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(57) Abstract

An oral pharmaceutical composition of a reversible proton pump inhibitor in pellet or tablet form, wherein the reversible proton pump inhibitor is at least partly in slow-release form, is distinguished, on combined administration with an antimicrobially-active ingredient, by an enhanced action of rapid onset against disorders caused by Helicobacter.

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ORAL PHARMACEUTICAL COMPOSITIONS WITH DELAYED RELEASE OF REVERSIBLE PROTON PUMP INHIBITORS

Field of the Invention

The present invention relates to oral pharmaceutical compositions in pellet or tablet form for reversible proton pump inhibitors for combined use with antimicrobially-active ingredients for the treatment of disorders caused by Helicobacter.

Prior Art

Control of the microbe Helicobacter pylori, which is thought to be responsible for certain gastric disorders, by combined use of an antimicrobially-active ingredient which is active against Helicobacter pylori and of an agent which reduces gastric acid has been regarded as the method of choice for some time.

Besides inhibitors of gastric acid secretion of the H_2 receptor antagonist type, in recent times use has been made, with more or less success, of compounds of the class of so-called irreversible proton pump inhibitors (such as pantoprazole, omeprazole or lansoprazole). Irreversible proton pump inhibitors are substances which covalently, and thus irreversibly, bind to the enzyme which is responsible for acid secretion in the stomach, the H^+/K^+ ATPase.

Besides so-called irreversible proton pump inhibitors, which essentially have a common basic chemical structure (pyridinylmethylsulfinylbenzimidazoles), there are the so-called reversible H^+/K^+ ATPase inhibitors which have different basic chemical structures and which, as the name indicates, reversibly bind to the enzyme responsible for gastric acid secretion. These are called reversible proton pump inhibitors in connection with the present invention. Reversible proton pump inhibitors are

disclosed, for example, in the documents DE-A-3917232, EP-A-0399267, EP-A-0387821, JP-A-3031280, JP-A-2270873, EP-A-0308917, EP-A-0268989, EP-A-0228006, EP-A-0204285, EP-A-0165545, EP-A-0125756, EP-A-0120589, EP-A-0509974, DE-A-3622036, EP-A-0537532, EP-A-0535529, JP-A-3284686, JP-A-3284622, US-P-4,833,149, EP-A-0261912, WO-A-9114677, WO-A-9315055, WO-A-9315071, WO-A-9315056, WO-A-9312090, WO-A-9212969, WO-A-9118887, EP-A-0393926, EP-A-0307078, US-P-5,041,442, EP-A-0266890, WO-A-9414795, EP-A-0264883, EP-A-0033094, EP-A-0259174, EP-A-0330485, WO-A-8900570, EP-A-0368158, WO-A-9117164, WO-A-9206979, WO-A-9312090, WO-A-9308190, WO-A-9418199, DE-A-3011490, US-P-4,464,372, EP-A-0068378 and WO-A-9424130.

Combined use of reversible proton pump inhibitors with antimicrobially-active ingredients has a good effect against Helicobacter in vitro. However, the clinical effect achieved with this combined use is disappointing.

Summary of the Invention

The action of an antimicrobially-active ingredient on Helicobacter is surprisingly enhanced by administering a reversible proton pump inhibitor in slow-release dosage form (extended release form). It must be regarded as particularly surprising that, in addition, administration of the slow-release reversible proton pump inhibitor results in the onset of action taking place significantly faster than on administration of a non-slow-release reversible proton pump inhibitor. The duration of treatment until Helicobacter is eradicated is shortened, saving considerable amounts of antibiotic and acid inhibitor.

The invention thus relates to an oral pharmaceutical composition for treating a disorder caused by Helicobacter comprising a reversible proton pump inhibitor in combination with at least one antimicrobially-active ingredient, wherein at least part of the reversible proton pump inhibitor is in slow-release form. Further subject-matters are evident from the claims.

Details

Reversible proton pump inhibitors are, for the purpose of the present invention, those active ingredients which reversibly bind to the enzyme responsible for gastric acid secretion, H^+/K^+ ATPase. Examples of reversible proton pump inhibitors are enumerated in the previously-noted documents. Examples of reversible proton pump inhibitors are, e.g., 8-(2-methoxycarbonylamino-6-methylbenzylamino)-2,3-dimethyl-imidazo[1,2-a]pyridine (hereinafter B9401-011), 3-hydroxymethyl-8-(2 -methoxycarbonylamino-6-methylbenzyloxy)-2 methylimidazo[1,2-a]pyridine, 3-hydroxymethyl-8- (2-methoxycarbonylamino-6-methylbenzyloxy)-2-methylimidazo[1,2-a]pyridine, 8-(2-methoxycarbonylamino-6-methylbenzyloxy)-2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-tert-butoxycarbonylamino-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-tert-butoxycarbonylamino-6-methylbenzyloxy)-2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-ethoxycarbonylamino-6-methylbenzylamino) -2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-isobutoxycarbonylamino-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-isopropoxycarbonylamino-6-methylbenzylamino) -2,3-dimethyl-imidazo[1,2-a]pyridine, 8-(2-tert-butoxycarbonylamino-6-methylbenzylamino)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine, 8-(2-tert-butoxycarbonylamino-6-methylbenzyloxy)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine, 8-{2-[(2 -methoxyethoxy)carbonylamino]-6-methylbenzyloxy}-2-methylimidazo[1,2-a]pyridine-3-methanol, 8-{2-[(2 -methoxyethoxy)carbonylamino]-6-methylbenzylamino}-2-methylimidazo[1,2-a]pyridine-3-methanol, 8-{2-[(2 -methoxyethoxy)carbonylamino]-6-methylbenzylamino}-2,3-dimethylimidazo[1,2-a]pyridine, 8- {2-[(2-methoxyethoxy)-carbonylamino] -6-methylbenzyloxy}-2-methylimidazo[1,2-a]pyridine-3-methanol, 8-{2-[(2 -methoxyethoxy) carbonylamino]-6-methylbenzyloxy}-2,3-dimethylimidazo[1,2-a]pyridine, 3-hydroxymethyl-2-methyl-8-benzyloxyimidazo-[1,2-a]pyridine, 3-hydroxymethyl-2-trifluoromethyl-8-benzyloxyimidazo-[1,2-a]pyridine, 1,2-dimethyl-3-cyanomethyl-8-benzyloxyimidazo[1,2-a]pyridine, 2-methyl-3-cyanomethyl-8-

benzyloxyimidazo[1,2-a]pyridine, 3-butyryl-8-methoxy-4-(2-methylphenylamino)quinoline and 3-butyryl-8-hydroxyethoxy-4- (2-methylphenylamino) quinoline.

Reversible proton pump inhibitors can, in this connection, be present as such, in the form of their salts and/or their solvates (e.g. hydrates), etc. Particularly suitable salts are (because all reversible proton pump inhibitors are substances with a basic reaction) all acid-addition salts. Particular mention may be made of the pharmacologically-acceptable salts of inorganic and organic acids customarily used in pharmaceutical technology, including water-soluble and water-insoluble acid-addition salts with acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid and 3-hydroxy-2-naphthoic acid, the acids being used in the preparation of the salt in a ratio of amounts which are equimolar or different therefrom - depending on whether the acid is mono- or polybasic and depending on the salt required.

Examples of suitable antimicrobially-active ingredients (active against Helicobacter pylori) are enumerated in European Patent Application EP-A-282131. These active ingredients include, for example, bismuth salts (such as bismuth subcitrate or bismuth subsalicylate), sulfonamides, nitrofurans (such as nitrofurazone, nitrofurantoin or furazolidone), metronidazole, tinidazole, nimorazole or antibiotics. Examples of antibiotics which may be mentioned in this connection are, arranged according to particular classes of active ingredient: aminoglycosides, such as gentamicin, neomycin, kanamycin, amikacin or streptomycin; macrolides, such as erythromycin, azithromycin, clarithromycin, clindamycin or rifampicin; penicillins, such as penicillin G, penicillin V, ampicillin, mezlocillin or amoxicillin; polypeptides, such as bacitracin or polymyxin; tetracyclines, such as tetracyline, chlorotetracycline,

oxytetracycline, minocycline or doxycycline; carbapenems, such as imipenem, loracarbef, meropenem or panipenem; cephalosporins, such as cefalexin, cefoxitin, cefuroxime axetil, cefotaxime, cefpodoxime proxetil, cefaclor, cefadroxil or cephalothin; gyrase inhibitors, such as ciprofloxacin, norfloxacin, ofloxacin or pefloxacin; or other different antibiotics, such as chloramphenicol. Particularly worthy of mention in this connection is also the combination of a plurality of antimicrobially-active ingredients, for example the combination of a bismuth salt and/or tetracycline with metronidazole, or the combination of amoxicillin or clarithromycin with metronidazole.

Particularly worthy of mention in this connection is also administration of a reversible proton pump inhibitor together with a plurality of antimicrobially-active ingredients, for example with the combination of a bismuth salt and/or tetracycline with metronidazole, or with the combination of amoxicillin or clarithromycin or with metronidazole.

The dosage of the active ingredients depends greatly on the nature of the reversible proton pump inhibitor used and of the antimicrobially-active ingredient(s) used. A typical dosage of a reversible proton pump inhibitor as disclosed, for example, in WO-A-9418199 can be regarded as a daily dose of from about 0.01 to about 20, preferably from 0.05 to 5, and in particular from 0.1 to 1.5, mg/kg of body weight, where appropriate in the form of a plurality of single doses. Penicillins, such as amoxicillin, are administered in a daily dose of from about 5 to 40, preferably from 10 to 20, mg/kg of body weight.

Antimicrobially-active ingredients which may be emphasized are erythromycin, azithromycin, clarithromycin, clindamycin, rifampicin, ampicillin, mezlocillin, amoxicillin, tetracycline, minocycline, doxycycline, imipenem, meropenem, cefalexin, cefuroxime axetil, cefpodoxime proxetil, cefaclor, cefadroxil, ciprofloxacin, norfloxacin, ofloxacin and pefloxacin.

Clarithromycin and amoxicillin may be mentioned as antimicrobially-active ingredients which should be particularly emphasized.

Combined administration means (for the purpose of the

present invention) fixed and, in particular, free combinations, i.e. the slow-release reversible proton pump inhibitor and the antimicrobially-active ingredient are present together in one dosage unit, or slow-release reversible proton pump inhibitor and antimicrobially-active ingredient, which are present in separate dosage units, are administered in direct succession or at a relatively large time interval; a relatively large time interval means within a time span of up to a maximum of 24 hours. For use as separate dosage units, these are preferably made available together in one pack. For example, the two dosage units are packed together in blister packs which are designed with regard to the relative arrangement of the two dosage units with respect to one another, the inscription and/or coloring in a manner known per se so that the times for taking the individual components (dosage regimen) of the two dosage units are evident to a patient.

A dosage unit means, in particular, those medicinal dosage forms in which slowing or extending of reversible proton pump inhibitor release is achieved with as few problems as possible. These include, in particular, tablets, coated tablets or pellets, and microtablets in capsules, with the dosage form advantageously being designed so that the two active ingredient components (reversible proton pump inhibitor on the one hand and antimicrobially-active ingredient on the other hand) are released, or made available effectively for the body, in such a way that an optimal active-ingredient profile (and thus action profile) is achieved.

For slowing release, various types and degrees of retarding release may be used to ensure a reversible proton pump inhibitor plasma level which persists as long as possible and is sufficient for raising pH.

The pharmaceutical formulation of the antimicrobially-active ingredient(s) is carried out in a manner which is familiar per se to the skilled worker for the individual active ingredients.

The rapid release of part of the reversible proton pump inhibitor and retarding release of another part is optionally achieved, for example, by layered tablets or multilayer tablets,

in which part of the reversible proton pump inhibitor is present in an outer coating in a form without slowing release; this is followed by another coating containing the antimicrobially-active ingredient and then the core with the reversible proton pump inhibitor whose release is slowed in a suitable manner.

The details of how to achieve slowing release are familiar to the skilled worker on the basis of his expert knowledge. The skilled worker is likewise familiar with suitable ancillary substances and vehicles for the required dosage forms (pharmaceutical formulations). Besides solvents, tablet ancillary substances and other active ingredient excipients it is possible to use, for example, tablet-coating compositions, plasticizers, antioxidants, preservatives, dyes, etc. Where incompatibilities between the active ingredients or between the active ingredients and ancillary substances are to be expected, suitable separating layers must be provided where appropriate.

The oral pharmaceutical compositions according to the invention are distinguished from the prior art by controlled release of active ingredients and increased stability.

Besides filler and binder, other ancillary substances, in particular lubricants and nonstick agents, and tablet disintegrants, are used in the manufacture of the tablet cores. A suitable binder is, in particular, polyvinylpyrrolidone in various degrees of polymerization. Examples of lubricants and nonstick agents are higher fatty acids and their alkali-metal and alkaline-earth-metal salts, such as calcium stearate. Suitable tablet disintegrants are, in particular, chemically-inert agents. Preferred tablet disintegrants include cross-linked polyvinylpyrrolidone, crosslinked sodium carboxymethylcelluloses and sodium starch glycolate.

Examples of suitable film-forming polymers, in respect of the water-insoluble release-slowing intermediate layer(s) to be applied to the pellet or tablet core, include ethylcellulose, polyvinyl acetate, ammonio methacrylate copolymer type A (e.g. Eudragit® RL) and type B (Eudragit® RS) etc. The release rate can be controlled not only by incorporating suitable water-soluble pore formers such as PEG, lactose, mannitol, sorbitol, HPMC, etc., but also by the thickness of the coating layer applied.

The solvents or dispersants used for the release-controlling polymer dispersion are non-aqueous organic solvents, such as alcohols, ketones, halogenated hydrocarbons or mixtures of such solvents.

It is possible in a similar way to use osmotic systems with semipermeable membranes of cellulose acetate, cellulose acetate butyrate or cellulose acetate propionate (as described in US-A 3845770, US-A 3916899, US-A 4036227, US-A 4093708, US-A 4096238, US-A 4135514 and US-A 4142526) to control the release of active ingredients. These can be coated with aqueous dispersions of enteric lacquers without changing the release rate.

Examples of suitable polymers for the enteric coating are methacrylic acid/methyl methacrylate copolymer or methacrylic acid/ethyl methacrylate copolymer (Eudragit® L) or cellulose derivatives, such as carboxymethylethylcellulose (CMEC, Duodcel), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropylmethylcellulose phthalate (HP50, HP55), hydroxypropylmethylcellulose acetate succinate (HPMCAS) or polyvinyl acetate phthalate, to which it is also possible to add, if desired, plasticizer (such as propylene glycol) and/or other additives and ancillary substances (e.g. buffer; base, such as, preferably, aluminum hydroxide; or pigment). The layers are applied in conventional ways using equipment customary for these purposes.

Susceptibility of Commercial Application

The combined use according to the invention of a slow-release reversible proton pump inhibitor with an antimicrobially-active ingredient meets all the requirements for a pharmaceutical product or combination pharmaceutical product for the treatment of gastric disorders attributable to the microbe, Helicobacter pylori. The particular advantages connected with the combined use of the slow-release drug form with an antimicrobially-active ingredient which may be mentioned are: the rapid onset of action with pH values as far as neutral in the lumen of the stomach and in the wall of the stomach and an optimal displaying of the effect of the antimicrobially-active ingredient. The

short duration of treatment which can be achieved increases the compliance, which is extremely important for antibiotic treatments.

Examples

The following formulation examples explain the invention in detail without restricting it.

Example 1

Tablets:

I. Production of uncoated core:

a)	B9401-011 (hemimalate)	119.8 mg
b)	Sodium carboxymethylstarch	21.0 mg
c)	Microcrystalline cellulose (e.g.: Avicel PH 101)	21.0 mg
d)	Maize starch	19.4 mg
e)	Magnesium stearate	5.0 mg
		186.2 mg

a) is mixed with b), c) and part of d). A paste is prepared with the remainder of d). The latter is used for granulation of the powder mixture in a suitable mixer. The granules are dried in a drying oven or fluidized bed. e) is added to the dried granules, and the granules are compressed in a suitable tabletting machine.

II. Release-slowing layer

f)	Ethylcellulose	9.85 mg
g)	Lactose micronized	2.37 mg
h)	Propylene glycol	0.98 mg
		14. 00 mg

f) is dissolved in 165 ml of isopropanol. h) is stirred in for a sufficient length of time using a suitable agitator to form a solution (A). g) is suspended in 165 ml of isopropanol using a rotor-stator agitator to form a fine suspension (B). (A) and (B) are combined.

The tablet cores obtained under I are coated to an adequate layer thickness with the suspension obtained above in suitable apparatus.

Example 2

Tablets:

I. Production of uncoated core:

Production of the cores takes place as in Example 1, I.

II. Release-slowing layer:

f)	Polyvinyl acetate	10.38 mg
g)	Lactose micronized	2.59 mg
h)	Propylene glycol	1.03 mg
		13 .13 mg

f) is dissolved in 150 ml of a 1:1 acetone/chloroform mixture. h) is stirred in for a sufficient length of time, using a suitable agitator to prepare a solution (A).

g) is suspended in 150 ml of a 1:1 acetone/chloroform mixture, using rotor-stator agitator to prepare a fine dispersion (B). (A) and (B) are combined.

The tablet cores obtained under I are coated to a sufficient layer thickness with the thus-obtained dispersion in suitable apparatus.

Example 3

Pellets:

I. Starter pellets

a)	Sucrose pellets (0.7-0.85 mm)	950.0 g
b)	Hydroxypropylmethylcellulose 2910 (USP)	40.0 g
c)	Propylene glycol	10.0 g

a) is sprayed with an aqueous solution of b) and c) in a fluidized bed (Wurster method).

II. Active pellets

d)	B9401-011 (Hemimalate)	403.0 g
e)	Hydroxypropylmethylcellulose 2910 (USP)	403.0 g
f)	Propylene glycol	201.5 g

d), e) , f) are successively dissolved in 4 liters of purified water and sprayed onto 900 g of the pellets obtained under I in a fluidized bed (Wurster method).

III. Slow-release pellets

A release-slowing layer is applied in analogy to the procedure described for tablets in a pan or fluidized bed.

Example 4

Pellets:

I. Active pellets

a)	B9401-011 (Hemimalate)	403.0 g
b)	Microcrystalline cellulose (Avicel PH101)	117.0 g
c)	Na carboxymethylcellulose	18.0 g

a) and b) are premixed dry and subsequently moistened to a paste-like consistency with a solution of Na carboxymethylcellulose in water in a conventional kneader or high-speed mixer. The resulting composition is then extruded and shaped into pellets by the extruder/rounder method familiar to the skilled worker. The moistened pellets are dried in suitable equipment (drying oven, fluidized bed, etc.).

III. Slow-release pellets:

The release-slowing layer is applied in analogy to the procedure described for tablets in a pan or fluidized bed.

The invention and its advantages are readily understood from the foregoing description. As is apparent, various changes can be made in the products and methods without departing from the spirit and scope of the invention or sacrificing its material advantages. The products and processes hereinbefore described are merely illustrative of preferred embodiments of the invention.

WHAT IS CLAIMED:

1. An oral pharmaceutical composition for treating a disorder caused by Helicobacter comprising a reversible proton pump inhibitor in combination with at least one antimicrobially-active ingredient, wherein at least part of the reversible proton pump inhibitor is in slow-release form.

2. An oral pharmaceutical composition as claimed in claim 1, wherein the reversible proton pump inhibitor, which is wholly or partly in slow-release form, is in fixed combination with at least one antimicrobially-active ingredient in a single dosage unit.

3. An oral pharmaceutical composition as claimed in claim 2, wherein the reversible proton pump inhibitor is in pellet form together with at least one antimicrobially-active ingredient in a capsule as a dosage unit.

4. An oral pharmaceutical composition as claimed in claim 2, wherein the reversible proton pump inhibitor, which is wholly or partly in slow-release form, is together with at least one antimicrobially-active ingredient in a multilayer tablet.

5. An oral pharmaceutical composition as claimed in claim 1, wherein the reversible proton pump inhibitor and at least one antimicrobially-active ingredient are in separate dosage units in a single package.

6. An oral pharmaceutical composition as claimed in claim 5, wherein the single package is a blister pack which is designed by the relative arrangement of individual components of the dosage units, by inscription and/or by coloring to communicate the dosage regimen to a patient.

7. A pharmaceutical as claimed in claim 1, wherein the reversible proton pump inhibitor is a member selected from group consisting of 8-(2-methoxycarbonylamino-6-methyl-benzylamino) -2,3-dimethylimidazo[1,2-a]pyridine, 3-hydroxymethyl-8-(2-methoxycarbonylamino-6-methylbenzylamino)-2-methylimidazo[1,2-a]pyridine, 3-hydroxymethyl-8- (2-methoxycarbonylamino-6-methylbenzyloxy)-2-methylimidazo[1,2-a]pyridine, 8-(2-methoxycarbonylamino-6-methylbenzyloxy)-2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-tert-butoxy-carbonylamino-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-tert-butoxycarbonylamino-6-methylbenzyloxy)-2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-ethoxycarbonylamino-6-methylbenzylamino) -2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-isobutoxycarbonylamino-6-methylbenzylamino)-2,3-di-methylimidazo[1,2-a]pyridine, 8-(2-isopropoxycarbonylamino-6-methylbenzylamino) -2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-tert-butoxycarbonylamino-6-methylbenzylamino)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine, 8-(2-tert-butoxycarbonylamino-6-methylbenzyloxy)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine, 8-{2 -[(2 -methoxyethoxy)carbonylamino] -6-methylbenzyloxy} -2-methylimidazo[1,2-a]pyridine-3-methanol, 8-{2-[(2 -methoxyethoxy)carbonylamino] -6-methylbenzyl-amino}-2-methylimidazo[1,2-a]pyridine-3-methanol, 8-{2-[(2-methoxyethoxy) carbonylamino] -6-methylbenzylamino}-2,3-dimethylimidazo[1,2-a]pyridine, 8-{2-[(2-methoxyethoxy) carbonylamino] -6-methylbenzyloxy}-2-methylimidazo[1,2-a]pyridine-3-methanol, 8-{2-[(2 -methoxyethoxy)carbonylamino] -6-methylbenzyloxy}-2,3-dimethylimidazo[1,2-a]pyridine, 3-hydroxymethyl-2-methyl-8-benzyloxyimidazo[1,2-a]pyridine, 3-hydroxymethyl-2-trifluoromethyl-8-benzyloxyimidazo[1,2-a]pyridine, 1,2-dimethyl-3-cyanomethyl-8-benzyloxy-imidazo[1,2-a]pyridine, 2-methyl-3-cyanomethyl-8-benzyloxy-imidazo[1,2-a]pyridine, 3-butyryl-8-methoxy-4-(2-methylphenylamino)quinoline and 3-butyryl-8-hydroxyethoxy-4-(2- methylphenylamino)quinoline, or a salt thereof.

8. A pharmaceutical composition as claimed in claim 1, wherein the reversible proton pump inhibitor is a member selected from the group consisting of 8-(2-methoxycarbonylamino-6-methylbenzylamino)-2,3-dimethyl-imidazo[1,2-a]pyridine, 8-(2-methoxycarbonylamino-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine, and 8-(2-methoxycarbonylamino-6-methylbenzylamino)-2,3-dimethyl-imidazo[1,2-a]pyridine, or a salt thereof.

9. A pharmaceutical composition as claimed in claim 1, wherein the antimicrobially-active ingredient is a member selected from the group consisting of bismuth subcitrate, bismuth subsalicylate, nitrofurazone, nitrofurantoin, furazolidone, metronidazole, tinidazole, nimorazole, gentamicin, neomycin, kanamycin, amikacin, streptomycin, erythromycin, azithromycin, clarithromycin, clindamycin, rifampicin, penicillin G, penicillin V, ampicillin, mezlocillin, amoxicillin, bacitracin, polymyxin, tetracycline, chlorotetracycline, oxytetracycline, minocycline, doxycycline, imipenem, loracarbef, meropenem, panipenem, cefalexin, cefoxitin, cefuroxime axetil, cefotaxime, cefpodoxime proxetil, cefaclor, cefadroxil, cephalothin, ciprofloxacin, norfloxacin, ofloxacin, pefloxacin and chloramphenicol.

10. The use of a reversible proton pump inhibitor in combination with at least one antimicrobially-active ingredient for the preparation of a pharmaceutical composition for the treatment of disorders caused by Helicobacter wherein at least part of the reversible proton pump inhibitor is in slow-release form.

11. A process for producing an oral pharmaceutical composition in pellet or tablet form for a reversible proton pump inhibitor, as active ingredient, or for combined use thereof with at least one antimicrobially-active ingredient for treating a disorder caused by Helicobacter, which comprises a) incorporating the active ingredient into a pellet or tablet core, b) applying thereto at least one release-slowing intermediate layer essentially comprising a water-insoluble, release-slowing acidic film former and c) subsequently applying an outer enteric layer which is soluble in the small intestine.

INTERNATIONAL SEARCH REPORT

Interr onal Application No
PCT/EP 96/02893

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/28 A61K9/50

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.
A	WO,A,94 18199 (BYK GULDEN LOMBERG) 18 August 1994 cited in the application see claims 1-9 see page 15, paragraph 3 - page 16, paragraph 3 -----	1-11

☐ Further documents are listed in the continuation of box C.

☒ 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 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 when the document is taken alone

"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

Date of the actual completion of the international search	Date of mailing of the international search report
2 December 1996	11. 12. 96

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr ional Application No
PC1/EP 96/02893

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9418199	18-08-94	AU-A- 6039194	29-08-94
		BG-A- 99855	30-04-96
		CA-A- 2156078	18-08-94
		CN-A- 1119863	03-04-96
		CZ-A- 9502088	13-12-95
		EP-A- 0683780	29-11-95
		FI-A- 953838	06-09-95
		HU-A- 72436	29-04-96
		JP-T- 8506333	09-07-96
		NO-A- 953187	14-08-95
		PL-A- 310171	27-11-95
		SK-A- 99795	06-12-95
		ZA-A- 9400990	17-08-94