Description

The present invention relates to pharmaceutical compositions useful for treating or preventing gastrointestinal disorders. These compositions comprise a bismuth-containing agent and a histamine-2 receptor blocking anti-secretory agent. The present invention further relates to the use of these compositions for treating or preventing gastrointestinal disorders in humans or lower animals by administering a bismuth-containing agent and a histamine-2 receptor blocking anti-secretory agent. This use may involve either concurrent or non-concurrent administration of the bismuth-containing agent and the histamine-2 receptor blocking anti-secretory agent. This use may involve either concurrent or non-current administration of the campylobacter-inhibiting antimicrobial agent and the histamine-2 receptor blocking anti-secretory agent.

Factors adversely affecting the function of the gastrointestinal system in humans are exceedingly varied in their nature. Such disorders may arise in the upper or lower gastrointestinal tracts or both. There is a broad range of causes of gastrointestinal disorders, including genetic, physiological, environmental, and psychogenic factors. Accordingly, the diagnosis and management of these disorders can be exceptionally difficult. A detailed discussion of gastrointestinal tract functions, disorders, causes, and treatments can be found in Sprio, Clinical Gastroenterology (3d. edition 1983).

Among the chronic disorders of the upper gastrointestinal tract are those which fall under the general categories of gastritis and peptic ulcer disease. Gastritis is, by definition, typified by an inflammation of the stomach mucosa. In practice, though, the disorder is manifested by a broad range of poorly-defined, and heretofore inadequately treated, symptoms such as indigestion, "hear burn", dyspepsia and excessive eructation. A general discussion of gastritis appears in B. J. Marshall and J. R. Warren, "Unidentified Curved Bacilli in the Stomach of Patients with Gastritis and Peptic Ulceration", The Lancet, (1984), pp. 1311-1315, and in R. Greenlaw, et al., "Gastroduodenitis, A Broader Concept of Peptic Ulcer Disease", Digestive Diseases and Sciences, Vol. 25 (1980), pp. 660-672.

Peptic ulcers and lesions of the gastrointestinal tract lining, characterized by loss of tissue due to the action of digestive acids and pepsin. It has been generally held that peptic ulcers are caused either by gastric hypersecretion, or (more often) by decreased resistance of the gastric lining to digestive acids and pepsin. The medical literature is replete with methods for treating ulcers, including modification of the diet, surgical removal of the lesions, and the use of drugs. Such drugs include: antacids, which serve to counteract excess gastric secretions; anticholinergics, which reduce acid secretion; H_2 antagonists, which also block the release of gastric acids; prostaglandins, which increase the resistance of the gastric lining to digestive fluids, and may also inhibit acid secretion; prokinetic agents, which enhance gastrointestinal tract motility; and compositions which form protective barriers over gastric lesions. Prescription and non-prescription drug therapies are generally described in Garnet, "Antacid Products", Handbook of Non-prescription Drugs, 7th edition (1982), Chapter 3.

Regardless of the particular drug composition used in treating gastrointestinal disorders, such as gastritis or peptic ulcer disease, the treatment is often inprecise and incomplete. Actual "cures", i.e., successful treatment resulting in total remission of disease, are very often not effected. See A. J. McLean, et al., "Cyto-protective Agents and Ulcer Relapse", 142 The Medical Journal of Australia, Special Supplement S25-S28 (1985). Furthermore, many conventional treatments may render subject hypochlorhydric (i.e., with low levels of hydrochloric acid in the stomach) which may predispose them to other disorders, e.g., gastrointestinal infection, halitosis, and gastric carcinomas.

The treatment and prophylaxis of gastrointestinal disorders with bismuth-containing agents is well-known in the art. For example, bismuth subsalicylate (the active ingredient in Pepto-Bismol®, sold by The Procter & Gamble Company) has demonstrated utility for protecting against ulcer formation (Gastroenterology, 69, pp. 636-640 (1975)). Also, bismuth subcitrate (the active ingredient in DeNol®, sold by Gist-Brocades, N.V.) has been reported to be effective for treating ulcers (Gut, 21, pp. 329-333 (1980)). In addition, bismuth subcitrate (Aust. and N.Z. J. of Medicine, 14, p. 907 (1984)) and bismuth subsalicylate (Gastroenterology, 90, p. 1547 (1986)) have been used to treat gastritis in patients having Campylobacter pyloridis infection.

The treatment of gastrointestinal disorders with histamine-2 (hereinafter "H_2") receptor blocking anti-secretory agents is also well-known in the art. For example, cimetidine (marketed under the tradename Tagamet®; Smith Kline & French Laboratories, Philadelphia, PA.) is a H_2 receptor block anti-secretory agent widely used in the treatment of gastric ulcers. This compound, as well as others of this type, are thought to act by blocking the histamine receptors within the stomach mucosa (labeled H_2 receptors, to distinguish from those histamine receptors generally associated with allergic response) thereby preventing histamine molecules from signaling the stomach cells to secrete acid. H_2 receptor blocking agents which are either more potent and/or longer acting than cimetidine (e.g., ranitidine) are also well-known. (See C&E News,

April 12, 1982, pp. 24-26). However, while H_2 receptor blocking anti-secretory agents have demonstrated effectiveness in treating gastrointestinal disorders and therefore are widely prescribed for this purpose, their utility is questioned in light of the poor long-term outcomes associated with their use (e.g., high relapse rate associated with cimetidine treatment of gastric ulcers; see The Lancet, September 1, 1984, pp. 525-526).

Recent research has noted an association between gastritis, peptic ulceration, and the presence of Campylobacter pyloridis and campylobacter-like organisims (The Lancet, June 16, 1984, pages 1311-1315). This has led to speculation that the high relapse rate observed when treating ulcers with cimetidine is the result of cimetidine allowing healing but adversely affecting the subsequent ability of the gastrointestinal tract to resist ulcerogenic activity of a pathogenic agent (The Lancet, September 1, 1984, pages 525-526). However, subsequent research indicates that cimetidine inhibits Campylobacter pyloridis growth at low concentrations (Z. Antimikrob. Antineoplast. Chemother., 4 (2), pages 45-49 (1986); J. Antimicrob. Chemother., 17 (3), pages 309-314 (1986)). Furthermore, preliminary findings support the concept that campylobacter-like organisms are not important in the etiology of duodenal ulcer disease (Gastroenterology, 88 (5 part 2), p. 1462 (1985)). Thus, it is currently not clear whether the high relapse rate associated with cimetidine treatment is, in fact, due to an adverse affect on the ability of the gastrointestinal tract to resist pathogenic agents.

Clearly, there remains a continuing need to identify new compositions which are effective for treating and preventing gastrointestinal disorders. The present invention provides such novel pharmaceutical compositions, comprising bismuth-containing agents and H_2 receptor blocking anti-secretory agents, useful for treating and preventing gastrointestinal disorders.

While, as noted hereinbefore, H_2 receptor blocking anti-secretory agents and bismuth-containing agents are individually known for treating and/or preventing gastrointestinal disorders, conventional wisdom regarding their use would mandate that these agents are not compatible for co-administration as taught by the present invention. This is because current understanding of the mode of action of bismuth-containing agents links the activity of these agents to the ability of the bismuth to precipitate onto the gastrointestinal walls in the low pH (i.e., acidic) environment of the gastrointestinal tract. H_2 receptor blocking anti-secretory agents, which are known to neutralize the pH of the gastrointestinal tract, are therefore viewed as counterproductive to effective utilization of bismuth-containing agents. However, contrary to conventional teaching, the unconventional compositions and methods of the present invention combine these two agents into compositions and methods which are effective for treating and preventing gastrointestinal disorders.

It is therefore an object of the present invention to provide novel pharmaceutical compositions comprising bismuth-containing agents and H_2 receptor blocking anti-secretory agents. It is a further object to provide improved methods for treating or preventing gastrointestinal disorders in humans or lower animals. An additional object is to provide compositions and methods which have improved ability to treat and prevent gastritis and gastrointestinal ulcers, and to improve the long-term outcomes of ulcer treatments. Finally, an object of the present invention is to reduce the incidence of gastritis following ulcer treatment with H_2 receptor blocking anti-secretory agents and/or reduce the ulcer relapse rate observed following ulcer treatment with H_2 receptor blocking anti-secretory agents.

These and other objects will become readily apparent from the detailed description which follows.

The present invention relates to pharmaceutical compositions useful for treating or preventing gastrointestinal disorders. These compositions comprise a bismuth-containing agent, especially a bismuth-containing agent effective for inhibiting campylobacter-like organisims (e.g. bismuth subsalicylate; bismuth subcitrate), and a H_2 receptor blocking anti-secretory agent (e.g., cimetidine; ranitidine).

The present invention further relates to the use of these compositions for the manufacture of a medicament for treating or preventing gastrointestinal disorders in humans or lower animals, said treatment comprising administering to a human or lower animal in need of such treatment or prevention a safe and effective amount of a bismuth-containing agent and a safe and effective amount of a H_2 receptor blocking anti-secretory agent.

The pharmaceutical compositions of the present invention essentially comprise a bismuth-containing agent, preferably in the form of a pharmaceutically-acceptable salt. Such bismuth-containing agents include, for example, bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, bismuth citrate, tripotassium dicitrato bismuthate, bismuth subgalate, bismuth subnitrate, bismuth tartrate, bismuth subsalicylate, and mixtures thereof. Bismuth citrate, bismuth subcitrate, tripotassium dicitrato bismuthate, bismuth tartrate, bismuth subsalicylate, and mixtures thereof are preferred bismuth salts for use in this invention. More preferred are bismuth subcitrate and bismuth subsalicylate, with bismuth subsalicylate most preferred.

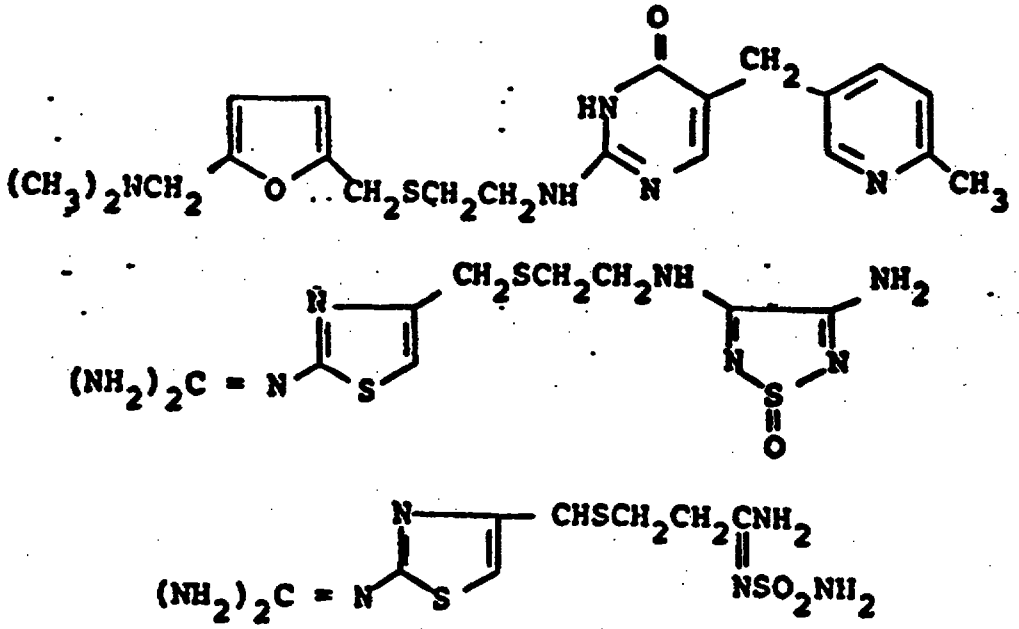
These agents are well known in the art, and are commercially-available. Their formulation and use in commercial compositions are also well-known, being sold, for example, as DeNol^R (bismuth subcitrate; sold by Gist-Brocades, N.V.), Noralac^R (containing bismuth aluminate, alginic acid, and magnesium carbonate;

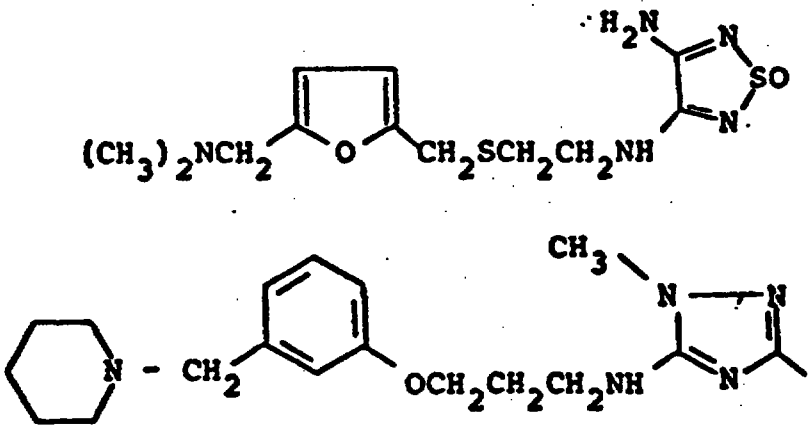
manufactured by North American Pharmaceuticals), Roter bismuth^{R} (containing bismuth subnitrate; sold by Roter Laboratories), Fensobar Polvo^{R} (containing bismuth subcarbonate among other materials; manufactured by USV Pharmaceutical Corporation), and Pepto-Bismol^{R} (containing bismuth subsalicylate; sold by The Procter & Gamble Company).

Especially preferred for use herein are campylobacter-inhibiting bismuth-containing agents. The term "campylobacter-inhibiting bismuth-containing agents", as used herein, means any naturally-occuring, synthetic or semi-synthetic bismuth-containing compound or composition, or mixture thereof, which is safe for human use as used in the compositions and methods of the present invention, and is effective in killing or substantially inhibiting the growth of campylobacter-like organisms, e.g., Campylobacter pyloridis, when used in the compositions and methods of this invention. Such campylobacter-like organisms include those described in J. R. Warren and B. J. Marshall, "Unidentified Curved Bacilli on Gastric Epithelium in Active Chronic Gastritis", The Lancet, pp. 1273-1275 (1983), and G. Kasper and N. Dickgiesser, "Isolation from Gastric Epithelium of Campylobacter-like Bacteria that are Distinct from 'Campylobacter pyloridis'", The Lancet, pp. 111-112 (1985). The effectiveness of bismuth-containing agents to kill or substantially inhibit the growth of campylobacter-like organisms may be demonstrated using the various in vitro or in vivo assays known to those skilled in the art. For example, the effectiveness of the preferred subcitrate and bismuth subsalicylate for inhibiting campylobacter-like organisms are discussed in Hislop et al., "Histological Improvement of Active Chronic Gastritis in Patients Treated with De-Nol^{R}", Aust. and N.Z. J. of Medicine, 14, p. 907 (1984); and McNulty et al., "Successful Therapy of Campylobacter Pyloroids", Gastroenterology, 90, p. 1547 (1986).

The pharmaceutical compositions of the present invention typically comprise, by weight, from 0.1% to 99.8% of the bismuth-containing agent, preferably from 0.1% to 75%, and most preferably from 1% to 50%.

In addition to the bismuth-containing agent described hereinbefore, the pharmaceutical compositions of the present invention also comprise an H_2 receptor blocking anti-secretory agent. The H_2 receptor blocking anti-secretory agents useful in the present invention include cimetidine, ranitidine, burimamide, metiamide, tiotidine, and oxmetidine, as well as compounds of the formula:





The above structures are well-known in the art (see C&E News, April 12, 1982, pp 24-26. Mixtures of the above H_2 receptor blocking anti-secretory agents may also be employed. The most preferred of these compounds are cimetidine, ranitidine, and mixtures thereof, with cimetidine being especially preferred.

The preparation and use of H_2 receptor blocking anti-secretory agents as described hereinbefore are well-known in the art. For example, the preparation and use of cimetidine are discussed in U.S. Patent 3,950,333, to Durant et al., issued April 13, 1976; Brimblecombe, et al., J. Int. Med. Res., 3, 86 (1975); Brimblecombe, et al., Brit. J. Pharmacol., 53, 435 (1975); and Brogden, et al., Drugs, 15, 93-131 (1978). Also, for example, the preparation and use of ranitidine are discussed in U.S. Patent 4,128,658, to Price et al., issued December 5, 1978; Bradshaw et al., Brit. J. Pharmacol., 66, 464 (1979); Daly, et al., Gut, 21, 408 (1980); Berstad, et al., Scand. J. Gastroenterol., 15, 637 (1980) and Walt, et al., Gut, 22, 49 (1981).

The pharmaceutical compositions of the present invention typically comprise, by weight, from 0.1% to 99.8% of the H_2 receptor blocking anti-secretory agent, preferably from 0.1% to 75%, and most preferably from 1% to 50%.

In addition to the bismuth-containing agent and the H_2 receptor blocking anti-secretory agent as described hereinbefore, the pharmaceutical compositions of the present invention also essentially contain a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a human or lower animal. The term "compatible", as used herein, means that the components of the pharmaceutical composition are capable of being commingled with the bismuth-containing agent and the H_2 receptor blocking anti-secretory agent, and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the pharmaceutical composition under ordinary use situations. Pharmaceutically-acceptable carriers must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the human or lower animal being treated.

A variety of pharmaceutically-acceptable carriers may be included, depending on the particular dosage form to be used. Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated or multiple compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring, and flavoring agents. Liquid oral composition typically comprise water and suspending agents, such as magnesium aluminum silicate (e.g., Veegum, manufactured by R. T. Vanderbilt Company, Inc.), as part of the pharmaceutically-acceptable carrier.

Some examples of substances which can serve as pharmaceutically-acceptably carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethylcellulose, ethylcellulose, cellulose acetate; powdered tragacanth; malt; gelatin; talc; stearic acid; magnesium stearate; calcium sulfate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; agar; alginic acid; pyrogen-free water; isotonic saline; and phosphate buffer solutions, as well as other non-toxic compatible substances used in pharmaceutical formulations. Wetting agents and lubricants such as sodium lauryl sulfate, as well as coloring agents,

flavoring agents, excipients, tableting agents, stabilizers, anti-oxidants, and preservatives can also be present. Other compatible pharmaceutical additives and actives (e.g., NSAI drugs; pain killers; muscle relaxants) may be included in the pharmaceutically-acceptable carrier for use in the compositions of the present invention.

Specific examples of pharmaceutically-acceptable carriers that may be used to formulate oral dosage forms of the present invention are described in U.S. Patent 3,903,297, Robert, issued September 2, 1975. Techniques and compositions for making dosage forms useful herein are described in the following references: 7 Modern Pharmaceuticals, Chapters 9 and 10 (Banker and Rhodes, Ed., 1979); Lieberman, et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms (2nd Edition, 1976).

The choice of a pharmaceutically-acceptable carrier to be used in conjunction with the bismuth-containing agent and H_2 receptor blocking anti-secretory agent combination of the present invention is basically determined by the way the composition is to be administered. The preferred mode of administering the compositions of the present invention is orally. The preferred unit dosage form is therefore tablets or capsules, comprising a safe and effective amount of the bismuth-containing agent and the H_2 receptor blocking anti-secretory agent combination of the present invention. Pharmaceutically-acceptable carriers suitable for the preparation of unit dosage forms for oral administration are well known in the art. Their selection will depend on secondary considerations like taste, cost, shelf stability, which are not critical for the purposes of the present invention, and can be made without difficulty by a person skilled in the art.

The pharmaceutically-acceptable carrier employed in conjunction with the bismuth-containing agent and the H_2 receptor blocking anti-secretory agent combination of the present invention is used at a concentration sufficient to provide a practical size to dosage relationship. The pharmaceutically-acceptable carriers, in total, may comprise from 0.1% to 99.8%, by weight, of the pharmaceutical compositions of the present invention, preferably from 25% to 99.8%, and most preferably from 50% to 99%.

Another aspect of the present invention is the use of a bismuth-containing agent and a H_2 receptor blocking antisecretory agent for the manufacture of a medicament for treating or preventing gastrointestinal disorders, said treatment comprising administering, to a human or lower animal in need of such treatment or prevention, a safe and effective amount of a bismuth-containing agent and safe and effective amount of a H_2 receptor blocking anti-secretory agent.

The term "administering", as used herein, refers to any method which, in sound medical practice, delivers the bismuth-containing agent and the H_2 receptor blocking anti-secretory agent to the subject to be treated in such a manner so as to be effective in the treatment of the gastrointestinal disorder. Preferably, both these agents are administered orally.

The term "gastrointestinal disorder", as used herein, encompasses any disease or other disorder of the upper gastrointestinal tract of a human or lower animal. The term "upper gastrointestinal tract", as used herein, is defined to include the esophagus, the stomach, the duodenum, and the jejunum. Such gastrointestinal disorders include, for example: disorders not manifested by presence of ulcerations in the gastric mucosa (herein "non-ulcerative gastrointestinal disorders"), including chronic or atrophic gastritis, non-ulcer dyspepsia, esophageal reflux disease and gastric motility disorders; and "peptic ulcer disease", i.e., gastric, duodenal and jejunal ulcers. Gastrointestinal disorders especially refers to such disorders of the upper gastrointestinal tract which are conventionally treated with H_2 receptor blocking anti-secretory agents alone.

The phrase "safe and effective amount", as used herein, means an amount of a bismuth-containing agent or H_2 receptor blocking anti-secretory agent, when used in combination with each other according to the compositions and methods of the present invention, high enough to significantly positively modify the condition to be treated but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. The safe and effective amount of the agents of the present invention will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of treatment, the nature of concurrent therapy, the specific agents employed, the particular pharmaceutically-acceptable carrier utilized, and like factors within the knowledge and expertise of the attending physician.

The methods of the present invention typically involve administering the bismuth-containing agent in an amount of from 50 mg to 5000 mg of bismuth per day. (As used herein, the quantity of the bismuth-containing agents to be administered is indicated by the weight of elemental bismuth present in the dose of the bismuth-containing agent. Thus, the actual weight of a dose of a bismuth-containing agent will be greater than the amount of bismuth indicated.) Preferably, from 500 mg to 1500 mg of bismuth are administered per day. Most preferably, the bismuth-containing agent is bismuth subcitrate and, especially, bismuth subsalicylate.

The method of the present invention typically involves administering the H_2 receptor blocking anti-secretory agent in an amount of from 1 mg to 10 g per day. Preferably from 50 mg to 5000 mg, more preferably from 100 mg to 1500 mg, most preferably from 400 mg to 1200 mg, of cimetidine is administered per day.

The methods of the present invention comprise administering the bismuth-containing agent and the H_2 receptor blocking anti-secretory agent either concurrently or non-concurrently. The term "concurrently", as used herein, 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 4 minutes of each other; and includes co-administration of the agents by administering a composition of the present invention. The term "non-concurrently", as used herein, means that the two agents are administered more than 24 hours apart.

The methods of the present invention in which the agents are administered concurrently comprise any dosing regimen in which part or all of the dosing of the agents is preformed concurrently. Thus, for example, methods comprising concurrent dosing of the agents include:

1. 14 days of administration of a pharmaceutical composition of the present invention.
2. 21 days of a regimen wherein the bismuth-containing agent is administered in the morning and the H_2 receptor blocking anti-secretory agent is administered at night (approximately 12 hours apart).
3. 28 days of administration of the bismuth-containing agent and the H_2 receptor blocking anti-secretory agent essentially simultaneously (i.e., within about 5 minutes of each other), followed by 7 days of treatment with only the bismuth-containing agent.
4. 3 days of administration of only the bismuth-containing agent, followed by 21 days of administration of the bismuth-containing agent and the H_2 receptor blocking anti-secretory agent essentially simultaneously (i.e., within about 5 minutes of each other).

The methods of the present invention in which the agents are administered non-concurrently comprise any dosing regimen in which none of the dosing of the agents is performed concurrently. Thus, for example, methods comprising non-concurrent dosing of the agents include:

1. 28 days of alternating daily dosing of the bismuth-containing agent and the H_2 receptor blocking anti-secretory agent, starting with the H_2 receptor blocking anti-secretory agent and ending with the bismuth-containing agent.
2. 14 days of administration of the H_2 receptor blocking anti-secretory agent followed by 14 days of administration of the bismuth-containing agent.
3. 7 days of administration of the bismuth-containing agent, followed by 14 days of administration of the H_2 receptor blocking anti-secretory agent.

For the methods of the present invention, the duration of administration of the agents during either concurrent or non-concurrent dosing of the agents will vary according to the specific gastrointestinal disorder being treated, but typically is within the range of from 1 to 60 days. In general, however, in methods for treatment of non-ulcerative gastrointestinal disorders the duration of treatment comprises administering the agents for from 3 to 21 days. In methods for treatment of peptic ulcer disease, the duration of treatment comprises administering the agents for from 14 to 56 days. If the compositions of the present application are administered, similar durations are utilized depending on the gastrointestinal disorder to be treated.

The following examples further describe and demonstrate the preferred embodiments within the scope of the present invention.

Example I

Pharmaceutical Compositions in Tablet Form

Tablets are prepared by conventional methods, such as mixing and direct compaction, formulated as follows:

Ingredients	Mg per Tablet
Bismuth subsalicylate	300 of bismuth
Cimetidine	300
Microcrystalline cellulose	100
Sodium starch glycolate	30
Magnesium stearate	3

When one tablet is administered orally 4 times per day for 14 days, the above compositions significantly improve the condition of a patient suffering from gastritis. A significant long-lasting benefit is also acheived by daily administration for 28 days (4 tablets per day) of this composition to a patient suffering from gastric ulcers.

Similar results are achieved with tablets formulated as above but replacing the bismuth subsalicylate with bismuth subcitrate, bismuth citrate, tripotassium dicitrato bismuthate, bismuth tartrate, or a mixture of bismuth subsalicylate and bismuth subcitrate. Similar results are also achieved with tablets formulated as above but replacing the cimetidine with ranitidine, or a mixture of cimetidine and ranitidine.

Example II

Pharmaceutical Compositions in Capsule Form

Capsules are prepared by conventional methods, comprised as follows:

Ingredients	Mg/Capsule
Bismuth subcitrate	300 of bismuth
Cimetidine	300
Lactose	To fill to volume of capsule

One of the above capsules administered orally 4 times a day for 21 days substantially reduces the symptomology of a patient afflicted with a gastric ulcer. Similar results are obtained with capsules formulated above but replacing the bismuth subcitrate with subsalicylate; or by replacing the cimetidine with ranitidine.

Example III

Pharmaceutical Compositions in Liquid Form

A composition, according to the present invention, is made comprising:

Component	% (by Weight)
bismuth subsalicylate	1.7500
cimetidine	1.0000
magnesium aluminum silicate[1]	0.9850
methyl cellulose	1.0790
FD&C Red 3 dye	0.0104
FD&C Red 40 dye	0.0054
salicylic acid	0.0706
sodium salicylate	0.0598
flavorant	0.0881
sodium saccharin	0.0608
water	Balance

1) Veegum® manufactured by R. T. Vanderbilt Company, Inc.

A batch composition, comprised as above, is made by first mixing the Veegum in a quantity of water, followed by addition of the methyl cellulose. The suspension system is then mixed for approximately 30 minutes. The bismuth subsalicylate and cimetidine are added, as a slurry or approximately 9% in water, and mixed for approximately 25 minutes. The FD&C Red 3 dye is then added, and the product mixed for approximately 10 minutes. The FD&C Red 40 dye is added, and mixed for approximately 12 minutes. The salicylic acid, sodium salicylate, flavorant and sodium saccharin are then added, and mixed for approximately 9 minutes. The batch product is then filled into individual bottles.

Two tablespoons of this liquid administered orally four times a day for ten days to a patient suffering from gastritis caused by Campylobacter pyloridis infection substantially improves the patient's condition.

Example IV

Methods Comprising Concurrent Administration

A patient suffering from gastritis is treated according to a regimen comprising 28 days of oral administration of bismuth subsalicylate (as two tablespoons of Pepto-Bismol®; sold by the Procter & Gamble Company) in the morning and oral administration of 400 mg of cimetidine (as 2 Tagamet® tablets; sold by Smith Kline and French Laboratories) in the evening before bedtime. This regimen significantly improves the condition of the patient being treated. Similar results are obtained when the bismuth subsalicylate is replaced with bismuth subcitrate (DeNol®; sold by Gist-Brocades N.V.).

Similarly effective treatment of a patient suffering from gastritis is achieved by the following regimens utilizing bismuth subsalicylate (supplied as Pepto-Bismol®) and cimetidine (supplied as Tagamet®): 21 days of daily oral administration of the two agents within about 5 minutes of each other; 21 days of daily oral administration of the two agents within about 5 minutes of each other followed by 7 days of treatment with only bismuth subsalicylate; and 7 days of treatment with bismuth subsalicylate followed by 21 days of daily oral administration of the two agents within about 5 minutes of each other.

Example V

Methods Comprising Non-concurrent Administration

A patient suffering from gastritis is treated according to a regimen comprising 29 days of alternating daily oral dosing of bismuth subsalicylate (as 2 tablespoons of Pepto-Bismol®; sold by the Procter & Gamble Company); and 400 mg of cimetidine (as 2 Tagamet® tablets; sold by the Smith Kline and French Laboratories), with the treatment regimen beginning on day 1 with administration of the bismuth sub-

salicylate and alternating the agents daily through day 29 which is also the administration of bismuth subsalicylate. This regimen significantly improves the condition of the patient being treated.

Similarly effective treatment of a patient suffering from gastritis is achieved by the following regimens utilizing bismuth subsalicylate and cimetidine: 14 days of daily oral administration of cimetidine, followed by 14 days of daily oral administration of bismuth subsalicylate; 7 days of daily oral administration of bismuth subsalicylate, followed by 14 days of daily oral administration of cimetidine; and 7 days of daily oral administration of bismuth subsalicylate, followed by 14 days of daily oral administration of cimetidine, followed by 7 days of daily oral administration of bismuth subsalicylate.

Claims

1. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, said compositions comprising :
   (a) a bismuth-containing agent, or a pharmaceutically acceptable salt thereof;
   (b) an H_2 receptor blocking anti-secretory agent; and
   (c) a pharmaceutically-acceptable carrier.

2. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, according to claim 1, wherein the H_2 receptor blocking anti-secretory agent is selected from cimetidine, ranitidine and mixtures thereof.

3. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, according to claims 1 or 2, wherein the bismuth-containing agent is selected from bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, bismuth citrate, tripotassium dicitrato bismuthate, bismuth subgalate, bismuth subnitrate, bismuth tartrate, bismuth subsalicylate and mixtures thereof.

4. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, according to any of claims 1-3, wherein the bismuth-containing agent is a campylobacter-inhibiting bismuth-containing agent.

5. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, according to any of claims 1-4, wherein the campylobacter-inhibiting bismuth-containing agent is selected from bismuth subsalicylate, bismuth subcitrate and mixtures thereof.

6. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, according to any of claims 1-5, wherein the bismuth-containing agent is bismuth subsalicylate, and the H_2 receptor blocking anti-secretory agent is cimetidine.

7. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, according to any of claims 1-5, wherein the bismuth-containing agent is bismuth subsalicylate, and the H_2 receptor blocking anti-secretory agent is ranitidine.

8. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, according to any of claims 1-5, wherein the bismuth-containing agent is bismuth citrate, and the H_2 receptor blocking anti-secretory agent is ranitidine.

9. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, according to any of claims 1-5, wherein the bismuth-containing agent is bismuth subcitrate, and the H_2 receptor blocking anti-secretory agent is ranitidine.

10. The use of a bismuth-containing agent and a H_2 receptor blocking antisecretory agent for the manufacture of a medicament for the treatment or prevention of gastrointestinal disorders in humans or lower animals, said treatment or prevention comprising administering to said human or lower animal a composition comprising, by weight, from 0,1 to 99,8% of the bismuth-containing agent, and administering to said human or lower animal a safe and effective amount of an H_2 receptor blocking anti-secretory agent.

11. The use of a bismuth-containing agent and a H_2 receptor blocking antisecretory agent according to

salicylate and alternating the agents daily through day 29 which is also the administration of bismuth subsalicylate. This regimen significantly improves the condition of the patient being treated.

Similarly effective treatment of a patient suffering from gastritis is achieved by the following regimens utilizing bismuth subsalicylate and cimetidine: 14 days of daily oral administration of cimetidine, followed by 14 days of daily oral administration of bismuth subsalicylate; 7 days of daily oral administration of bismuth subsalicylate, followed by 14 days of daily oral administration of cimetidine; and 7 days of daily oral administration of bismuth subsalicylate, followed by 14 days of daily oral administration of cimetidine, followed by 7 days of daily oral administration of bismuth subsalicylate.

Claims

1. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, said compositions comprising :
   (a) a bismuth-containing agent, or a pharmaceutically acceptable salt thereof;
   (b) an H_2 receptor blocking anti-secretory agent; and
   (c) a pharmaceutically-acceptable carrier.

2. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, according to claim 1, wherein the H_2 receptor blocking anti-secretory agent is selected from cimetidine, ranitidine and mixtures thereof.

3. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, according to claims 1 or 2, wherein the bismuth-containing agent is selected from bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, bismuth citrate, tripotassium dicitrato bismuthate, bismuth subgalate, bismuth subnitrate, bismuth tartrate, bismuth subsalicylate and mixtures thereof.

4. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, according to any of claims 1-3, wherein the bismuth-containing agent is a campylobacter-inhibiting bismuth-containing agent.

5. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, according to any of claims 1-4, wherein the campylobacter-inhibiting bismuth-containing agent is selected from bismuth subsalicylate, bismuth subcitrate and mixtures thereof.

6. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, according to any of claims 1-5, wherein the bismuth-containing agent is bismuth subsalicylate, and the H_2 receptor blocking anti-secretory agent is cimetidine.

7. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, according to any of claims 1-5, wherein the bismuth-containing agent is bismuth subsalicylate, and the H_2 receptor blocking anti-secretory agent is ranitidine.

8. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, according to any of claims 1-5, wherein the bismuth-containing agent is bismuth citrate, and the H_2 receptor blocking anti-secretory agent is ranitidine.

9. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, according to any of claims 1-5, wherein the bismuth-containing agent is bismuth subcitrate, and the H_2 receptor blocking anti-secretory agent is ranitidine.

10. The use of a bismuth-containing agent and a H_2 receptor blocking antisecretory agent for the manufacture of a medicament for the treatment or prevention of gastrointestinal disorders in humans or lower animals, said treatment or prevention comprising administering to said human or lower animal a composition comprising, by weight, from 0,1 to 99,8% of the bismuth-containing agent, and administering to said human or lower animal a safe and effective amount of an H_2 receptor blocking anti-secretory agent.

11. The use of a bismuth-containing agent and a H_2 receptor blocking antisecretory agent according to

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claim 10, wherein said treatment or prevention comprises concurrent administration of a bismuth-containing agent selected from bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, bismuth citrate, tripotassium dicitrato bismuthate, bismuth subgalate, bismuth subnitrate, bismuth tartrate, bismuth subsalicylate, and mixtures thereof, and an H_2 receptor blocking anti-secretory agent selected from cimetidine, ranitidine, and mixtures thereof.

12. The use of a bismuth-containing agent and a H_2 receptor blocking antisecretory agent according to claim 10, wherein said treatment or prevention comprises non-concurrent administration of a bismuth-containing agent selected from bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, bismuth citrate, tripotassium dicitrato bismuthate, bismuth subgalate, bismuth subnitrate, bismuth tartrate, bismuth subsalicylate, and mixtures thereof, and an H_2 receptor blocking anti-secretory agent selected from cimetidine, ranitidine, and mixtures thereof.

13. The use of a bismuth-containing agent and a H_2 receptor blocking antisecretory agent according to any of claims 10-12, wherein said bismuth-containing agent is bismuth subsalicylate.

14. The use of a bismuth-containing agent and a H_2 receptor blocking antisecretory agent according to any of claims 10-12, wherein said bismuth-containing agent is tripotassium dicitrato bismuthate.

15. The use of a bismuth-containing agent and a H_2 receptor blocking antisecretory agent according to any of claims 10-14, wherein said H_2 receptor blocking anti-secretory agent is cimetidine.

16. The use of a bismuth-containing agent and a H_2 receptor blocking antisecretory agent according to any of claims 10-14, wherein said H_2 receptor blocking anti-secretory agent is ranitidine.

17. The use of a bismuth-containing agent and a H_2 receptor blocking antisecretory agent according to any of claims 10-16, wherein said gastrointestinal disorder is a nonulcerative gastrointestinal disorder.

18. The use of a bismuth-containing agent and a H_2 receptor blocking antisecretory agent according to any of claims 10-16, wherein said gastrointestinal disorder is a peptic ulcer disease.

19. Pharmaceutical compositions according to any of claims 1-9, characterized in that said compositions are in the form of dosage units for oral administration.

20. Pharmaceutical compositions according to claim 19, characterized in that the oral form is selected from tablets, capsules, granules, powders, aqueous solutions, emulsions, suspensions and effervescent preparations.

21. Pharmaceutical compositions according to any of claims 19-20, characterized in that each dosage unit contains from 50 mg to 1,500 mg of bismuth and from 1 mg to 1,200 mg of the H_2 receptor blocking antisecretory agent.

22. Pharmaceutical compositions according to claim 21, characterized in that each dosage unit contains 300 mg of bismuth and 300 mg of the H_2 receptor blocking antisecretory agent.

Patentansprüche

1. Zur Behandlung oder Verhütung von Magen-Darm-Störungen geeignete pharmazeutische Zussammensetzungen, welche Zusammensetzungen
   (a) ein Bismut enthaltendes Mittel oder ein pharmazeutisch annehmbares Salz hievon;
   (b) ein H_2-Rezeptor blockierendes, antisekretorisches Mittel; und
   (c) einen pharmazeutisch annehmbaren Träger
   umfassen.

2. Zur Behandlung oder Verhütung von Magen-D-Störungen geeignete pharmazeutische Zusammensetzungen nach Anspruch 1, worin das H_2-Rezeptor blockierende, antisekretorische Mittel unter Cimetidin, Ranitidin und Gemischen hievon ausgewählt ist.

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3. Zur Behandlung oder Verhütung von Magen-Darm-Störungen geeignete pharmazeutische Zusammensetzungen nach den Ansprüchen 1 oder 2, worin das Bismut enthaltende Mittel unter Bismutaluminat, Bismutsubcarbonat, Bismutsubcitrat, Bismutcitrat, Trikaliumdicitratobismutat, Bismutsubgalat, Bismutsubnitrat, Bismuttartrat, Bismutsubsalicylat und Gemischen hievon ausgewählt ist.

4. Zur Behandlung oder Verhütung von Magen-Darm-Störungen geeignete pharmazeutische Zusammensetzungen nach einem der Ansprüche 1 bis 3, worin das Bismut enthaltende Mittel ein Campylobacter inhibierendes Bismut enthaltendes Mittel ist.

5. Zur Behandlung oder Verhütung von Magen-Darm-Störungen geeignete pharmazeutische Zusammensetzungen nach einem der Ansprüche 1 bis 4, worin das Campylobacter inhibierende Bismut enthaltende Mittel unter Bismutsubsalicylat, Bismutsubcitrat und Gemischen hievon ausgewählt ist.

6. Zur Behandlung oder Verhütung von Magen-Darm-Störungen geeignete pharmazeutische Zusammensetzungen nach einem der Ansprüche 1 bis 5, worin das Bismut enthaltende Mittel Bismutsubsalicylat ist und das H_2-Rezeptor blockierende antisekretorische Mittel Cimetidin ist.

7. Zur Behandlung oder Verhütung von Magen-Darm-Störungen geeignete pharmazeutische Zusammensetzungen nach einem der Ansprüche 1 bis 5, worin das Bismut enthaltende Mittel Bismutsubsalicylat ist und das H_2-Rezeptor blockierende antisekretorische Mittel Ranitidin ist.

8. Zur Behandlung oder Verhütung von Magen-Darm-Störungen geeignete pharmazeutische Zusammensetzungen nach einem der Ansprüche 1 bis 5, worin das Bismut enthaltende Mittel Bismutcitrat ist und das H_2-Rezeptor blockierende antisekretorische Mittel Ranitidin ist.

9. Zur Behandlung oder Verhütung von Magen-Darm-Störungen geeignete phatmazeutische Zusammensetzungen nach einem der Ansprüche 1 bis 5, worin das Bismut enthaltende Mittel Bismutsubcitrat ist und das H_2-Rezeptor blockierende antisekretorische Mittel Ranitidin ist.

10. Verwendung eines Bismut enthaltenden Mittels und eines H_2-Rezeptor blockierenden antisekretorischen Mittels zur Herstellung eines Medikaments zur Behandlung oder Verhütung von Magen-Darm-Störungen bei Menschen oder niedrigeren Tieren, welche Behandlung oder Verhütung ein Verabreichen einer Zusammensetzung, die 0,1 bis 99,8 Gew.-% des Bismut enthaltenden Mittels umfaßt, und ein Versbreichen einer sicheren und wirksamen Menge eines H_2-Rezeptor blockierenden antisekretorischen Mittels an den Menschen oder das niedrigere tierische Lebewesen umfaßt.

11. Verwendung eines Bismut enthaltenden Mittels und eines H_2-Rezeptor blockierenden antisekretorischen Mittels nach Anspruch 10, worin die Behandlung oder Verhütung das gleichzeitige Verabreichen eines Bismut enthaltenden Mittels, ausgewählt unter Bismutaluminat, Bismutsubcarbonat, Bismutsubcitrat, Bismutcitrat, Trikaliumdicitratobismutat, Bismutsubgalat, Bismutsubnitrat, Bismuttartrat, Bismutsubsalicylat und Gemischen hievon, und eines H_2-Rezeptor blockierenden antisekretorischen Mittels, ausgewählt unter Cimetidin, Ranitidin und Gemischen hievon, umfaßt.

12. Verwendung eines Bismut enthaltenden Mittels und eines H_2-Rezeptor blockierenden antisekretorischen Mittels nach Anspruch 10, worin die Behandlung oder Verhütung eine nicht gleichzeitige Verabreichung eines Bismut enthaltenden Mittels, ausgewählt unter Bismutaluminat, Bismutsubcarbonat, Bismutsubcitrat, Bismutcitrat, Trikaliumdicitratobismutat, Bismutsubgalat, Bismutsubnitrat, Bismuttartrat, Bismutsubsalicylat und Gemischen hievon, und eines H_2-Rezeptor blockierenden antisekretorischen Mittels, ausgewählt unter Cimetidin, Ranitidin und Gemischen hievon, umfaßt.

13. Verwendung eines Bismut enthaltenden Mittels und eines H_2-Rezeptor blockierenden antisektorischen Mittels nach einem der Ansprüche 10 bis 12, worin das Bismut enthaltende Mittel Bismutsubsalicylat ist.

14. Verwendung eines Bismut enthaltenden Mittels und eines H_2-Rezeptor blockierenden antisekretorischen Mittels nach einem der Ansprüche 10 bis 12, worin das Bismut enthaltende Mittel Trikaliumdicitratobismutat ist.

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15. Verwendung eines Bismut enthaltenden Mittels und eines H_2-Rezeptor blockierenden antisekretorischen Mittels nach einem der Ansprüche 10 bis 14, worin das H_2-Rezeptor blockierende antisekretorische Mittel Cimetidin ist.

16. Verwendung eines Bismut enthaltenden Mittels und eines H_2-Rezeptor blockierenden antisekretorischen Mittels nach einem der Ansprüche 10 bis 14, worin das H_2-Rezeptor blockierende antisekretorische Mittel Ranitidin ist.

17. Verwendung eines Bismut enthaltenden Mittels und eines H_2-Rezeptor blockierenden antisekretorischen Mittels nach einem der Ansprüche 10 bis 16, worin die Magen-Darm-Störung eine nicht-ulcerative gastrointestinale Störung ist.

18. Verwendung eines Bismut enthaltenden Mittels und eines H_2-Rezeptor blockierenden antisekretorischen Mittels nach einem der Ansprüche 10 bis 16, worin die Magen-Darm-Störung eine Magengeschwürkrankheit ist.

19. Pharmazeutische Zusammensetzungen nach einem der Ansprüche 1 bis 9, dadurch gekennzeichnet, daß diese Zusammensetzungen in Form von Dosierungseinheiten für die orale Verabreichung vorliegen.

20. Pharmazeutische Zusammensetzungen nach Anspruch 19, dadurch gekennzeichnet, daß die Oralform unter Tabletten, Kapseln, Granulaten, Pulvern, wäßrigen Lösungen, Emulsionen, Suspensionen und Brausepräparaten ausgewählt ist.

21. Pharmazeutische Zusammensetzungen nach einem der Ansprüche 19 bis 20, dadurch gekennzeichnet, daß jede Dosiseinheit von 50 mg bis 1500 mg Bismut und von 1 mg bis 1200 mg des H_2-Rezeptor blockierenden antisekretorischen Mittels enthält.

22. Pharmazeutische Zusammensetzungen nach Anspruch 21, dadurch gekennzeichnet, daß jede Dosiseinheit 300 mg Bismut und 300 mg des H_2-Rezeptor blockierenden antisekretorischen Mittels enthält.

Revendications

1. Compositions pharmaceutiques utiles pour le traitement ou la prévention des troubles gastro-intestinaux, lesdites compositions comprenant :
   (a) un agent contenant du bismuth, ou un de ses sels pharmaceutiquement acceptables;
   (b) un agent antisecréteur bloquant les récepteurs H_2;
   (c) un support pharmaceutiquement acceptable.

2. Compositions pharmaceutiques utiles pour le traitement ou la prévention des troubles gastro-intestinaux, selon la revendication 1, dans lesquelles l'agent antisecréteur bloquant les récepteurs H_2 est choisi parmi la cimétidine, la ranitidine et leurs mélanges.

3. Compositions pharmaceutiques utiles pour le traitement ou la prévention des troubles gastro-intestinaux, selon les revendications 1 ou 2, dans lesquelles l'agent contenant du bismuth est choisi parmi l'aluminate de bismuth, le subcarbonate de bismuth, le subcitrate de bismuth, le citrate de bismuth, le dicitrato-bismuthate tripotassique, le subgalate de bismuth, le subnitrate de bismuth, le tartrate de bismuth, le subsalicylate de bismuth et leurs mélanges.

4. Compositions pharmaceutiques utiles pour le traitement ou la prévention des troubles gastro-intestinaux, selon l'une quelconque des revendications 1-3, dans lesquelles l'agent contenant du bismuth est un agent contenant du bismuth inhibiteur de Campylobacter.

5. Compositions pharmaceutiques utiles pour le traitement ou la prévention des troubles gastro-intestinaux, selon l'une quelconque des revendications 1-4, dans lesquelles l'agent contenant du bismuth inhibiteur de Campylobacter est choisi parmi le subsalicylate de bismuth, le subcitrate de bismuth et leurs mélanges.

6. Compositions pharmaceutiques utiles pour le traitement ou la prévention des troubles gastro-intesti-

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naux, selon l'une quelconque des revendications 1-5, dans lesquelles l'agent contenant du bismuth est le subsalicylate de bismuth et l'agent antisecréteur bloquant les récepteurs H_2 est la cimétidine.

7. Compositions pharmaceutiques utiles pour le traitement ou la prévention des troubles gastro-intestinaux, selon l'une quelconque des revendications 1-5, dans lesquelles l'agent contenant du bismuth est un subsalicylate de bismuth, et l'agent antisecréteur bloquant les récepteurs H_2 est la ranitidine.

8. Compositions pharmaceutiques utiles pour le traitement ou la prévention des troubles gastro-intestinaux, selon l'une quelconque des revendications 1-5, dans lesquelles l'agent contenant du bismuth est le citrate de bismuth, et l'agent antisecréteur bloquant les récepteurs H_2 est la ranitidine.

9. Compositions pharmaceutiques utiles pour le traitement ou la prévention des troubles gastro-intestinaux, selon l'une quelconque des revendications 1-5, dans lesquelles l'agent contenant du bismuth est le subcitrate de bismuth, et l'agent antisecréteur bloquant les récepteurs H_2 est la ranitidine.

10. L'utilisation d'un agent contenant du bismuth et d'un agent antisecréteur bloquant les récepteurs H_2, pour la fabrication d'un médicament pour le traitement ou la prévention des troubles gastro-intestinaux chez l'homme ou les animaux inférieurs, ledit traitement ou prévention comprenant l'administration audit homme ou animal inférieur d'une composition comprenant, en poids, de 0,1 à 99,8% de l'agent contenant du bismuth, et l'administration audit homme ou animal inférieur d'une quantité sûre et efficace d'un agent antisecréteur bloquant les récepteurs H_2.

11. L'utilisation d'un agent contenant du bismuth et d'un agent antisecréteur bloquant les récepteurs H_2 selon la revendication 10, dans laquelle ledit traitement ou prévention comprend l'administration concurrente d'un agent contenant du bismuth choisi parmi l'aluminate de bismuth, le subcarbonate de bismuth, le subcitrate de bismuth, le dicitrato bismuthate tripotassique, le subgalate de bismuth, le subnitrate de bismuth, le tartrate de bismuth, le subsalicylate de bismuth, et leurs mélanges, et d'un agent antisecréteur bloquant les récepteurs H_2 choisi parmi la cimétidine, la ranitidine et leurs mélanges.

12. L'utilisation d'un agent contenant du bismuth et d'un agent antisecréteur bloquant les récepteurs H_2 selon la revendication 10, dans laquelle ledit traitement ou prévention comprend l'administration non concurrente d'un agent contenant du bismuth choisi parmi l'aluminate de bismuth, le subcarbonate de bismuth, le subcitrate de bismuth, le dicitrato bismuthate tripotassique, le subgalate de bismuth, le subnitrate de bismuth, le tartrate de bismuth, le subsalicylate de bismuth, et leurs mélanges, et d'un agent antisecréteur bloquant les récepteurs H_2 choisi parmi la cimétidine, la ranitidine et leurs mélanges.

13. L'utilisation d'un agent contenant du bismuth et d'un agent antisecréteur bloquant les récepteurs H_2 selon l'une quelconque des revendications 10-12, dans laquelle ledit agent contenant du bismuth est le subsalicylate de bismuth.

14. L'utilisation d'un agent contenant du bismuth et d'un agent antisecréteur bloquant les récepteurs H_2 selon l'une quelconque des revendications 10-12, dans laquelle ledit agent contenant du bismuth est le dicitrato-bismuthate tripotassique.

15. L'utilisation d'un agent contenant du bismuth et d'un agent antisecréteur bloquant les récepteurs H_2 selon l'une quelconque des revendications 10-14, dans laquelle ledit agent antisecréteur bloquant les récepteurs H_2 est la cimétidine.

16. L'utilisation d'un agent contenant du bismuth et d'un agent antisecréteur bloquant les récepteurs H_2 selon l'une quelconque des revendications 10-14, dans laquelle ledit agent antisecréteur bloquant les récepteurs H_2 est la ranitidine.

17. L'utilisation d'un agent contenant du bismuth et d'un agent antisecréteur bloquant les récepteurs H_2 selon l'une quelconque des revendications 10-16, dans laquelle ledit trouble gastro-intestinal est un désordre gastro-intestinal non ulcérant.

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18. L'utilisation d'un agent contenant du bismuth et d'un agent antisecréteur bloquant les récepteurs H_2 selon l'une quelconque des revendications 10-16, dans laquelle ledit trouble gastro-intestinal est un ulcère simple de l'estomac.

19. Compositions pharmaceutiques selon l'une quelconque des revendications 1-9, caractérisées en ce que lesdites compositions sont sous forme de dosage unitaire pour administration orale.

20. Compositions pharmaceutiques selon la revendication 19, caractérisées en ce que la forme orale est choisie parmi les comprimés, les gélules, les granulés, les poudres, les solutions aqueuses, les émulsions, les suspensions et les préparations effervescentes.

21. Compositions pharmaceutiques selon l'une quelconque des revendications 19-20, caractérisées en ce que chaque dose unitaire contient de 50 mg à 1.500 mg de bismuth et de 1 mg à 1.200 mg de l'agent antisecréteur bloquant les récepteurs H_2.

22. Compositions pharmaceutiques selon la revendication 21, caractérisées en ce que chaque dose unitaire contient 300 mg de bismuth et 300 mg de l'agent antisecréteur bloquant les récepteurs H_2.