Title: NEW COMBINATION FOR THE TREATMENT OF HELICOBACTER PYLORI

Abstract: 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.
New combination for the treatment of Helicobacter pylori

Technical field

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.

Technical background

In U. S. Patent 5,888,535, according to the abstract of said patent "methods and compositions are disclosed utilizing optically pure (-) pantoprazole for the treatment of ulcers in humans while substantially reducing the concomitant liability of adverse effects associated with the racemic mixture of pantoprazole."

For the treatment of Helicobacter pylori disorders, the BDA (Professional association of general practitioners in Germany: Künzel D.; BDA-Leitfaden: Unklare Oberbauchbeschwerden; published by: Kybermed GmbH, Emsdetten, 1st edition, Emsdetten 1999) and the ESPCG (European Society for Primary Care Gastroenterology: Rubin G.P.; European Journal of General Practice, Vol. 5, 1999) recommend a combination therapy in which a proton pump inhibitor is administered at the same time as two different antibiotics. It is possible with such a triple therapy to achieve impressive eradication results (Huang J.Q., Hunt R. H.; GUT Vol. 45, Suppl. 1, 1999, i40).

In European Patent 544760, pharmaceutical compositions comprising a helicobacter-inhibiting antimicrobial agent and pantoprazole and/or its salts are disclosed.

In International Patent Application WO 00/74654 novel administration forms and preparations for acid-labile active compounds are described. As acid-labile active compounds, pantoprazole and (-)- pantoprazole are mentioned inter alia. The novel administration forms contain individual active compound units, the active compound being present in the active compound units in a matrix made of a mixture comprising at least one fatty alcohol and at least one solid paraffin, in a matrix made of a mixture of a triglyceride and at least one solid paraffin or in a matrix made of a mixture comprising at least one fatty acid ester and at least one solid paraffin. In particular, the active compound units are microspheres which can be produced by prilling. The novel administration forms can be combined, inter alia, with antimicrobial agents.

In International Patent Application WO 02/00161 a medicinal product with blister cards is claimed in which pantoprazole can be contained in conjunction with an antibiotic.

In U. S. Patent 6,410,569 the dihydrate of the magnesium salt of pantoprazole is disclosed.


**Description of the invention**

The compositions of the invention, which are outstandingly suited to achieve Helicobacter pylori eradication, thus favouring ulcer healing in patients with gastric ulcer, comprise a helicobacter-inhibiting anti-microbial agent and (S)-pantoprazole and/or its salts.

Within the scope of this invention, "(S)-pantoprazole and/or its salts" is understood to include:
- (S)-pantoprazole and/or its salts [which is the same as (-)-pantoprazole and its salts]
- (S)-pantoprazole [(+)-pantoprazole]
- salts of (S)-pantoprazole [(+)-pantoprazole]
- (S)-pantoprazole [(-)-pantoprazole] and/or its salts being substantially free of (R)-pantoprazole [(+)-pantoprazole] and/or its salts
- (S)-pantoprazole [(-)-pantoprazole] being substantially free of (R)-pantoprazole [(+)-pantoprazole]
- salts of (S)-pantoprazole [(-)-pantoprazole] being substantially free of salts of (R)-pantoprazole [(+)-pantoprazole].

"Salts" in the context of the invention means all pharmaceutically acceptable salts prepared by reacting (S)-pantoprazole [(-)-pantoprazole] with a suitable inorganic or organic base. Examples of salts with bases which may be mentioned are aluminium, sodium, potassium, lithium, magnesium, zinc or calcium salts. Particularly preferred is the magnesium salt. If (S)-pantoprazole and/or its salts are isolated in crystalline form, the crystals may contain variable amounts of solvent. Accordingly, according to the invention, the term "(S)-pantoprazole and/or its salts" also includes all solvates, in particular all hydrates, of (S)-pantoprazole and/or its salts. An exemplary hydrate of (S)-pantoprazole and/or its salts, which may be mentioned, is (S)-pantoprazole-sodium sesquihydrate [= (S)-pantoprazole-sodium x 1.5 H₂O]. A particularly preferred hydrate of (S)-pantoprazole and/or its salts is the (S)-pantoprazole-magnesium dihydrate.

"Substantially free" in the context of the invention means that (S)-pantoprazole and/or its salts contains less than 10 % by weight of (R)-pantoprazole. Preferably, "substantially free" means that (S)-pantoprazole and/or its salts contains less than 5 % by weight of (R)-pantoprazole. In the most preferred embodiment, "substantially free" means that (S)-pantoprazole and/or its salts contains less than 1 % by weight of (R)-pantoprazole.
The present invention further relates to the use of a helicobacter-inhibiting anti-microbial agent and (S)-pantoprazole and/or its salts 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 antimicrobial agent and (S)-pantoprazole and/or its salts.

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.

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-O 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 \( \beta \)-lactam antibiotics, for example penicillins (such as benzylpenicillin, phenoxymethylpenicillin, propicillin, azidocillin, dicloxacillin, flucloxacin, oxazolin, amoxicillin, aspoxicillin, bacampicillin, ampicillin, mezlocillin, piperacillin or azlocillin), cephalosporins (such as cefadroxil, cefaclor, cefalexin, cefixim, cefuroxim, cefuroxime axetil, cefetamet, cefadroxil, ceflbuten, cepodoxim, cefotetan, cefazolin, cefoperazon, cefixim, cefotaxim, ceftazidim, cefozopran, cefcapene, cefmetazole, cefdinir, cefamandol, cefepim, cefixitin, cefodizim, cefsolodin, ceftriaxon, cefotiam, cefmoxin, cefpodoxime proxetil, cefpimizol, cefsuloxis, cefitoren axetil, cefotiam hexetil or cefmenoxim) or other \( \beta \)-lactam antibiotics (e.g. aztreonam, loracarbef, flomoxef, faropenem, carumonam, ertapenem, panipenem or meropenem); enzyme inhibitors, for example sulbactam, tazobactam, tacryclines, for example tetracycline, oxytetracycline, minocycline or doxycycline; aminoglycosides, for example tobramycin, gentamicin, isepamicin, neomycin, streptomycin, amikacin, netilmicin, semduramycin, paromomycin or spectinomycin; amphenicol, for example chloramphenicol or thiamphenicol; rifamycines, for example rifamycine, rifampicin, rifapentine, rifaximin, rifabutin, lincomycins and macrolide antibiotics, for example clindamycin, lincomycin, spiramycin, erythromycins, for example erythromycin, clarithromycin, dirithromycin, telithromycin, florithromycin, cethromycin, roxithromycin or azithromycin; polypeptide antibiotics, for example colistin, polymixin B, teicoplanin or vancomycin; pristinamycins, for example pristinamycin, dalfopristin or quinupristin, lantibiotics, for example nisin, act agaridin, duramycin, anconenin, cinnaminycin, gyrase inhibitors, for example norfloxacin, cinoxacin, ciprofloxacin, clinafloxacine, tosufloxacin, sparfloxacin, lomefloxacine, enrofloxacine, prulifloxacin, levo-floxacin, gatifloxacin, marbofloxacin, danofloxacin, grepafloxacin, pazufloxacin, trovafloxacin, gemifloxacin, moxifloxacin, pipemidic acid, enoxacin, nalidixic acid, pefloxacin, fleroxacin or ofloxacin; nitroimidazoles, for example metronidazole, antibacterials, for example linezolid, posizolid, eperezolid or ranbezolid, or other antibiotics, for example fosfomycin, fosfomycin trometamol, mycophenolic acid or fucidic acid.
It is understood that the helicobacter-inhibiting anti-microbial agents can be administered on their own or alternatively can be combined with one another. Accordingly, the expression "a helicobacter-inhibiting anti-microbial agent" is understood within the scope of the invention to include two, three or more different helicobacter-inhibiting substances, which are present together.

The preferred helicobacter-inhibiting anti-microbial agents are amoxicillin, clarithromycin, azithromycin, tetracycline, metronidazole, levofloxacin, rifabutin and tinidazole. The more preferred helicobacter-inhibiting agent is a combination of two or three anti-microbial compounds, which are used together with known proton pump inhibitors - in the so-called triple or quadruple therapy. Accordingly, exemplary preferred compositions (combinations) according to the invention are those, which include:

Pharmaceutical composition of (S)-pantoprazole and/or its salts with amoxicillin and clarithromycin.
Pharmaceutical composition of (S)-pantoprazole and/or its salts with amoxicillin and metronidazole.
Pharmaceutical composition of (S)-pantoprazole and/or its salts with levofloxacin and rifabutin.
Pharmaceutical composition of (S)-pantoprazole and/or its salts with amoxicillin, tetracyclin and a bismuth salt.
Pharmaceutical composition of (S)-pantoprazole and/or its salts with tetracyclin, metronidazol and a bismuth salt.
Pharmaceutical composition of (S)-pantoprazole and/or its salts with metronidazol and clarithromycin.

The pharmaceutical composition 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 (S)-pantoprazole and/or its salts alone.

The use of the present invention in therapy comprises administering the helicobacter-inhibiting anti-microbial agent and (S)-pantoprazole and/or its salts 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 Helicobacter pylori infection and elevated levels of gastric acid which comprises administering to a subject in need thereof, an effective amount of (S)-pantoprazole and/or its salts and a helicobacter-inhibiting anti-microbial agent. In therapeutic use the anti-microbial agent and (S)-pantoprazole and/or its salts 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.

The daily dose regimen for an adult patient involves administering the helicobacter-inhibiting anti-microbial agent in an amount from 1 mg to 10000 mg. 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 500 mg to about 3000 mg per day, preferably from about 750 mg to about 1500 mg per day; bismuth salts such as bismuth subcitrate and bismuth subsalicylate are administered in an amount of from about 5mg to about 5000 mg per day, preferably from about 50 mg to about 250 mg per day. The skilled person is familiar in the amount customary for the anti-microbial agent in standard triple or quadruple therapy. The therapy is normally carried out for a period of from seven to fourteen days.

In general, it has proven advantageous in human medicine to administer (S)-pantoprazole and/or its salts in the case of oral administration in a daily dose from approximately 10 to approximately 80, preferably 20 to 40 mg as calculated for the free acid (S)-pantoprazole. In the case of parenteral treatment, similar or [in particular in the case of intravenous administration of (S)-pantoprazole and/or its salts], as a rule, lower doses can be used.

Suitably the anti-microbial agent and (S)-pantoprazole and/or its salts 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 further aspect, the present invention provides the use of a helicobacter-inhibiting anti-microbial agent and (S)-pantoprazole and/or its salts in the manufacture of a medicament for treating or preventing gastrointestinal disorders, in particular ulcer relapse.

In a still further aspect, the present invention provides a pharmaceutical composition comprising a helicobacter-inhibiting anti-microbial agent and (S)-pantoprazole and/or its salts for use in Helicobacter pylori eradication and ulcer healing in patients with gastric ulcer.

It is to be understood that when used herein, 'medicament' or 'pharmaceutical composition' shall be taken to refer to a composition comprising both the helicobacter-inhibiting anti-microbial agent(s) and (S)-pantoprazole and/or its salts in a fixed combination (fixed unit dosage form), or a medicament pack comprising the two, three (in case of triple therapy) or four (in case of quadruple therapy) active ingredients as discrete separate dosage forms. In case of a medicament pack comprising the two, three or four active ingredients, the active ingredients are preferably packed into blister cards which are suited for improving compliance.
Each blister card preferably contains the medicaments to be taken on one day of treatment. If the medicaments are to be taken at different times of day, the medicaments can be disposed in different sections on the blister card according to the different ranges of times of day at which the medicaments are to be taken (for example morning and evening or morning, midday and evening). The blister cavities for the medicaments to be taken together at a particular time of day are accommodated in the respective range of times of day. The various times of day are, of course, also put on the blister in a clearly visible way. It is also possible, of course, for example to indicate a period in which the medicaments are to be taken, for example stating the times.

The daily sections may represent one line of the blister card, and the times of day are then identified in chronological sequence in this column.

Medicaments which must be taken together at a particular time of day are placed together at the appropriate time on the blister card, preferably a narrow distance apart, allowing them to be pushed out of the blister easily, and having the effect that removal of the dosage form from the blister is not forgotten.

A preferable medicament pack to be used in connection with the invention is that disclosed in International Patent Application WO 02000161.
Examples

**Magnesium (-)-bis[[5-(difluoromethoxy)]-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphonyl]-1H-benzimidazolide] dihydrate**

At 20-25°C, 20.2 g (52.7 mmol) of (-)-pantoprazole ((-)-[5-(difluoromethoxy)]-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphonyl]-1H-benzimidazolide) were suspended in 200 ml of purified water. A solution of (55.2 mmol) sodium hydroxide in 10 ml of water was added, and the mixture was stirred at 20-30°C for 30 min. With addition of a filter aid (1g Hyflo-Super-Cel), the turbid solution was filtered. 6.32 g (31.2 mmol) of magnesium dichloride hexahydrate in 150 ml of water were then added drop by drop with stirring over a period of 30 min. After a further 30 min., the precipitated solid was filtered off with suction using a suction filter, stirred with water (2 x 50 ml) and again filtered off with suction. Drying under reduced pressure at 50-60°C gave, in a yield of 17.36 g (80%), a hydrate of magnesium (-)-bis[[5-(difluoromethoxy)]-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphonyl]-1H-benzimidazolide] having a water content of 4.5-4.7 % as a colourless to beige powder (m. p. 158-161°C, with decomposition).

Specific rotation: \[ \alpha_0^{25\circ} = -114^\circ \ (c = 0.5, \text{measured in methanol}) \]

For recrystallisation, 1.88 g of the hydrate were, at 55°C, dissolved in 6 ml of methanol, and 20 ml of water were added with stirring. A colourless to beige solid crystallized out. This gave the title compound of m. p. 160-163°C (with decomposition) having a water content of 4.3-4.4 %.

Alternatively, the title compound can also be prepared from organic-aqueous solvent mixtures. To this end, (-)-pantoprazole sodium, or (-)-pantoprazole together with one equivalent of aqueous, for example 2N, sodium hydroxide solution, is dissolved in an organic solvent, for example warm acetone. 0.5 to 0.55 equivalents of a magnesium salt (for example magnesium chloride hexahydrate), dissolved in water, are added drop by drop, and the mixture is cooled with stirring. The precipitated solid is filtered off, washed with the solvent mixture in question and dried at 50°C under reduced pressure until the weight remains constant. This gives the title compound as a colourless to beige powder.

**Magnesium (-)-bis[[5-(difluoromethoxy)]-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphonyl]-1H-benzimidazolide] dihydrate**

A. (-)-Pantoprazole-Na

36 g of (-)-pantoprazole were suspended in 180 ml of methyl isobutyl ketone (MIBK) and 18 ml of 2-propanol and heated to an internal temperature of 45°C. The suspension was stirred at this temperature for 15 min. At 50°C, 11 g of 30% (w/w) aqueous sodium hydroxide solution were slowly added drop by drop to this suspension. A clear to slightly turbid solution resulted. This solution was stirred for a bit longer and then filtered to give a clear solution.
The clear filtrate was slowly cooled to room temperature. Between 4.5°C and 30°C, crystallization, which could be accelerated by seeding with (−)-pantoprazole sodium, began. The resulting suspension was stirred at an internal temperature of < 20°C for another 2 h. The suspension was then filtered, and the crystals were washed with 40 ml of MIBK.

Drying was carried out in a vacuum drying cabinet at < 50 mbar and 40-45°C. [It is also possible to dispense with drying and to use the moist product (having an MIBK content of 10-20 %) directly for step B]. The white-beige crystalline product obtained after drying was hygroscopic. The water content was from 2 to 12 %. The absorption and release of water were reversible. Yield: 34 g = 90 % of theory (based on anhydrous product). Specific rotation: \( \alpha_0^{20^\circ} = -95 \) (c = 0.5, measured in methanol, sodium salt having a water content of 12%). m. p.: 145-165°C (decomposition, sodium salt having a water content of 2 %); 102-109°C (decomposition, sodium salt having a water content of 12 %).

B. (−)-Pantoprazole-Mg
30 g of (−)-pantoprazole sodium salt (calculated anhydrous substance) were suspended in 260 ml of water. The suspension was heated to 35-40°C and stirred at 35-40°C for another 10 min. This gave a clear solution. The clear solution was cooled to 22-27°C. 14.3 g of magnesium chloride hexahydrate were dissolved in 100 ml of water, and at room temperature and with stirring, the solution was slowly added dropwise to the (−)-pantoprazole sodium salt solution. The resulting suspension was then stirred at room temperature for another 4 h. The suspension was, under pressure, filtered through a Nutsche filter, and the product was, a little at a time, washed twice with 300 ml of water. Drying in a vacuum drying cabinet at < 50 mbar and 40-45°C gave 27.5 g (90 %) of the title compound of m. p. 160-163°C. Water content 4.3-4.4 %; specific rotation: \( \alpha_0^{20^\circ} = -129 \) (c= 0.5, measured in methanol).

Recrystallisation of (−)-pantoprazole-Mg
For recrystallisation, 6.0 g of the (−)-pantoprazole-Mg-dihydrate were, at 55°C, dissolved in 18 ml of methanol. After 15 min, 90 ml of water were added with stirring to the orange-brown-solution. A colourless to beige solid crystallised out. The resulting suspension was then stirred at 20-25°C for another 1 hour. The solid was filtered off, washed with 10 ml of water and dried under vacuum for 20 hours at 50°C. The yield for the title compound was 88 % (5.26 g) with the following data:

M.P.: 161-165°C (with decomposition)
Specific rotation: \( \alpha_0^{20^\circ} = -130^\circ \) (c = 0.5, measured in methanol)
Claims:

1. A pharmaceutical composition comprising a helicobacter-inhibiting anti-microbial agent and (S)-pantoprazole and/or its salt.

2. A pharmaceutical composition according to claim 1, wherein the salt is the magnesium salt.

3. A pharmaceutical composition according to claim 1, wherein the salt is the magnesium salt in the form of its dihydrate.

4. A pharmaceutical composition according to claim 1 or 2 or 3, wherein the helicobacter-inhibiting antimicrobial agent is selected from one or more of bismuth salt, amoxicillin, clarithromycin, azithromycin, tetracycline, metronidazole, levofloxacin, rifabutin and tinidazole.

5. A pharmaceutical composition according to claim 1 or 2 or 3, wherein the helicobacter-inhibiting antimicrobial agent is amoxicillin and clarithromycin.

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

7. A pharmaceutical composition according to any one of claims 1 to 5 for use in Helicobacter pylori eradication and ulcer healing in patients with gastric ulcer.

8. A pharmaceutical composition according to any one of claims 1 to 5, wherein (S)-pantoprazole and/or its salt and the helicobacter-inhibiting antimicrobial agent are present in a fixed combination (fixed unit dosage form).

9. A pharmaceutical composition according to any one of claims 1 to 5, wherein (S)-pantoprazole and/or its salt and the helicobacter-inhibiting antimicrobial agent are present in a medicament pack comprising the two, three (in case of triple therapy) or four (in case of quadruple therapy) active ingredients as discrete separate dosage forms.

10. A pharmaceutical composition according to any one of claims 1 to 5, wherein (S)-pantoprazole and/or its salt and the helicobacter-inhibiting antimicrobial agent are present in a medicament pack with blister cards comprising the two, three (in case of triple therapy) or four (in case of quadruple therapy) active ingredients as discrete separate dosage forms.