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(54) TAUROLIDINE ET/OU TAURULTAM DESTINES A LA LUTTE CONTRE LES ULCERES OU LES GASTRITES D'ORIGINE INFECTIEUSE

(54) TAUROLIDINE AND/OR TAURULTAM AGAINST INFECTIOUS ULCER OR GASTRITIS

(57) A method for the treatment of infectious gastrointestinal ulcer disease or infectious gastritis disease of microbially infected gastrointestinal tissue in a mammal involves administration of an antimicrobial amount of an antimicrobial medicament which is cell wall constituent-inactivating by chemical reaction with cell wall constituents, endotoxin non-releasing, exotoxin-inactivating or a combination thereof.

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(57) Abstract

A method for the treatment of infectious gastrointestinal ulcer disease or infectious gastritis disease of microbially infected gastrointestinal tissue in a mammal involves administration of an antimicrobial amount of an antimicrobial medicament which is cell wall constituent–inactivating by chemical reaction with cell wall constituents, endotoxin non–releasing, exotoxin–inactivating or a combination thereof.

TAUROLIDINE AND/OR TAURULTAM AGAINST INFECTIOUS ULCER OR GASTRITIS

The present invention relates to the field of treating patients having gastrointestinal ulcers or gastritis caused by microbial infection.

The stomach's infection with the germ Helicobacter pylori (H.p.) is one of the most frequent infectious diseases in the world; in developing countries, more than 80% of the population is already infected with H.p. during childhood.

In the past, chronic gastritis with prolonged dyspeptic symptoms in the upper stomach, the peptic ulcer, duodenal ulcer (UD) and ventral ulcer (UV) with pain in the upper stomach after meals, or epigastric pain on an empty stomach had been a syndrome with unclear etiology. Its pathogenesis had not been clarified in detail. Generally, it can still be said today that there is no peptic ulcer without proteolytic gastric acid. Differential-diagnostic measures usually succeed in differentiating the peptic formation of ulcers from psychogenic gastrointestinal malfunctions. The final diagnosis depends on X-ray results.

Initially, treatment of chronic gastritis was based on administering antacids, such as magnesium or aluminum compounds, calcium carbonates, alkaline bismuth salts, e.g. bismuth aluminate, colloidal bismuth salts. However, a high relapse rate of over 80% and side effects, such as the rebound effect of acid secretion, deposits of aluminum and bismuth salts in the tissue, bismuth nephropathy, and bismuth encephalopathy forced the medical field to pursue new paths.

The selective proximal vagotomy with surgical exclusion of the appropriate vagus branches or the acid-producing stomach sections in the case of relapsing stomach duodenal ulcers was another medical path that usually went nowhere. The relapse rate usually did not

change with this serious surgical procedure.

In acid secretion, H_2-receptors are involved. The introduction of the H_2-receptor antagonists Cimetidine (Tagamet®) in 1977, and then Ranitidine (Zantac®, Sostril™) represented a milestone in medicinal ulcer therapy. This led to rapid pain elimination with the healing of UD and UV. Side effects of long-term therapy, such as infectious diarrhea, persistent hypergastrinemia with germ settlements on the antacid stomach lumen and nitrosamine formation, had to be accepted. Despite progress in acute therapy and the short-term prophylaxis of peptic lesions, the course of ulcers and the relapse rate has not been influenced by the H_2-receptor antagonists.

The currently most potent molecule in the stemming of gastric acid is Omeprazol (Antra®). It specifically blocks the H^+/K^+ adenosinetriphosphatases (ATP) of the mucosa of the stomach and thus hinders acid secretion. A suspected disadvantage is that, under permanent hypergastrinemia during Omeprazol therapy, a hyperplasia of neuroendocrine cells occurs and can lead to carcinoid tumors. The high effectiveness compared to the H_2-receptor antagonists, however, led to shorter treatment times at lower dosage (20 mg/day). The relapse rate remained unchanged.

Marshall et al. only succeeded in 1983-1985 to prove the connection between the infection and gastritis through the rediscovery and ability to cultivate the germ Campylobacter pylori and through an oral infection in a self-test. This way the actual pathogenic factor of the ulcer was recognized. Initially, the germ was gained from biopsies of the antrum and corpus mucous membrane. *In vitro* cultivation did not succeed until later.

According to examinations conducted by C.S. Goodwin, in Perth, Australia, the spiral-shaped Campylobacter pylori has little in common with other

Campylobacter types (different fat composition, different enzyme metabolism, different genetic set-up). Therefore, it had to be renamed Helicobacter pylori (H.p.).

H.p. is a spiral bent gram-negative germ having rods with lophotric flagellate, so-called clusters. Culturing is successful from stomach biopsies (antrum) on accumulation and selective media under microaerobic conditions of 90% N_2, 5% CO_2, 5% 0_2 for 3-4 days.

Identification succeeds through additional proof of the enzymes oxidase, catalase, and urease. The germ is able to break down carbamide into ammonia in order to survive in an alkaline environment (cloud) in the acidic environment of the stomach.

H.p. only occurs in humans and is transmitted fecal-orally. The pathogen infects and settles in the mucosa of the stomach.

Helicobacter heilmanni, a variation of H.p., can be found in nearly all cats, dogs, and pigs. It can be passed on to humans. Infected people can develop disorders ranging from ulcers to stomach carcinomas.

Due to the flagellated clusters, H.p. is particularly mobile and excels through increased adherence to surface cells of the stomach epithelium. The mucous membrane is attacked by proteases of the germ. Vacuolizing cytokinin (VacA), which destroys the epithelium cells, is released.

With the ELISA test, H.p. IgG antibody levels can be proven over an extended period of time, even after the infection has subsided. This immune reaction leads in turn to tissue damage. After the infection, an acute B-gastritis type develops. When untreated, the gastritis becomes chronic, and duodenal and stomach ulcers occur.

This can then develop into an adenocarcinoma of the stomach. The World Health Organization (WHO) has included H.p. into Category 4 - Cancerogenes. The germ

is to be interpreted as a resistance-weakening factor, which promotes early digestion of the mucosa of the stomach through the hydrochloric-acidic proteolytically active gastric juice.

Modern ulcer therapy has two goals:

1. alleviation of pain; initially, the patient is interested in quick relief of the pain and less in fast healing, i.e. Helicobacter pylori eradication; and

2. prevention of complications and relapse rate.

After an H.p. infection has healed, reinfection is to be avoided. Flies, e.g., can take on H.p. bacteria and excrete them in a form that is capable of living in their excreta. Foods must be covered, and general hygienic conditions must be improved as an important preventive measure.

After proof has been secured of H.p. following gastroscopy and removal of the mucosa of the stomach from the antrum or corpus, eradication of the germ through antibiotics combination therapy is necessary. Serious H.p.-related forms of gastritis and underdevelopment should be treated in accordance with cancer prophylaxis - stomach carcinoma and lymphoma (MALT). However, treatment through combination therapy is very difficult. Due to a high relapse rate, mono- and dual-therapy is insufficient. For mono-therapy with bismuth compounds, and for dual-therapy with Amoxicillin and Omeprazol, the eradication rate is only between 35 and 60%.

Through the combination of bismuth, Amoxicillin and Metronidazole, healing was achieved for the first time in 85-95% of the cases after a 4-week treatment. The toxicity of this 3-fold combination or 'triple therapy', however, has not yet been clarified, especially when taking the long treatment time of 4 weeks into consideration.

Italian and French triple therapies have also been proposed. The triple therapy is a 7-day treatment with the proton pump inhibitor as well as two antibiotics:

Italian Triple Therapy: Clarithromycine and Metronidazole;

French Triple Therapy: Clarithromycine and Amoxicillin.

The medication must be taken twice daily each in standard dosages. This means that the patient must take 12 tablets a day. Also, there are side effects of the antibiotics, especially diarrhea, taste changes, etc. An antibiotics resistance development is also disadvantageous. H.p. resistance to Metronidazole and Amoxicillin has already been found.

The antimicrobial agents taurolidine and taurultam have been proposed for use against some microbial infections of the digestive or intestinal tract, in particular those involving such antibiotic resistant strains as VRE and MRSA - see e.g. Published PCT Application No. WO 99/34805. There still remains, however, an urgent need in the art for improved methods of treating gastrointestinal ulcers or gastritis caused by microbial infections, in which Helicobacter strains are implicated.

In one aspect the present invention provides the use of an antimicrobial medicament selected from taurolidine, taurultam or a combination thereof in the manufacture of a therapeutic agent for use in treating infectious gastrointestinal disease of microbially infected gastrointestinal tissue in a mammal caused by a microorganism selected from *Helicobacter pylori*, *Helicobacter heilmanni* or a combination thereof, preferably in a human.

In a further aspect the invention provides a method of treatment of infectious gastrointestinal disease in a mammal caused by infection of gastrointestinal tissue

with a microorganism selected from *Helicobacter pylori*, *Helicobacter heilmanni* or a combination thereof, said method comprising administering to said mammal an antimicrobial amount of an antimicrobial medicament selected from taurolidine, taurultam or a combination thereof, so as to contact said infected gastrointestinal tissue with said antimicrobial medicament and treat said disease in said mammal.

The invention also is applicable to compositions useful for treating infectious gastrointestinal ulcer disease and infectious gastritis disease.

In a yet further aspect the invention thus provides a pharmaceutical composition, particularly preferably a pharmaceutical composition for treating infectious gastrointestinal ulcer disease and infectious gastritis disease, said composition comprising an antimicrobial medicament selected from taurolidine, taurultam or a combination thereof, and a pharmaceutically acceptable proton pump inhibitor, optionally in combination with one or more pharmaceutically acceptable compounds selected from the group consisting of:

(a) a stomach-coating medication which forms a protective coating on a patient's stomach mucosa so as to prevent stomach irritation by said antimicrobial medicament; and

(b) a gastric acid-neutralizing stomach antacid.

The antimicrobial compounds utilized in accordance with the invention are cell wall constituent-inactivating by chemical reaction with cell wall constituents, endotoxin non-releasing, and/or exotoxin inactivating antimicrobial compounds, which typically are slow-acting bactericides. Preferably, the compounds are cell wall-crosslinking compounds such as Taurolidine and Taurultam. Taurolidine is a unique antimicrobial agent having an exceptionally broad spectrum of antimicrobial and antibacterial activity including

activity against gram positive and gram negative, aerobic, and anaerobic bacteria. Resistance has not been observed either *in vivo* or *in vitro*.

The compounds Taurolidine and Taurultam are as disclosed in U.S. Patent No. 5,210,083, incorporated herein by reference.

The antimicrobial compounds utilized in the present invention are distinguished from conventional antibiotics as ordinarily understood in the art, i.e., antibiotics that act by attacking, breaking and/or rupturing microbial cell walls (disturbance of murein-biosynthesis, protein-biosynthesis, DNA topology, etc.), resulting in release of microbial toxins from the microbial cells.

While the invention is further described with respect to Taurolidine and Taurultam, the invention also is applicable to use of other cell wall constituent-inactivating, antimicrobial compounds which release no or a substantially insignificant amount of toxins. Thus, the invention is applicable to Taurolidine, Taurultam, and antimicrobial medicaments which act in a substantially similar manner.

Due to the complete bactericidal effectiveness of Taurolidine for the destruction of fine cell wall structures, Taurolidine is particularly suitable for the eradication of H.p. Although not wishing to be bound by theory, adherence of the bacterium to the surface cells of the mucosa of the stomach is believed to be blocked so that the bacteria become apathogenic. Additionally, bacteria cell walls are believed to become net-like so that the release of endotoxins (Zytotoxin VacA) is prevented.

With its microaerobic conditions, Taurolidine is especially effective towards anaerobes and H.p. The minimal inhibitory concentration (MIC) is generally about 70-128 mg/l, the minimal bactericidal concentration (MBC) is generally about 400-600 mg/l.

Due to its chemical mechanism, the cell wall of the bacteria displays no resistance to Taurolidine, which is therefore particularly suitable for the antibacterial mono-therapy of an H.p. infection.

A slight temporary irritation or a burning of the stomach lining has become known as a side effect of Taurolidine or Taurultam. Through appropriate galenic formulation, such as the utilization of gel-forming agents which settle on the stomach mucosa and create a protective coating, the irritation can be suppressed almost completely.

In another aspect the invention thus provides the use of an antimicrobial medicament selected from the group consisting of taurolidine, taurultam and a combination thereof, in the manufacture of a therapeutic agent for use in treating infectious gastrointestinal disease of microbially infected gastrointestinal tissue in a mammal caused by a microorganism selected from *Helicobacter pylori*, *Helicobacter heilmanni* or a combination thereof, wherein said medicament is administered in combination with a pharmaceutically acceptable, stomach-coating medication which forms a protective coating on a patient's stomach mucosa so as to prevent stomach irritation by said antimicrobial medicament.

Without being exhaustive, suitable gel-forming agents include: polysaccharides with antiphlogistic properties, protective colloids or polymers such as PVP, methylcellulose, carboxylmethylcellulose, methylhydroxypropylcellulose, gelatin, micro-crystalline collagen fibers, micro-crystalline cellulose, xanthan gum, tragacanth, dextrin, Macrogol 6000, glycogen, micro-crystalline rice starch, absorbent silicate, highly dispersed silicic acid, etc.

Micro-encapsulated compounds, which slowly release the active ingredient in the stomach without irritating the stomach lining, can also be produced. Dosages

containing about 200-1,000 mg Taurolidine are possible, with about 300-500 mg Taurolidine being preferred. This makes it possible to get by with 1-2 tablets, coated tablets, dragees or capsules per day for 5 days to eradicate H.p. It is also possible to apply suspensions or syrup with a dosage of about 5 ml twice daily. 5 ml syrup typically contains 300 mg Taurolidine as the active ingredient.

Another preferred combination is the application of Taurolidine together with an antacid in order to neutralize gastric acid and thus obtain faster pain alleviation.

In a yet further aspect the invention thus provides the use of an antimicrobial medicament selected from the group consisting of taurolidine, taurultam and a combination thereof, in the manufacture of a therapeutic agent for use in treating infectious gastrointestinal disease of microbially infected gastrointestinal tissue in a mammal caused by a microorganism selected from *Helicobacter pylori*, *Helicobacter heilmanni* or a combination thereof, wherein said medicament is administered in combination with a pharmaceutically acceptable gastric acid-neutralizing stomach antacid.

Particularly preferred pharmaceutical compositions for use in accordance with the invention include those comprising an antimicrobial medicament selected from the group consisting of Taurolidine, Taurultam and a combination thereof, said composition further comprising a pharmaceutically acceptable, stomach-coating medication which forms a protective coating on a patient's stomach mucosa so as to prevent stomach irritation by said antimicrobial medicament, together with a pharmaceutically acceptable gastric acid-neutralizing stomach antacid.

The following compounds or combinations can be combined with the active ingredient Taurolidine: sodiumhydrogencarbonate, hydrotalcite, aluminum-

magnesium-hydroxide-carbonate-hydrate, calcium carbonate, magnesium trisilicate, aluminium-magnesium-hydroxide-sulfate-hydrate (Magaldrate), aluminium-magnesium-silicatehydrate, alkaline magnesium carbonate, calcium carbonate, etc.

AMENDED SHEET

In general, the antacid is added to the tablet mixture or the granules to fill hard gelatin capsules. It can also be advantageous to add dry extracts out of licorice roots with a high content of glyceric acid, chamomile blossom dry extract, peppermint dry extract or other dry plant extracts such as yarrow milfoil, balm, salvia officinalis (sage), foeniculum vulgare (fennel) that are used for gastritis treatment, to the Taurolidine or Taurultam compound at a dosage of about 200 mg.

For increased efficacy of Taurolidine as well as prolongation of contact time on the mucosa of the stomach it is advantageous to use Taurolidine in micro-crystalline form. Preferred embodiments include formulations with high bioadhesion on mucous cells. The galenic form of preferred embodiments is an oral suspension with the addition of antacids such as Malgaldrate USP XXIII, with added stabilizers, and polymers with bioadhesive properties such as Carbopol™ resins of BF Goodrich.

In preferred embodiments, disintegration of the tablets in the stomach is swift, preferably into an amorphous to microcrystalline powder.

Substances with high mucous affinity and adhesion are the Carbopol™ types 934P and 971P. In addition to synthetic products, suitable additives include natural polymers and phytogums, such as gum arabic, xanthan gum, pectin, agar, calcium alginate, etc.

Suitable tablet disintegrants with high mucuous tolerability include natural and semi-synthetic cellulose and starch products, such as microcrystalline cellulose, rice starch, carboxymethyl cellulose and hydroxyethyl cellulose.

The addition of milk powder or blood serum in some cases may be advantageous.

A further preferred combination is Taurolidine in combination with a proton pump inhibitor (PPI) such as

Omeprazol, Rabeprazol or the like.

In a yet still further aspect the invention thus provides a pharmaceutical composition, particularly preferably a pharmaceutical composition for treatment of infectious gastrointestinal ulcer disease or infectious gastritis disease, said composition comprising an antimicrobial amount of an antimicrobial medicament selected from the group consisting of Taurolidine, Taurultam and a combination thereof, together with a pharmaceutically acceptable proton pump inhibitor.

PPI's typically are prodrugs which are metabolized at a certain pH. Omeprazol metabolizes at a pH of about 3.9-4.1, whereas Rabeprazol metabolizes at a pH of about 4.9. Since Taurolidine is less irritating to the stomach at a pH of about 5, Rabeprazol is preferred when combined therewith. In particularly preferred embodiments, the sodium salt of Rabeprazol is utilized, with preferred dosages of Rabeprazol-Na of 10mg or 20mg in the combination.

The invention is further illustrated by way of the following non-limiting Examples:

Example 1 - Hard Gelatin Capsules

CAPSUGEL, transparent, size 0 elongated

Contents:	300 mg	Taurolidine (micro-crystalline) or Taurultam
	6 mg	Talc, Aerosil 200*, Mg-stearates 8:1:1 (additive)
	100 mg	Micro-crystalline rice starch

CAPSUGEL, transparent, size 0

Contents:	300 mg	Taurolidine or Taurultam
	6 mg	Talc, Aerosil 200*, Mg-stearates 8:1:1 (additive)
	10 mg	Omeprazol, micro-encapsulated, gastric juice-neutral

*Aerosil 200 = Colloidal Silicone

Example 2 - Tablets or Coated Tablets (direct tablet dispensing)

Contents:	300 mg	Taurolidine or Taurultam
	200 mg	Emdex™*
	10 mg	Magnesium stearates
	167 mg	Ranitidine-HCl
	5-10 mg	Disintegrant for tablets**

Contents:	300 mg	Taurolidine or Taurultam
	500 mg	Aluminium-magnesium-silicate-hydrate Aromatic substances and Saccharose
	5-10 mg	Disintegrant for tablets**

Contents:	250 mg	Taurolidine or Taurultam
	500 mg	Calcium Carbonate
	10 mg	Magnesium stearates
	60 mg	Rice or corn starch
	5-10 mg	Disintegrant for tablets**

Contents:	200 mg	Taurolidine
	200 mg	Emdex™
	10 mg	Magnesium stearates
	10 mg	Crospovidone USP 23/NF 18
	200 mg	fine dry powder of plants (33% yarrow milfoil herbal, 33% Camomilla flower, 33% Melissa

foliate)

Example 3 - Taurolidine Tablets (Granule Production with subsequent dispensing)

Contents:	350 mg	Taurolidine
	150 mg	Aluminiumhydroxide-magnesium carbonate complex
	80 mg	Corn starch
	45 mg	Kollidon 25
	5 mg	Aerosil 200***
	40 mg	Potato starch
	15 mg	Talcum siliconesatum 10%
	15 mg	Slip additives (Talc, Aerosil 200***, Mg-stearates 8:1:1 (additive)
		Aroma: strawberry, cocoa, saccharine
	370 mg	Alcohol 96%

* Dextrates (Mendell Carmel, New York, U.S.A.)

** For example: Sodium carboxymethylstarch, Carboxymethylcellulose or Crospovidone

*** Aerosil 200 = Colloidal Silicone Dioxide

Production of the Granulates

1. Corn starch and Taurolidine are pre-mixed together with saccharine.
2. Kollidon 25 is dissolved in alcohol.
3. Aluminiumhydroxide-magnesiumcarbonate complex, pre-blended (see under 1.) as well as the remaining components, such as Aerosil 200, are mixed together in a blunger. The alcohol-damp mass is dried in a vacuum dryer at 30°C, and finally pressed through a 4 mm strainer, then a 2 mm strainer and thus refined into granules.

The dry granules obtained this way are finally mixed

well with the potato starch, the slip additive, the talcum siliconesatum 10% and pressed into 700 mg tablets with a 13 mm stamp.

Example 4 - Syrup

Contents: 100 ml syrup contains:

6,000 mg	Taurolidine micr. or Taurultam
680 mg	Xanthan gum
680 mg	Carboxylmethylcellulose
20,000 mg	Saccharine Ph. Eur. 3 crystalline
	Vanilla, Aroma, Distilled Water
	100ml

Per dose, 5 ml syrup (300 mg Taurolidine/Taurultam) is taken twice daily.

Example 5 - Taurolidine Tablets 200 mg

Aluminium Hydroxide Magnesium Carbonate FMA-11 H.D.

1. Composition:

Substance	**mg/Tablet**
Taurolidine	200
Emdex™	90
Starch 1500	90
Aluminium Hydroxide Magnesium Carbonate FMA-11 H.D.	50
Talc	16
Mg-Stearate	3
Aerosil 200	1
Tablet weight	450

Example 6 - Taurolidine Tablets 300 mg

Aluminium Hydroxide Magnesium Carbonate FMA-11 H.D.

1. Composition:

Substance	mg/Tablet
Taurolidine	300
Emdex™	135
Starch 1500	135
Aluminium Hydroxide Magnesium Carbonate FMA-11 H.D.	75
Talc	24
Mg-Stearate	4.5
Aerosil 200	1.5
Tablet weight	675

Claims:

1. Use of an antimicrobial medicament selected from taurolidine, taurultam or a combination thereof in the manufacture of a therapeutic agent for use in treating infectious gastrointestinal disease of microbially infected gastrointestinal tissue in a mammal caused by a microorganism selected from *Helicobacter pylori*, *Helicobacter heilmanni* or a combination thereof.

2. Use as claimed in claim 1 wherein said antimicrobial medicament is administered in the form of a tablet, capsule, liquid, suspension or syrup.

3. Use as claimed in claim 1 or claim 2 wherein said antimicrobial medicament is administered at a dosage equivalent to from 200-1,000 mg taurolidine.

4. Use as claimed in claim 3 wherein said antimicrobial compound is administered at a dosage equivalent to from 300-500 mg taurolidine.

5. Use as claimed in any preceding claim wherein said antimicrobial medicament is administered in combination with a pharmaceutically acceptable stomach-coating medication which forms a protective coating on a patient's stomach mucosa so as to prevent stomach irritation by said antimicrobial medicament.

6. Use as claimed in any preceding claim wherein said antimicrobial medicament is administered in combination with a pharmaceutically acceptable gastric acid-neutralizing stomach antacid.

7. Use as claimed in any preceding claim wherein said antimicrobial medicament is administered in combination with a proton pump inhibitor.

8. Use as claimed in claim 7 wherein said proton pump inhibitor is Omeprazol or Rabeprazol.

9. Use as claimed in claim 8 wherein said proton pump inhibitor is Rabeprazol.

10. A pharmaceutical composition comprising an antimicrobial medicament selected from taurolidine, taurultam or a combination thereof, and a pharmaceutically acceptable proton pump inhibitor, optionally in combination with one or more pharmaceutically acceptable compounds selected from the group consisting of:

(a) a stomach-coating medication which forms a protective coating on a patient's stomach mucosa so as to prevent stomach irritation by said antimicrobial medicament; and

(b) a gastric acid-neutralizing stomach antacid.

11. A pharmaceutical composition as claimed in claim 10 wherein said proton pump inhibitor is Omeprazol or Rabeprazol.

12. A pharmaceutical composition as claimed in claim 11 wherein said proton pump inhibitor is Rabeprazol.

13. A method of treatment of infectious gastrointestinal disease in a mammal caused by infection of gastrointestinal tissue with a microorganism selected from *Helicobacter pylori*, *Helicobacter heilmanni* or a combination thereof, said method comprising administering to said mammal an antimicrobial amount of an antimicrobial medicament selected from taurolidine, taurultam or a combination thereof, so as to contact said infected gastrointestinal tissue with said antimicrobial medicament and treat said disease in said mammal.

14. Pharmaceutical products containing an antimicrobial medicament selected from taurolidine, taurultam or a combination thereof, and separately one or more pharmaceutically acceptable compounds selected from the group consisting of:

(a) a stomach-coating medication which forms a protective coating on a patient's stomach mucosa so as to prevent stomach irritation by said antimicrobial medicament;

(b) a gastric acid-neutralizing stomach antacid; and

(c) a proton pump inhibitor;

as a combined preparation for simultaneous, separate or sequential use, preferably in a method of treatment of an infectious gastrointestinal ulcer disease or infectious gastritis disease, wherein said pharmaceutical products each comprise at least one pharmaceutically acceptable proton pump inhibitor.