### Abstract

Pharmaceutical compositions comprising a helicobacter-inhibiting anti-microbial agent and a benzimidazole derivative having gastric acid secretion inhibitory activity.
FOR THE PURPOSES OF INFORMATION ONLY

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+ Any designation of “SU” has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.
PHARMACEUTICAL COMPOSITIONS CONTAINING 5-DIFLUOROMETHOXY-2-[(3,4-DIMETHOXY-2-PYRIDYL) Methyl ULFINYL] BENZIMIDAZOLE AND AN ANTI-HELCOBACTER AGENT FOR THE TREATMENT OF GASTRO-INTESTINAL DISORDERS.

The present invention relates to pharmaceutical compositions and their use in treating or preventing gastrointestinal disorders, in particular disorders caused or exacerbated by helicobacter infection and secreted gastric acid.

The compositions of the invention comprise a helicobacter-inhibiting anti-microbial agent and a compound of formula (I):

![Chemical Structure](image)

(I)

or a pharmaceutically acceptable salt thereof.

The present invention further relates to the use of a helicobacter-inhibiting anti-microbial agent and a compound of formula (I) or a pharmaceutically acceptable salt thereof in treating or preventing gastrointestinal disorders in mammals, in particular humans. This use may involve either concurrent or non-concurrent administration of the helicobacter-inhibiting anti-microbial agent and a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The term "helicobacter-inhibiting anti-microbial agent" means any natural, synthetic, or semi-synthetic compound or mixture thereof which is effective in eradicating helicobacter pylori organisms (formerly known as campylobacter pylori organisms).
Such helicobacter-like organisms and helicobacter-inhibiting anti-microbial agents, as well as the various in vitro and in vivo assays used to determine the effectiveness of such agents, have been described in EP-A-0 282 131.

Suitable anti-microbial agents include antibiotics, and bismuth salts such as bismuth subcitrate or bismuth subsalicylate.

Antibiotics are the preferred helicobacter-inhibiting anti-microbial agents useful herein. Specific examples of such helicobacter-inhibiting anti-microbial agents include penicillin, mezlocillin, ampicillin, amoxicillin, cefalothin, cefoxitin, cefotaxime, imipenem, gentamicin, amikacin, erythromycin, ciprofloxacin, tetracyclines, metronidazole, cephalosporins, and combinations thereof. The preferred helicobacter-inhibiting anti-microbial agent is amoxicillin. The more preferred helicobacter-inhibiting agent is amoxicillin in combination with metronidazole. The most preferred helicobacter-inhibiting anti-microbial agent is a combination of amoxicillin, metronidazole and a bismuth salt as disclosed in WO 89/03219.

The compound of formula (I) can be prepared using the procedures described in EP 0 166 287-B. In particular, the compound of formula (I) in the form of its sodium salt is preferred.

The compositions of the present invention may be used in therapy to treat gastrointestinal diseases caused or exacerbated by helicobacter infection and secreted gastric acid. For example, they may be used to treat
duodenal and gastric ulcer disease, in particular having a positive effect in lowering the relapse rate of such diseases compared to the relapse rate observed by treatment with a compound of structure (I) alone.

The use of the present invention in therapy comprises administering the helicobacter-inhibiting anti-microbial agent and a compound of formula (I) or a pharmaceutically acceptable salt thereof either concurrently or non-concurrently. Concurrently means that the two agents are administered within 24 hours or less of each other, preferably within about 12 hours of each other, more preferably within about 1 hour of each other and most preferably within about 5 minutes of each other; and includes co-administration of the agents by administering a composition of the present invention. The term non-concurrently means that the two agents are administered more than 24 hours apart.

In a still further aspect, the present invention provides a method of treatment of gastrointestinal diseases caused or exacerbated by H. pylori infection and elevated levels of gastric acid which comprises administering to a subject in need thereof, an effective amount of a compound of structure (I) or a pharmaceutically acceptable salt thereof and a helicobacter-inhibiting anti-microbial agent.

In therapeutic use the anti-microbial agent and the compound of formula (I) or a pharmaceutically acceptable salt thereof can be administered separately in a standard pharmaceutical composition, or together in a single composition.
Standard compositions can be prepared by techniques well-known in the art of pharmacy, for example as described in EP-0 166 287-B.

The daily dose regimen for an adult patient involves administering the helicobacter-inhibiting anti-microbial agent in an amount from 1mg to 10000mg. The specific quantity depends on the particular anti-microbial agent used. For example, penicillins such as amoxicillin are administered in an amount of from about 500mg to about 3000mg per day, preferably from about 750mg to about 1500mg per day; bismuth salts such as bismuth subcitrate and bismuth subsalicylate are administered in an amount of from about 5mg to about 5000mg per day, preferably from about 50mg to about 250mg per day.

The daily dosage regimen for an adult patient for the compound of formula (I) or a pharmaceutically acceptable salt thereof involves administering from about 0.7mg to about 1400mg per day calculated as the free base. Preferably the dose is from about 3.5mg to about 350mg per day calculated as the free base and most preferably from about 7mg to about 100mg per day calculated as the free base.

Suitably the anti-microbial agent and the compound of formula (I) or a pharmaceutically acceptable salt thereof can be administered together in several unit doses, preferably 1-4 times per day. In the case of parenteral treatment lower doses can generally be used. Suitably the compounds will be administered for a period of continuous therapy, for example a week or more.

In a still further aspect, the present invention provides the use of a helicobacter-inhibiting
anti-microbial agent and a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing gastrointestinal disorders, in particular ulcer relapse.

It is to be understood that when used herein, 'medicament' shall be taken to refer to a composition comprising both the helicobacter-inhibiting anti-microbial agent and the compound of formula (I) or a pharmaceutically acceptable salt thereof, or a medicament pack comprising the two active ingredients as discrete separate dosage forms.
Claims:

1. A pharmaceutical composition comprising a helicobacter-inhibiting anti-microbial agent and a compound of formula (I):

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

2. A pharmaceutical composition according to claim 1 wherein the compound of formula (I) is in the form of its sodium salt.

3. A pharmaceutical composition according to claim 2 wherein the helicobacter-inhibiting anti-microbial agent is amoxicillin.

4. A pharmaceutical composition according to claim 2 wherein the helicobacter-inhibiting anti-microbial agent is amoxicillin and metronidazole.

5. A pharmaceutical composition according to any one of claims 2-4 wherein the helicobacter-inhibiting anti-microbial agent further comprises a pharmaceutically acceptable bismuth salt.

6. A pharmaceutical composition according to claim 1 wherein the helicobacter-inhibiting anti-microbial agent is a pharmaceutically acceptable bismuth salt.
7. A pharmaceutical composition according to any one of claims 1-6 for use in therapy.

8. A pharmaceutical composition according to any one of claims 1-6 for use in treating or preventing gastrointestinal disorders.

9. The use of a helicobacter-inhibiting antimicrobial agent and a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing gastrointestinal disorders.

10. The use of a helicobacter-inhibiting antimicrobial agent and a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating duodenal or gastric ulcer relapse.
**INTERNATIONAL SEARCH REPORT**

**I. CLASSIFICATION OF SUBJECT MATTER**

According to International Patent Classification (IPC) or to both National Classification and IPC

| Int.Cl.5 | A 61 K 31/44 |

**II. FIELDS SEARCHED**

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**III. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<th>Citation of Document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to Claim No.</th>
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<tr>
<td>A</td>
<td>EP.A,0282131 (PROCTER &amp; GAMBLE) 14 September 1988, see abstract; claims 1-3,12; page 7, lines 24-29 (cited in the application)</td>
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<td>Antimicrobial Agents and Chemotherapy, volume 28, no. 6, December 1985, C.A.M.McNulty et al.: &quot;Susceptibility of clinical isolates of campylobacter pylorides to 11 antimicrobial agents&quot;, pages 837-838, see abstract; page 837, column 1, paragraph 2; page 838, table 1, paragraphs 2 and 3</td>
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**IV. CERTIFICATION**

Date of the Actual Completion of the International Search: 18-10-1991

Date of Mailing of this International Search Report: 26. 11. 91

International Searching Authority: EUROPEAN PATENT OFFICE

Signature of Authorized Officer: T. MORTENSEN
ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.  GB 9101427
                                           SA 50729

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 13/11/91. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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For more details about this annex: see Official Journal of the European Patent Office, No. 12/82.