



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b>  <b>A61K 31/44</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 92/03135</b>  <b>(43) International Publication Date:</b> 5 March 1992 (05.03.92)
<b>(21) International Application Number:</b> PCT/GB91/01427 <b>(22) International Filing Date:</b> 23 August 1991 (23.08.91)  <b>(30) Priority data:</b> 9018603.2                      24 August 1990 (24.08.90)                      GB  <b>(71) Applicant (for all designated States except US):</b> SMITH KLINE & FRENCH LABORATORIES LIMITED [GB/GB]; Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB).  <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only) :</b> PARSONS, Michael, E. [GB/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB).		<b>(74) Agent:</b> GIDDINGS, Peter, J.; Corporate Patents, Smith-Kline Beecham, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB).  <b>(81) Designated States:</b> AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US.  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> PHARMACEUTICAL COMPOSITIONS CONTAINING 5-DIFLUOROMETHOXY-2-[(3,4-DIMETHOXY-2-PYRIDYL) METHYLSULFINYL] BENZIMIDAZOLE AND AN ANTI-HELICOBACTER AGENT FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS  <b>(57) Abstract</b>  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**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

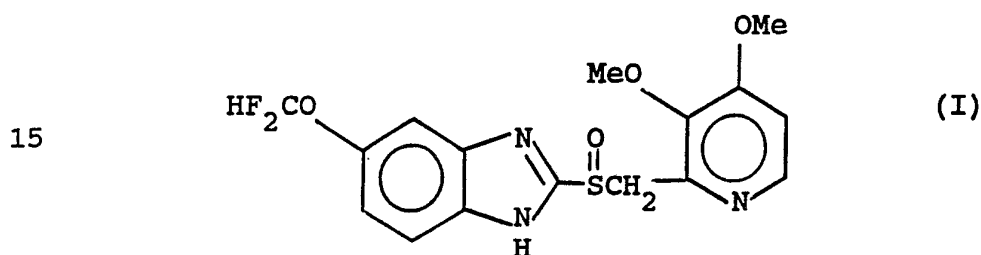
<b>AT</b>	Austria	<b>ES</b>	Spain	<b>MG</b>	Madagascar
<b>AU</b>	Australia	<b>FI</b>	Finland	<b>ML</b>	Mali
<b>BB</b>	Barbados	<b>FR</b>	France	<b>MN</b>	Mongolia
<b>BE</b>	Belgium	<b>GA</b>	Gabon	<b>MR</b>	Mauritania
<b>BF</b>	Burkina Faso	<b>GB</b>	United Kingdom	<b>MW</b>	Malawi
<b>BG</b>	Bulgaria	<b>GN</b>	Guinea	<b>NL</b>	Netherlands
<b>BJ</b>	Benin	<b>GR</b>	Greece	<b>NO</b>	Norway
<b>BR</b>	Brazil	<b>HU</b>	Hungary	<b>PL</b>	Poland
<b>CA</b>	Canada	<b>IT</b>	Italy	<b>RO</b>	Romania
<b>CF</b>	Central African Republic	<b>JP</b>	Japan	<b>SD</b>	Sudan
<b>CG</b>	Congo	<b>KP</b>	Democratic People's Republic of Korea	<b>SE</b>	Sweden
<b>CH</b>	Switzerland	<b>KR</b>	Republic of Korea	<b>SN</b>	Senegal
<b>CI</b>	Côte d'Ivoire	<b>LI</b>	Liechtenstein	<b>SU<sup>+</sup></b>	Soviet Union
<b>CM</b>	Cameroon	<b>LK</b>	Sri Lanka	<b>TD</b>	Chad
<b>CS</b>	Czechoslovakia	<b>LU</b>	Luxembourg	<b>TG</b>	Togo
<b>DE*</b>	Germany	<b>MC</b>	Monaco	<b>US</b>	United States of America
<b>DK</b>	Denmark				

**+ 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 SULFINYL] BENZIMIDAZOLE AND AN ANTI-HELICOBACTER 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 (1):



20 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.

30 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).

35

-2-

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

-3-

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.

5

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

10 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

15 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.

20 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

25 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

30 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.

-4-

Standard compositions can be prepared by techniques well-known in the art of pharmacy, for example as described in EP-0 166 287-B.

5           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  
10 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  
15 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  
20 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.

25           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  
30 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.

35           In a still further aspect, the present invention provides the use of a helicobacter-inhibiting

-5-

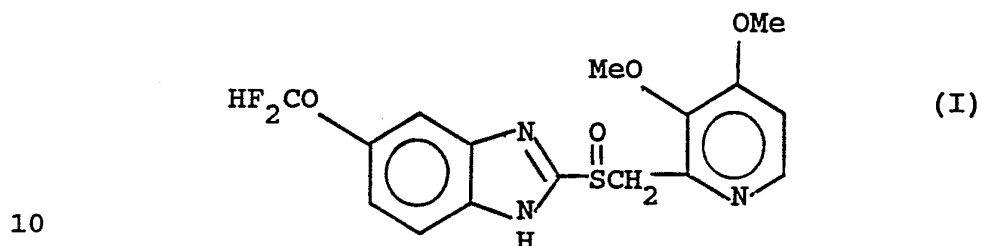
anti-microbial agent and a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing gastrointestinal disorders, in particular ulcer relapse.

5 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  
10 active ingredients as discrete separate dosage forms.

-6-

Claims:

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



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-

7. A pharmaceutical composition according to any one of claims 1-6 for use in therapy.

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

10 9. 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.

15 10. 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 duodenal or gastric ulcer relapse.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 91/01427

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)<sup>6</sup>

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

Int.C1.5 A 61 K 31/44

## II. FIELDS SEARCHED

Minimum Documentation Searched<sup>7</sup>

Classification System

Classification Symbols

Int.C1.5

A 61 K

Documentation Searched other than Minimum Documentation  
to the Extent that such Documents are Included in the Fields Searched<sup>8</sup>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup>

Category <sup>o</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
A	EP,A,0282131 (PROCTER & GAMBLE) 14 September 1988, see abstract; claims 1-3,12; page 7, lines 24-29 (cited in the application) ---	1-10
A	WO,A,8903219 (BORODY) 20 April 1989, see abstract; claims 1-6,8,10,18-20 (cited in the application) ---	1-10
A	Antimicrobial Agents and Chemotherapy, volume 28, no. 6, December 1985, C.A.M.McNulty et al.: "Susceptibility of clinical isolates of campylobacter pylorides to 11 antimicrobial agents", pages 837-838, see abstract; page 837, column 1, paragraph 2; page 838, table 1, paragraphs 2 and 3 ---	1-10
A	WO,A,9009175 (AB HÄSSLE) 23 August 1990, see abstract -----	1-10

<sup>o</sup> Special categories of cited documents : <sup>10</sup>

- "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 claim(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

"Y" 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.

"&" document member of the same patent family

## 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   Miss 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.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0282131	14-09-88	AU-A- 1279388	08-09-88
		JP-A- 63290831	28-11-88
		ZA-A- 8801678	07-09-88
-----			
WO-A- 8903219	20-04-89	AU-A- 2540588	02-05-89
		EP-A- 0439453	07-08-91
-----			
WO-A- 9009175	23-08-90	JP-A- 2209809	21-08-90
		AU-A- 5038190	05-09-90
		EP-A- 0414847	06-03-91
-----			