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(21) International Application Number: PCT/EP98/04553 (22) International Filing Date: 21 July 1998 (21.07.98) (30) Priority Data: 97112795.6 25 July 1997 (25.07.97) EP (71) Applicant (for all designated States except US): BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH [DE/DE]; Byk-Gulden-Strasse 2, D-78467 Konstanz (DE). (72) Inventor; and (75) Inventor/Applicant (for US only): TUCH, Klaus [DE/DE]; Schimmelmanstrasse 20, D-22926 Ahrensburg (DE). (74) Common Representative: BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH; Byk-Gulden-Strasse 2, D-78467 Konstanz (DE).		(81) Designated States: AL, AU, BA, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, JP, KR, LT, LV, MK, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, US, VN, YU, ZW, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: PROTON PUMP INHIBITOR IN THERAPEUTIC COMBINATION WITH ANTIBACTERIAL SUBSTANCES (57) Abstract The invention relates to the use of proton pump inhibitors as combination therapeutics in the treatment of bacterial diseases which do not affect the gastrointestinal tract using antibacterially active compounds.		

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PROTON PUMP INHIBITOR IN THERAPEUTIC COMBINATION WITH ANTIBACTERIAL SUBSTANCES**Field of application of the invention**

The invention relates to the use of proton pump inhibitors as combination therapeutics in the treatment of bacterial diseases which do not affect the gastrointestinal tract using antibacterially active compounds.

Known technical background

A large number of patent applications and patents describe variously substituted 2-(2-pyridinylmethylsulfinyl)-1H-benzimidazoles. This class of compound is able to specifically inhibit gastric acid production and is therefore also described as the proton pump inhibitors class. A whole series of proton pump inhibitors are in an advanced stage of clinical testing or already on the market. The following compounds, designated by the INN, which may be mentioned as examples are: omeprazole (EP-B 005 129), pantoprazole (EP-B 166 287), lansoprazole (EP-B 174 726), rabeprazole (EP-B 268 956), leminoprazole (DE-A 35 31 487) and nepaprazole (EP-A 434 999).

European Patent 166 287, in which, inter alia, the compound pantoprazole (INN) is patented, states that the compounds according to the invention are suitable for the prevention and treatment of gastrointestinal diseases, such as can be caused, for example, by microorganisms, bacterial toxins, antiinflammatories, antirheumatics, ethanol, gastric acid or stress situations. - European Patent 544 760 describes combinations of pantoprazole with antibacterially active compounds for controlling the bacterium *Helicobacter pylori*, which populates the stomach.

Description of the invention

Surprisingly, it has now been found that, using proton pump inhibitors as combination components, side effects caused by antibacterially active compounds can be avoided.

The invention therefore relates to the use of proton pump inhibitors as combination therapeutics in the treatment of bacterial diseases which do not affect the gastrointestinal tract using antibacterially active compounds.

The invention further relates to the use of proton pump inhibitors for the production of medicaments for combined use in the treatment of bacterial diseases which do not affect the gastrointestinal tract using antibacterially active compounds.

The invention likewise relates to the combination of proton pump inhibitors with an antibacterially active substance for use in the treatment of bacterial diseases which do not affect the gastrointestinal tract.

The invention furthermore relates to the use of proton pump inhibitors for avoiding side effects which can be caused by antibacterially active substances.

The following compounds, designated by the INN, may be primarily mentioned as proton pump inhibitors: omeprazole, lansoprazole, rabeprazole, leminoprazole, nepaprazole and in particular pantoprazole. The designation "proton pump inhibitors" is intended to mean both the compounds themselves and also their pharmacologically tolerable salts, in particular the salts with bases. Thus the designation "pantoprazole" additionally includes the pharmacologically tolerable salts of pantoprazole, especially the salts with bases, such as are described in European Patent 166 287, in particular the sodium salt.

Examples which may be mentioned of bacterial diseases which do not affect the gastrointestinal tract are infections of the bones and joints, the soft parts, the skin and mucous membranes, the kidneys and the renal pelvis, the efferent ureters, the sex organs and the CNS, in particular infections of the ENT region and of the respiratory tract, such as, for example, bronchitis or pneumonia.

Antibacterially active compounds which may be mentioned are β -lactam antibiotics, for example penicillins (such as benzylpenicillin, phenoxymethylpenicillin, propicillin, azidocillin, dicloxacillin, flucloxacillin, oxacillin, amoxicillin, bacampicillin, ampicillin, mezlocillin, piperacillin or azlocillin), cephalosporins (such as cefadroxil, cefaclor, cefalexin, cefixim, cefuroxim, cefetamet, cefadroxil, ceftibuten, cefpodoxim, cefotetan, cefazolin, cefoperazon, ceftizoxim, cefotaxim, ceftazidim, cefamandol, cefepim, cefoxitin, cefodizim, cefsulodin, ceftriaxon, cefotiam or cefmenoxim) or other β -lactam antibiotics (e.g. aztreonam, loracarbef or meropenem); enzyme inhibitors, for example sulbactam, tetracyclines, for example tetracycline, oxytetracycline, minocycline or doxycycline; aminoglycosides, for example tobramycin, gentamicin, neomycin, streptomycin, amikacin, netilmicin, paromomycin or spectinomycin; amphenicols, for example chloramphenicol or thiamphenicol; lincomycins and macrolide antibiotics, for example clindamycin, lincomycin, erythromycin, clarithromycin, spiramycin, roxithromycin or azithromycin; polypeptide antibiotics, for example colistin, polymixin B, teicoplanin or vancomycin; gyrase inhibitors, for example norfloxacin, cinoxacin, ciprofloxacin, pipemidic acid, enoxacin, nalidixic acid, pefloxacin, fleroxacin or ofloxacin; nitroimidazoles, for example metronidazole; or other antibiotics, for example fosfomycin or fucidic acid, where these antibacterially active substances are administered on their own or alternatively can be combined with one another.

Side effects of the antibacterially active substances which may be mentioned, which can be avoided by the administration of proton pump inhibitors, are, in particular, atrophic gastritis.

"Combination therapeutic" or "combination" in the sense of the present invention is thus to be understood as meaning that the individual components (i.e. the proton pump inhibitor on the one hand and the antibacterially active substance or active substances on the other hand) can be administered in a manner which is known and customary per se simultaneously (in the form of a combination medication), more or less at the same time (from separate pack units) or successively (directly one after the other or else with a relatively large time interval).

In the case of administration of the individual components more or less at the same time from separate pack units and in the case of the administration of the individual components which takes place one after the other, it is possible, if desired, to select a different administration form. For example, one component can be orally administered, while the other component is intravenously administered.

The dosage of the antibacterially active substance(s) is carried out in the customary order of magnitude for the respective substance and the respective purpose, in the case of clarithromycin, for example, with a daily dose of 500 to 1000 mg. In the case of the combined use of a number of antibacterially active substances simultaneously, if appropriate, a lower dosage of the combination components in each case is carried out.

The proton pump inhibitors are administered in the dose customary for them, but preferably in a lower dosage.

Pantoprazole is administered in the customary daily dose of 40 mg, but preferably in a lower dosage (for example 10 to 20 mg/day). In particular in the case of a lower dosage, the proton pump inhibitors can be administered as combination therapeutics in the prophylactic sense in antibiotic therapy.

Investigation results

In the investigation on dogs described in detail below, it was possible to show that the atrophic gastritis caused by administration of antibacterially active substances can be avoided by the simultaneous administration of proton pump inhibitors:

Material and methodology

Animal material	22 dogs (beagles, CPB Harlan, Netherlands)
Age/weight	male: 12 months/13.8 kg female: 12.6 months/10.8 kg
Number of animals per group	3m / 3f
Experimental period	30 days
Recovery time	4 weeks (group 4)

Treatment

Group	Substances	Dosage (mg/kg of body weight per day)
1	pantoprazole	16
2	clarithromycin/metronidazole	75/50
3	pantoprazole/clarithromycin/metronidazole	16/75/50
4	as group 3; 4 weeks recovery time	
5	untreated control	

Group	Mucous membrane height (M + F)	Standard archives
1	1307	120
2	868	56
3	1233	43
4	1142	115
5	1086	185

The conclusion is drawn from this investigation that proton pump inhibitors, such as, for example, pantoprazole, are able to compensate deep-seated and serious morphological alterations to the mucous membrane, which are obviously caused by antibiotics (in this case the combination clarithromycin and metronidazole). Thus proton pump inhibitors should also be able in antibiotic therapy in man to decrease or to prevent the gastrointestinal side effects caused by the antibiotic.

Patent claims

1. The use of proton pump inhibitors and/or their salts as combination therapeutics in the treatment of bacterial diseases which do not affect the gastrointestinal tract using antibacterially active compounds.
2. The use of proton pump inhibitors and/or their salts for the production of medicaments for combined use in the treatment of bacterial diseases which do not affect the gastrointestinal tract using antibacterially active compounds.
3. The combination of proton pump inhibitors and/or their salts with an antibacterially active substance for use in the treatment of bacterial diseases which do not affect the gastrointestinal tract.
4. The use of proton pump inhibitors and/or their salts for avoiding side effects which can be caused by antibacterially active compounds.
5. The use as claimed in one of claims 1, 2 or 3, wherein the bacterial diseases which do not affect the gastrointestinal tract are infections of the bones and joints, the soft parts, the skin and mucous membranes, the kidneys and the renal pelvis, the efferent ureters, the sex organs and the CNS, the ENT region and the respiratory tract.
6. The use as claimed in claim 4, wherein the side effects of the antibacterially active substances which can be avoided by the administration of proton pump inhibitors are atrophic gastritis.
7. The use as claimed in one of claims 1, 2 or 3, wherein the proton pump inhibitor is pantoprazole.
8. The use as claimed in one of claims 1, 2 or 3, wherein the proton pump inhibitor is omeprazole, lansoprazole, leminoprazole, rabeprazole or nepaprazole.
9. The use as claimed in claim 4, wherein the proton pump inhibitor is pantoprazole.
10. The use as claimed in claim 4, wherein the side effects of the antibacterially active compounds which can be avoided by the administration of proton pump inhibitors are atrophic gastritis and the proton pump inhibitor is pantoprazole.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/04553

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K45/06 //(A61K45/06,31:44),(A61K45/06,31:415)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 097, no. 011, 28 November 1997 & JP 09 188624 A (AZUMA TAKESHI), 22 July 1997 see abstract	1-10
X	--- MURAKAMI K ET AL: "Atopic dermatitis successfully treated by eradication of Helicobacter pylori." J GASTROENTEROL, NOV 1996, 31 SUPPL 9 P77-82, XP002051213 JAPAN see abstract see page 79, paragraph 1-2 --- -/--	1-6,8



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

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3. Document member of the same patent family

Date of the actual completion of the international search

28 October 1998

Date of mailing of the international search report

01/12/1998

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/04553

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JONKERS D ET AL: "Omeprazole inhibits growth of gram-positive and gram-negative bacteria including Helicobacter pylori in vitro." J ANTIMICROB CHEMOTHER, JAN 1996, 37 (1) P145-50, XP002082027 ENGLAND see page 149 see abstract ---	1-10
X	GRECO S. ET AL: "Glossitis, stomatitis, and black tongue with lansoprazole plus clarithromycin and other antibiotics (1)" ANNALS OF PHARMACOTHERAPY, 1997, 31/12 (1548), XP002081783 United States see abstract ---	1-10
X	KALAS D ET AL: "'Connection between Helicobacter pylori infection and chronic gastrointestinal urticaria!" ORV HETIL, SEP 8 1996, 137 (36) P1969-72, XP002051214 HUNGARY see abstract ---	1-6,8
X	REINAUER S ET AL: "Schonlein-Henoch purpura associated with gastric Helicobacter pylori infection." J AM ACAD DERMATOL, NOV 1995, 33 (5 PT 2) P876-9, XP002051215 UNITED STATES see page 876, paragraph 1-2 see page 877, paragraph 4 - page 878, paragraph 1; table 1 ---	1-6,8
Y	MALFERTHEINER P.: "Current European concepts in the management of Helicobacter pylori infection. The Maastricht consensus report" GUT, 1997, 41/1 (8-13), XP002051216 UNITED KINGDOM see abstract; table 1 see page 11, column 1-2 ---	4,6,9,10
A	WO 97 02021 A (BYK GULDEN LOMBERG CHEM FAB) 23 January 1997 see page 4, paragraph 3 - page 5, paragraph 1; claim 1	1-10
Y	see page 1, paragraph 2 -----	4,6,9,10

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 98/04553

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
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see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ 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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
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4. ☐ 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

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/ EP 98 /04553

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims 1-3,5,7,8

The disclosure of claims 1-10 is not sustained by pharmacological data. Due to the absence of said pharmacological data in the disclosure of the invention (description or examples), the judgement of the state of the technique and the prior art for these claims will be questionable, subjective and considered as a mere desiderata. Therefore not a complete closes state of the art can have been cited in the search report.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/04553

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9702021 A	23-01-1997	AU 6517596 A	05-02-1997
		CA 2225628 A	23-01-1997
		EP 0841904 A	20-05-1998
