, diluents or
excipients and optionally other therapeutic ingredients. The salt may be conveniently
formulated into tablets, capsules, suspensions, dispersions, injectables and other
pharmaceutical forms. Any suitable route of administration may be employed for
example, peroral or parental.

In the following section preferred embodiments are described by way of examples
to illustrate the process of the invention. However, these are not intended in any way to
limit the scope of the present invention. Several variants of these examples would be
evident to persons ordinarily skilled in the art.
Examples

General Experimental Details - Powder XRD

X-Ray Diffraction (XRD) patterns were taken with an diffractometer manufactured by Rigaku Corporation, specifically the model RU-H3R. The goniometer was a CN2155A3, and the X-Ray tube was equipped with Cu target anode. The settings for the divergence slits were 1 0, for the receiving slit 0.15mm, and for the scatter slit 1 0. The operating power was 40 KV, 100 mA, the scanning speed was 2 deg/min step: 0.02 deg, and the wavelength was 1.5406 Å.

General Experimental Details – FT Infrared

Infrared spectra were taken with a Perkin Elmer,16 PC, with scan parameters of 16 scans, 4.0 cm⁻¹, according to the USP 25, general test methods page 1920. Infrared absorption spectra were obtained by the potassium bromide pellet method.

General Experimental Details – Differential Scanning Calorimetry

Differential Scanning Calorimetry was done by the model DSC821 e, manufactured by Mettler Toledo, with sample weights of 3-5 mg, and the sample temperature range of 25-100° C, heating rate of 1° C/min, nitrogen flow of 80.0 mL/min, with one hole in the crucible.

Example 1: A first preparation of (S)-omeprazole zinc

(-)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl]-methyl]sulfinyl]-1H-benzimidazole, zinc salt was prepared as follows.

The potassium salt of (S)-omeprazole ( 5.0g) was stirred in acetone (50ml) at 25 to 30°C and anhydrous zinc chloride (1.8 g) was added. The reaction mixture was stirred for 1 to 2 hours. The solid that separated out was filtered through filter aid under vacuum and the wet cake was washed with acetone (20ml). The filtrate was concentrated under reduced pressure at 40-45°C to a semisolid material. Methanol (50 ml) was added, the suspension stirred further for 1-2 hours at 20-25°C. The solid obtained was filtered, washed with methanol and air dried at 40 to 45°C for 7 to 8 hours to get (S)-omeprazole zinc (5.2g).
HPLC Purity = 98.56 %, Chiral Purity by HPLC= 99.89 %. MC% w/w by KF = 3.35 %, Zn content (w/w): 10.99%; Powder XRD, IR in KBr and DSC spectra are as shown in Figure 1, 2 and 3 respectively, as shown in the accompanying drawings.

Example 2:

(-)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfonyl]-1H-benzimidazole, zinc salt was also prepared as follows.

The potassium salt of (S)-omeprazole (5g,) was dissolved in water (60ml) at at 25-30°C to get a clear solution. Anhydrous zinc chloride (1.8g) dissolved in water (5ml) was slowly added to the above solution in 10 minutes at 25-30°C. The reaction mixture was further stirred for 1 to 2 hours, the obtained solid was filtered and washed with water. The product was air dried at 40 to 45°C for 8 to 10 hours to get (S)-omeprazole zinc (4.9g).

MC% w/w by KF = 3.31 %, Zn content (w/w): 9.42%; XRD, IR spectra, and DSC spectra are as shown in Figure 4, 5 and 6 respectively, as shown in the accompanying drawings.

Example 3:

(-)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfonyl]-1H-benzimidazole, zinc salt was also prepared as follows.

The potassium salt of (S)-omeprazole (5g,) was dissolved in water (60ml) at at 25-30°C to get a clear solution. Zinc sulphate heptahydrate (3.8 g) dissolved in water (10ml) was slowly added to the above solution in 10 minutes at 25-30°C. The reaction mixture was further stirred for 1 to 2 hours, the obtained solid was filtered and washed with water. The product was air dried at 40 to 45°C for 8 to 10 hours to get (S)-omeprazole zinc (4.2g).

HPLC Purity = 98.97 %, Chiral Purity by HPLC= 99.92%. MC% w/w by KF = 0.10 %. XRD and IR spectra are similar to those shown for Example 1 in Figure 1 and 2 respectively.
Example 4:

(-)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl]-methyl]sulfinyl]-1H-benzimidazole, zinc salt was also prepared as follows.

The potassium salt of (S)-omeprazole (100.0g) was stirred in acetone (1500ml) at 25 to 30°C and zinc sulphate pentahydrate (75.0 g) was added. The reaction mixture was stirred for 5-6 hours. The solid that separated out was filtered through filter aid under vacuum and the wet cake was washed with acetone (200ml). The filtrate was concentrated under reduced pressure at 40-45°C to a semisolid material. Methanol (400 ml) was added, the solution so obtained was stirred with activated carbon (5.0 g) for another 30 minutes at 20-25°C. The carbon was filtered off and the filtrate concentrated under vacuum to a semisolid material. Water (500ml) was then added and the mixture was stirred at 25 to 30°C for 2 to 3 hours. Solid thus obtained was filtered, washed with water and air dried at 40 to 45°C for 7 to 8 hours to get (S)-omeprazole zinc (59.0).

HPLC Purity = 99.69 %, Chiral Purity by HPLC= 99.96 %. MC% w/w by KF = 3.44 %, Zn content (w/w): 6.04%; Powder XRD, IR in KBr and DSC spectra are as shown in Figure 7, 8 and 9 respectively, as shown in the accompanying drawings.
We Claim:

1. The zinc salt of (S)-omeprazole.

2. The salt according to claim 1, which is in amorphous form.

3. A process for preparing (S)-omeprazole zinc, comprising contacting (S)-omeprazole freebase or its sodium/potassium salt with zinc salt of an acid to form (S)-omeprazole zinc, wherein the process is carried out in the presence of a base whenever (S)-omeprazole freebase is used.

4. The process according to claim 3, wherein the zinc salt of an inorganic acid is used.

5. The process according to claim 4, wherein the zinc salt is selected from the group consisting of zinc chloride, zinc nitrate, zinc phosphate, zinc carbonate, and zinc sulphate.

6. The process according to claim 3, wherein the zinc salt of an organic acid is used.

7. The process according to claim 6, wherein the zinc salt is selected from the group consisting of zinc oxalate, zinc acetate, zinc lactate, zinc succinate, zinc citrate, and zinc tartrate.

8. The process according to claim 3, wherein the base is selected from the group consisting of alkali metal hydroxides, alkali metal carbonates, alkali metal bicarbonates and ammonium hydroxide.

9. The process according to claim 8, wherein the base is selected from the group consisting of sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, and sodium bicarbonate.

10. The process according to claims 3, wherein the solvent is selected from the group consisting of water, ketones, alcohols, esters, cyclic ethers, chlorinated hydrocarbons, nitriles, dipolar aprotic solvents, and mixtures thereof.

11. The process according to claim 11, wherein the solvent is selected from the group consisting of water, acetone, methyl isobutyl ketone, acetonitrile,
dimethylsulfoxide, dimethylformamide, and mixtures thereof.

12. The process according to claim 3, wherein (S)-omeprazole zinc precipitates out spontaneously from the solvent.

13. The process according to claim 3, wherein amorphous form of (S)-omeprazole zinc is obtained.

14. A method for treating or preventing gastrointestinal inflammatory diseases, which comprises administering (S)-omeprazole zinc.

15. A method of inhibiting gastric acid secretion comprising administering (S)-omeprazole zinc.

16. The method according to claim 14 or 15, wherein (S)-omeprazole zinc is used for treatment or prophylaxis of gastric acid-related diseases and gastrointestinal inflammatory diseases selected from the group consisting of erosive or ulcerative gastroesophageal reflux disease (GERD), gastric ulcer, duodenal ulcer, reflux esophagitis, and gastritis.

17. The method according to claim 14 to 16, wherein amorphous form of the (S)-omeprazole zinc is used.

18. A pharmaceutical composition comprising (S)-omeprazole zinc and pharmaceutically acceptable carriers, diluents or excipients.

19. The pharmaceutical composition according to claim 19, wherein amorphous form of the (S)-omeprazole zinc is used.
INTERNATIONAL SEARCH REPORT

INTERNATIONAL APPLICATION NO

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/12 A61K31/4439 A61P1/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation: to the extent that such documents are included in the fields searched

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No.


X US 5 714 504 A (LINDBERG PER LENNART ET AL) 3 February 1998 (1998-02-03) cited in the application Claims, examples 1-19

Further documents are listed in the continuation of box C.

X Patent family members are listed in annex.

* Special categories of cited documents:

*A* document defining the general state of the art which is not considered to be of particular relevance

**E** earlier document but published on or after the international filing date

*L* document which may throw doubts on priority claims(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

**O** document referring to an oral disclosure, use, exhibition or other means

**P** document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'*X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'V' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

*A* document member of the same patent family

Date of the actual completion of the international search:

13 August 2004

Date of mailing of the international search report:

26/08/2004

Name and mailing address of the ISA:

European Patent Office, P.B. 5818 Patentlaan 2 NL–2280 Hl Hilversum Tel. (+31-70) 340-2000, Fax: 31 651 epos nl

Authorized officer:

Stroeter, T
### Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **X** Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
   Although claims 14-17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. **X** Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. **X** Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. **X** As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. **X** As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. **X** As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. **X** No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- **X** The additional search fees were accompanied by the applicant's protest.
- **X** No protest accompanied the payment of additional search fees.
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Form: PCT/ISA/210 (patent family annex) January 2004
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