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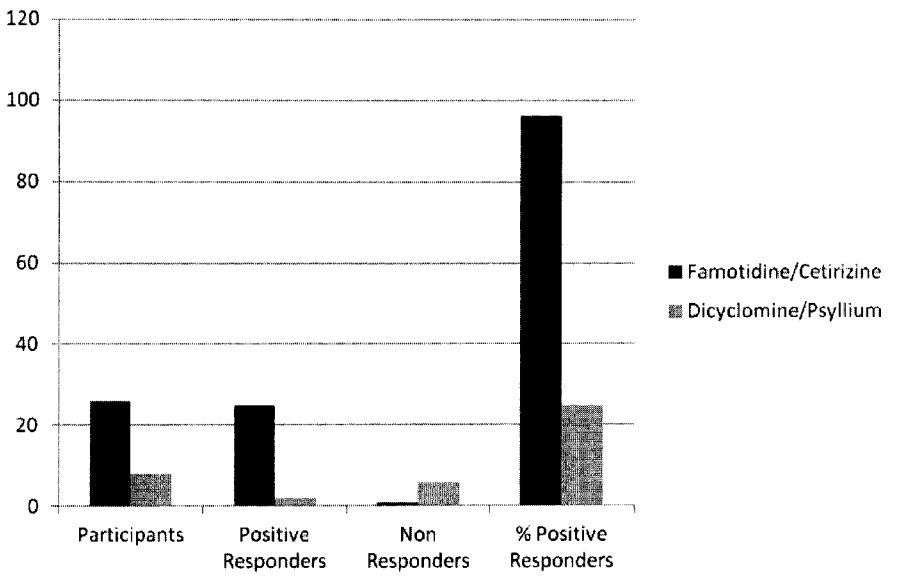


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A method of treating diarrhea in a patient includes administering an H1 receptor antagonist and an H2 receptor antagonist to the patient.

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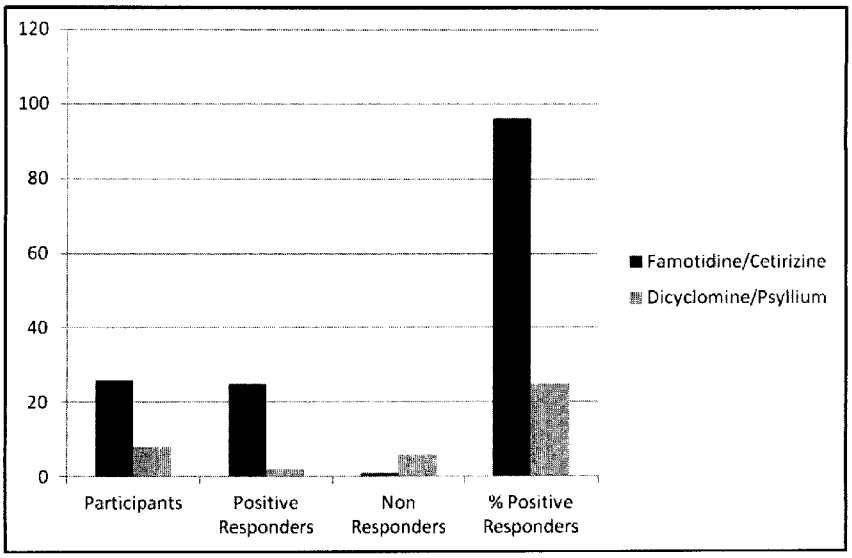


FIG. 1

(57) Abstract: A method of treating diarrhea in a patient includes administering an H1 receptor antagonist and an H2 receptor antagonist to the patient.

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# PRODUCT AND METHOD FOR TREATING DIARRHEA

## FIELD OF THE INVENTION

**[01]** The invention relates to the field of diarrhea treatment.

## BACKGROUND

**[02]** Diarrhea is a common condition characterized by increased frequency or fluidity of bowel movements. Diarrhea may cause dehydration and electrolyte abnormalities that may require hospitalization to replace lost fluids and electrolytes until the symptoms subside. Persistent, uncontrolled diarrhea can cause such severe malnutrition, electrolyte imbalances and dehydration that it may ultimately result in death. Acute diarrhea is usually treated with fluid and electrolyte replacement, dietary modifications and antidiarrheal or antimicrobial agents. Acute diarrhea complications may cause severe illness, especially in high-risk groups, for example patients with underlying immunosuppression or advanced age. Antidiarrheal treatment is also required in patients with chronic diarrhea. Empiric therapies routinely used for chronic diarrhea include: stool-modifying agents (such as psyllium and fiber), anticholinergic agents, opiates, antibiotics, and probiotics.

**[03]** Chronic diarrhea may be a symptom of a chronic disease, for example irritable bowel syndrome (IBS). It has been estimated that the prevalence of chronic diarrhea in the United States is approximately 5%. IBS alone is estimated to affect 15-20% of the U.S. population, and accounts for at least 30% of all gastroenterology health care costs. In many cases, the cause of the chronic diarrhea is not found, the diagnosis remains uncertain, and empiric treatments unsuccessful. Thus, there is an ongoing need for antidiarrheal agents that effectively stop or greatly reduce bowel movements and fluid loss in patients undergoing treatment, to remove the cause of diarrhea, or in patients in which the cause of diarrhea is not found.



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**[04]** H1 and H2 receptor antagonists are two classes of antihistamines. H1 receptor antagonists are used in the symptomatic treatment of multiple conditions, including allergic rhinoconjunctivitis, relief of pruritus in patients with urticaria, and in patients with chronic asthma. Newer H1 receptor antagonists, such as cetirizine, are referred to as second-generation H1 receptor antagonists, and are more selective for peripheral H1 receptors than first-generation H1 receptor antagonist, which antagonize both the central and peripheral nervous system H1 receptors as well as cholinergic receptors. The selectivity significantly reduces the occurrence of adverse drug reactions, such as sedation, while still providing effective relief of allergic conditions.

**[05]** H2 receptor antagonists are used primarily to treat symptoms of acid reflux, or gastroesophageal reflux disease. H2 receptor antagonists reduce the production of stomach acid. Often diarrhea is listed as a major side effect of H2 receptor antagonists.

**[06]** Diphenhydramine, a first-generation H1 receptor antagonist, together with either cimetidine or ranitidine, H2 receptor antagonists, have been studied for the treatment of acute allergic reactions. In a first study (Runge *et al.* "Histamine antagonists in the treatment of acute allergic reactions" *Ann Emerg Med* (Mar. 1992) 21:237-242), patients were treated by a single intravenous administration of a solution 300 mg cimetidine and placebo, 50 mg diphenhydramine and placebo, or diphenhydramine plus cimetidine; the treatment was found effective for acute urticaria. In a second study (Lin *et al.* "Improved outcomes in patients with acute allergic syndromes who are treated with combined H1 and H2 antagonists" *Ann Emerg Med* (Nov. 2000) 36:462-468), patients were treated by a single parenteral administration of a solution of either 50 mg diphenhydramine and saline or 50 mg diphenhydramine and 50 mg ranitidine; the treatment was found effective for acute allergic syndromes.



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## SUMMARY

**[07]** In a first aspect, the present invention is a method of treating diarrhea in a patient, comprising administering an H1 receptor antagonist and an H2 receptor antagonist to the patient. Preferably, the H1 receptor antagonist comprises cetirizine and the H2 receptor antagonist comprises famotidine.

**[08]** In a second aspect, the present invention is a method of treating diarrhea in a patient, comprising administering an H1 receptor antagonist and an H2 receptor antagonist to the patient. Preferably, the H2 receptor antagonist is not ranitidine.

**[09]** In a third aspect, the present invention is a method of treating diarrhea in a patient, comprising administering an H1 receptor antagonist and an H2 receptor antagonist to the patient.

**[10]** In a fourth aspect, the present invention is a method of treating diarrhea in a patient, comprising administering an H1 receptor antagonist and an H2 receptor antagonist to the patient. Preferably, the patient does not have mastocytic enterocolitis.

**[11]** In a fifth aspect, the present invention is a pharmaceutical composition for treating diarrhea, comprising an H1 receptor antagonist, and an H2 receptor antagonist. Preferably, the H2 receptor antagonist is not ranitidine, and the pharmaceutical composition is an oral dosage form.

**[12]** In a sixth aspect, the present invention is a pharmaceutical composition for treating diarrhea, comprising an H1 receptor antagonist, and an H2 receptor antagonist. Preferably, the H1 receptor antagonist is not diphenhydramine.

**[13]** In a seventh aspect, the present invention is a pharmaceutical composition for treating diarrhea in a patient, comprising an H1 receptor antagonist, and an H2 receptor antagonist. Preferalby, the patient does not have mastocytic enterocolitis.



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**[14]** In an eighth aspect, the present invention is use of an H1 receptor antagonist and an H2 receptor antagonist for the preparation of a medicament for treating a patient having diarrhea.

## [15] DEFINITIONS

**[16]** The term "diarrhea," means increased fluidity or frequency of stools.

**[17]** The term "acute diarrhea" is ongoing diarrhea which has occurred for at most 4 weeks.

**[18]** The term "chronic diarrhea" is ongoing diarrhea for more than 4 weeks.

**[19]** The term "unit dosage form," means a single pre-measured dose, and includes tablets, pills, capsules, packets, suspensions, transdermal patches, and rectal suppositories.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[20]** FIG. 1 illustrates participants and responses by treatment group of an IBS-D study.

## DETAILED DESCRIPTION

**[21]** The present invention makes use of the discovery that administering an H1 receptor antagonist and an H2 receptor antagonist to a patient, results in a significant reduction or cessation of diarrhea. Applicant discovered that the combination of an H1 receptor antagonist and an H2 receptor antagonist administered to patients with diarrhea, resulted in 85-90% positive responders (see Example 7 and Table 1). A positive responder is identified as having a 50% or more reduction in the number of stools per day or a change in stool formation from liquid to solid. No adverse reactions or events were reported. A control group was treated with fiber (Metamucyl®) and an anticholinergic (Bentyl®); positive responders in the control group were less than 25%.



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**[22]** In a prior study (Jakate, *et al.*, "Mastocytic Enterocolitis: Increased mucosal mast cells in chronic intractable diarrhea" *Arch Pathol Lab Med* (2006) 130:362-367), 33 patients who had increased mast cells (greater than 20 mast cells per high-power field) and were therefore identified by the authors as having "mastocytic enterocolitis," were administered a 2-week regimen of 10 mg per day of cetirizine hydrochloride (an H1 receptor antagonist) and 300 mg twice a day of ranitidine hydrochloride (an H2 receptor antagonist). In 8 of the 33 patients, a third drug, 200 mg/10 mL of cromolyn sodium (a mast cell mediator release inhibitor) was given 4 times daily for 4 to 6 weeks. The patients were followed for resolution, improvement, or persistence of symptoms. The patients who did not have mastocytic enterocolitis were not given these drugs. At follow-up, 22 (67%) of the 33 study patients showed cessation of diarrhea or significant reduction in diarrhea (defined as greater than or equal to 50% reduction in stool frequency or as greater than or equal to 50% improvement in stool consistency). However, because no control was used in the study, and because of the use of a third drug in some of the patients, it is not possible to determine how effective the treatment was for the selected patients. The placebo effect could account for up to about 11 of the patients with a positive outcome and the third drug could account for up to 8 of the patients with a positive outcome. The time frame of the follow-up was not provided. Furthermore, no statistical analysis or further studies were described.

**[23]** The present invention includes treating diarrhea by administering an H1 receptor antagonist and an H2 receptor antagonist in combination. The present invention also includes unit dosage forms, multi-dosage forms, and kits, including an H1 receptor antagonist and an H2 receptor antagonist. Preferably, the H1 receptor antagonist includes cetirizine and the H2 receptor antagonist includes famotidine.

**[24]** Diarrhea may be acute or chronic. Diarrhea may also be further classified:

**[25]** Secretory diarrhea: diarrhea which occurs when the intestine does not complete absorption of water from luminal contents and electrolyte absorption is impaired, often



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caused by bacterial toxins, surgically reduced absorptive area of the intestines, microscopic colitis and luminal secretagogues such as laxatives and bile acids.

**[26]** Osmotic diarrhea: diarrhea which results from intestinal malabsorption of ingested non-electrolytes.

**[27]** Inflammatory diarrhea: diarrhea which may be characterized by blood and pus in the stool and possibly an elevated fecal calprotectin level, and inflammation exhibited on intestinal biopsy, caused by, for example, Crohn's disease and ulcerative colitis.

**[28]** IBS-diarrhea predominate ("IBS-D"): chronic diarrhea associated with abdominal pain. In order to have IBS, a patient must have experienced onset of symptoms 6 months prior to diagnosis and must have recurrent abdominal pain or discomfort at least three days per month in the last three months associated with two or more of the following: improvement with defecation; onset associated with a change in frequency of stool; onset associated with a change in form of stool. Once IBS is diagnosed, it can be further classified based on the patients predominant symptom: diarrhea (IBS-D), or constipation (IBS-C), or mixed (IBS-M).

**[29]** Functional diarrhea: chronic diarrhea in a patient who does not meet the criteria for IBS, and for which no other cause can be determined. This type of diarrhea may also be referred to as chronic idiopathic diarrhea.

**[30]** Malabsorbtive diarrhea: diarrhea caused by an enteropathy such as celiac disease (celiac sprue) and giardiasis, which is characterized by excess gas, steatorrhea, and/or weight loss.

**[31]** Drug induced diarrhea: diarrhea caused by a drug or treatment for an unrelated disease state, such as chemotherapy, radiation therapy, antibiotic therapy, anti-ulcer therapy, and herbal therapies.

**[32]** Food intolerance diarrhea: diarrhea which is associated with dietary intake, such as lactose, sugar substitutes or other food substances.



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**[33]** Particularly common is IBS associated diarrhea, a chronic diarrhea, also referred to IBS-diarrhea predominate or simply "IBS-D". Some researchers claimed to have identified a subset of IBS-D, mastocytic enterocolitis, which they defined as a patient having greater than 20 mast cells per high-power field, based on an average of 10 high-power fields, for at least 2 separate biopsy pieces from random parts of the intestinal mucosa, using an original magnification of X400, an objective having magnification of X40 and an eyepiece having magnification of X10 (Jakate, *et al.*, "Mastocytic Enterocolitis: Increased mucosal mast cells in chronic intractable diarrhea" *Arch Pathol Lab Med* (2006) 130:362-367). In an aspect of the present invention, the patient does not have mastocytic enterocolitis.

**[34]** H1 receptor antagonists block H1 histamine receptors; first-generation H1 receptor antagonists block histamine receptors in the central and peripheral nervous systems, as well as cholinergic receptors, while second-generation H1 receptor antagonists are selective for H1 histamine receptors in the peripheral nervous system. First-generation H1 receptor antagonists include brompheniramine, chlorpheniramine, dexbrompheniramine, dexchlorpheniramine, pheniramine, triprolidine, carbinoxamine, clemastine, diphenhydramine, pyrilamine, promethazine, hydroxyzine, azatadine, cyproheptadine, and phenindamine. Second-generation H1 receptor antagonists include ketotifen, rupatadine, mizolastine, acrivastine, ebastine, bilastine, bepotastine, terfenadine, quifenadine, azelastined, cetirizine, levocetirizine, desloratadine, fexofenadine and loratadine. Preferably, the H1 receptor antagonist is a second-generation H1 receptor antagonist, more preferably the H1 receptor antagonist is cetirizine or levocetirizine, with cetirizine being particularly preferred. Mixtures and combination of H1 receptor antagonists may also be used.

**[35]** The H1 receptor antagonists may be used in an amount of from 0.1 to 10 times the amount typically used for the treatment of allergies, for example in an amount of 0.1 to 600 mg per dose, 0.5 to 500 mg per dose, 1.0 to 50 or 60 mg per dose, including 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40 and 45 mg



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per dose. Preferably, the H1 receptor antagonist is administered 1, 2, 3 or 4 times per day. The H1 receptor antagonist may be administered as an injectable formulation, for example intravenously, intraparenterally or intramuscularly; transdermally, via a transdermal patch; or, preferably, orally, as a powder, table or capsule, an oral solution or suspension, or sublingual or buccal tablets. Alternative forms of administration include rectal suppositories, inhaled, epidural, subcutaneous, nasal spray, transmucosal, and intradermal formulations.

**[36]** H2 receptor antagonists block H2 histamine receptors. H2 receptor antagonists include cimetidine, ranitidine, famotidine, and nizatidine, with famotidine being preferred. Mixtures and combinations of H2 receptor antagonists may also be used.

**[37]** The H2 receptor antagonists may be used in an amount of from 0.1 to 10 time the amount typically used for treatment dyspepsia, for example 1.0 to 8000 mg per dose, 2.0 to 1000 mg per dose, 5.0 to 800 mg per dose, including 6.0, 7.0, 8.0, 9.0, 10, 15, 20, 21, 22, 22.5, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 120, 140, 150, 175, 200, 250, 300, 350, 400, 450, 500, 600, and 700 mg per dose. Preferably, the H2 receptor antagonist is administered 1, 2, 3 or 4 times per day. The H2 receptor antagonist may be administered as an injectable formulation, for example intravenously, intraparenterally or intramuscularly; transdermally, via a transdermal patch; or, preferably, orally, as a powder, table or capsule, an oral solution or suspension, or sublingual or buccal tablets. Alternative forms of administration include rectal suppositories, inhaled, epidural, subcutaneous, nasal spray, transmucosal, and intradermal formulations.

**[38]** Patients often respond to treatment within 48 to 72 hours. However, treatment should be carried out for an amount of time to resolve any underlying cause in the case of acute diarrhea, for example 3 to 14 days, or 5 to 10 days. In the case of chronic diarrhea, a 30 day trial is reasonable, and if the underlying cause of



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the diarrhea cannot be resolved, for example in the case of IBS-D, then treatment should be continued indefinitely.

**[39]** Preferably, the H1 and H2 receptor antagonists are administered simultaneously, as a unit dosage form containing both receptor antagonists. Examples of unit dosage forms include oral compositions, such as tablets (for example, sublingual or buccal tablets), capsules (for example, hard gelatin and soft gelatin capsules), transmucosal and sublingual patches and films, pre-measured powder packets and saches, flavored and/or sweetened aqueous solutions or suspensions. Because diarrhea is often associated with dehydration, flavored and/or sweetened aqueous solutions or suspension may be oral rehydration solutions, or solutions which also contain sodium and glucose or a glucose-containing saccharide, in amounts of 250 ml, 500 ml or 1 liter of fluid. Furthermore, a pre-measured powder packet, containing the receptor antagonists, together with sodium (for example, as sodium chloride) and glucose or a glucose-containing saccharide, and optionally other excipients, flavorings and/or sweeteners, may be provided, which may be readily mixed with water prior to consumption. Preferably, the oral unit dosage form is present as a once-per-day dosage.

**[40]** Examples of oral dosage forms include a tablet containing famotidine, in an amount of 5, 10, 15, 20, 22.5, 25, 30, 35 or 40 mg, as a core, and a coating of cetirizine, in an amount of 2.5, 5, 8.5, 10, 15, or 20 mg. Another example includes a capsule containing granules of famotidine and cetirizine in water-soluble matrix. In another example, both the famotidine and the cetirizine are present as a mixture in a matrix, either as a table or within a capsule. In these examples, other H1 and/or H2 receptor antagonists may be used in place of, or in addition to, famotidine and/or cetirizine.

**[41]** Other unit dosage forms may also be provided, containing both H1 and H2 receptor antagonist. For example, injectable formulation containing a sterile solution or suspension, including formulation for administration intravenously,



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intraparenterally or intramuscularly, may be provided. A unit dosage form for administration transdermally, via a transdermal patch, may be provided. Other unit dosage forms include rectal suppositories, inhaled, epidural, subcutaneous, nasal spray, and intradermal formulations. Excipients and adjuvants maybe also be included in any of the unit dosage forms, both oral and non-oral.

**[42]** Multi-dosage forms, such as kits, containing 2 to 30, 3 to 25, or 5 to 14 unit dosage forms, for example 6, 7, 8, 9, 10, 11, 12, 13, 15, 20, 40, 50 or 60 unit dosage forms, may be provided. Preferably, the multi-dosage forms contain sufficient unit dosage forms for administration over a period of 2 to 30, 3 to 25, or 7 to 14 days, for example 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 20 or 30 days. Kits may also be provided, which include oral rehydration solutions, or powders which may be hydrated to form oral rehydration solutions, or kits containing sodium and glucose or a glucose-containing saccharide, as well as other excipients, flavorings and/or sweeteners, together with unit dosage forms.

**[43]** **EXAMPLES**

**[44]** Example 1: treatment of secretory diarrhea

**[45]** Patient #1, age 65, was hospitalized for more than one week for weight and fluid loss related to chronic diarrhea. The patient had from 20 to 40 stools per day and severe life threatening diarrhea. The patient was treated with 20 mg famotidine and 10 mg cetirizine, once per day. Symptoms subsided within 48 hours with a 95% decrease in the number of stools and the patient was discharged. The patient responded to treatment and now has 1 stool per day, occasionally two, but no diarrhea.

**[46]** Example 2: treatment of IBS diarrhea

**[47]** Seven patients, age 26 to 80, were treated for mild to severe diarrhea, ranging from 3 to 18 stools per day.



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**[48]** Patient #1, age 80, with mild to severe cramping and 4 to 5 stools a day. The patient was treated with 300 mg ranitidine and 10 mg cetirizine, once per day. The patient reported a 60% reduction in the number of stools.

**[49]** Patient #2, age 62, had severe weight loss, greater than 30 pounds, related to the diarrhea, 10 to 20 stools per day, and was opiate and steroid dependant. The patient was treated with 20 mg famotidine and 10 mg cetirizine, once per day. Treatment was successful with an 85 to 90% reduction in the number of stools. The patient now has 1 to 2 stools per day for over 8 months on treatment.

**[50]** Patient #3, age 65, prior to treatment was homebound, had 4 to 5 stools per day, each episode lasting an hour or two. The patient was treated with 300 mg ranitidine and 10 mg cetirizine, once per day. Treatment was successful, with the patient reporting a 90% reduction in the number of stools.

**[51]** Patient #4, age 67, with moderate diarrhea and cramping, had 4 to 5 stools per day. The patient was treated with 20 mg famotidine and 10 mg cetirizine, once per day. Treatment was successful, with a 75% reduction in the number of stools, no cramping and no side effects.

**[52]** Patient #5, age 26, had moderate to severe diarrhea with 7 to 8 stools per day. The patient was treated with 20 mg famotidine and 10 mg cetirizine, once per day. Treatment was successful, with a decrease in the number of stools by 50%, down to 3 to 4 per day, with no side effects.

**[53]** Patient #6, age 74, with severe diarrhea, had 8 stools per day and was homebound. The patient was treated with 300 mg ranitidine and 10 mg cetirizine, once per day. Treatment was successful, with a decrease in the number of stools by 75%, down to 2 stools per day and no side effects. Patient is presently only on cetirizine.

**[54]** Patient #7, age 51, with colon resection, had severe diarrhea with 15 to 20 stools per day. The patient was treated with 300 mg ranitidine and 10 mg cetirizine,



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once per day. Treatment was successful, with a decrease in the number of stools by 94%, to 1 to 2 stools per day and better consistency, with no side effects.

**[55]** Example 3: chronic idiopathic diarrhea

**[56]** A patient, age 81, with a complaint of moderate diarrhea and no additional diagnoses, had 4 to 6 stools per day, causing interference with activity level and lifestyle. The patient was treated with 20 mg famotidine and 10 mg cetirizine, once per day. Treatment was successful, with a decrease in the number of stools by 70%, to 1 to 2, mostly 1, per day and a repeat colonoscopy was cancelled because symptoms had resolved.

**[57]** Example 4: chemotherapy induced diarrhea

**[58]** Patient, age 64, with colon cancer and moderate to severe diarrhea, in a deconditioned state from chemotherapeutic agents, had 5 to 10 stools per day. The patient was treated with 20 mg famotidine and 10 mg cetirizine, once per day. Treatment was successful, with a decrease in the number of stools by 80%, to 1 to 2 per day and normal consistency, with no side effects.

**[59]** Example 5: inflammatory diarrhea – ulcerative colitis/Crohn's disease

**[60]** Three patients, age 35-64, were treated for severe diarrhea related to ulcerative colitis or Crohn's disease.

**[61]** Patient #1, age 64, with Crohn's disease, had 12 to 15 stools per day and severe diarrhea. The patient was treated with 20 mg famotidine and 10 mg cetirizine, once per day. Treatment was not successful, with a decrease in the number of stools only by 5%. There were no side effects.

**[62]** Patient #2, age 37, with Crohn's disease and colitis, had severe diarrhea with 4 to 5 stools per day. The patient was treated with 300 mg ranitidine and 10 mg cetirizine, once per day. Treatment was successful, with a decrease in the number



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of stools by 75%, to one stool per day and normal consistency. There were no side effects.

**[63]** Patient #3, age 35, with ulcerative colitis, had severe diarrhea with 4 to 6 stools per day. The patient was treated with 20 mg famotidine and 10 mg cetirizine, once per day. Treatment was successful, with a decrease in the number of stools by 50%. There were no side effects.

**[64]** Example 6: celiac disease

**[65]** Patient #1, age 57, with celiac disease had mild to moderate diarrhea, with 2 to 4 stools per day. The patient had no improvement from treatment with 20 mg famotidine and 10 mg cetirizine, once per day. There were no side effects.

**[66]** Patient #2, age 26, with celiac disease. The patient had little improvement from treatment.

**[67]** Example 7: IBS-D Treatment Study

**[68]** The study population age was 18 to 80, with the patients having chronic unexplained diarrhea from an outpatient population of a clinic and outpatients from a medical center, who gave consent for treatment. Patients were excluded who had a history of systemic or cutaneous mastocytosis, definable etiology of diarrhea (other than IBS-D or chronic idiopathic diarrhea) such as celiac disease, inflammatory bowel disease, or lactose intolerance, or who were pregnant. The study was initiated after IRB approval.

**[69]** Upon referral to the study coordinator, and after informed consent was obtained, patients were assigned to one of the two study arms. Patients underwent colonoscopy with biopsies that were then evaluated by a pathologist who was blind to the study arm. The study coordinator reviewed pathology results and documents accordingly. The patient was provided the treatment method that was randomly assigned and given a diary to document symptoms. Follow up phone conversations



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and a return visit was scheduled. At the completion of the four week medication treatment period, a telephone call or visit was carried out. At eight weeks, the diary was returned and the coordinator documented the data recorded by the subjects. There was a process for adverse event reporting and to date, no adverse reactions or events have been reported.

**[70]** One study arm received famotidine (20 mg per day) and cetirizine (10 mg per day), once per day. The second study arm received fiber (Metamucil®) and an anticholinergic (Bentyl®) once per day. Table 1 shows the results of the study. Tables 2 and 3 show the statistical analysis of the study results.

**[71]** Table 1: Study results

| Treatment Group | Number of Participants | Positive Responders | Non-Responders | Percent Responding |
|---|---|---|---|---|
| famotidine and cetirizine | 26 | 25 | 1 | 96% |
| dicylcomine and psyllium | 8 | 2 | 6 | 25% |

Positive responders = Appreciable decrease in # of stools per day
Non-responders = No appreciable decrease in # of stools per day

**[72]** Table 2: Group statistics

| Treatment Group | N | Mean | Std. Deviation | Std. Error Mean |
|---|---|---|---|---|
| dicylcomine and psyllium | 8 | 0.13 | 0.354 | 0.125 |
| famotidine and cetirizine | 26 | 1.00 | 0.000 | 0.000 |



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**[73]** Table 3: Independent samples test

| Independent Samples Test | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Status | Levene's Test for Equality of Variances | | t-test for Equality of Means | | | | | | |
| | F | Sig. | t | df | Sig. (2-tailed) | Mean Difference | Std. Error Difference | 95% Confidence Interval of the Difference | |
| | | | | | | | | Lower | Upper |
| Equal variances assumed | 19.033 | 0.000 | -13.088 | 32 | 0.000 | -8.75 | 0.67 | -1.011 | -.739 |
| Equal variances not assumed | 19.033 | 0.000 | -7.000 | 7.000 | 0.000 | -8.75 | 0.125 | -1.171 | -.579 |

**[74]** Figure 1 illustrates participants and responses by treatment group. The bars on the left represent the patients who received famotidine and cetirizine, while the bars on the right represent the patients who received fiber and anticholinergic. As indicated in the table and the figure, 90% of the patients receiving famotidine and cetirizine responded to the treatment, while only 10% of those receiving fiber and anticholinergic responded to the treatment.

**[75]** Tables 4 and 5 show the percent decrease in number of stools per day, for the famotidine and cetirizine study arm, and the dicylcomine and psyllium study arm, respectively.



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**[76]** Table 4: Percent decrease in number of stools per day, for the famotidine and cetirizine study arm

| Number of Subjects | Percent Stool Decrease |
|---|---|
| 1 | 0% |
| 1 | 10-25% |
| 2 | 28-45% |
| 11 | 50-65% |
| 11 | 66-85% |
| 0 | > 86 % |

**[77]** Table 5: Percent decrease in number of stools per day, for the dicylcomine and psyllium study arm

| Number of Subjects | Percent Stool Decrease |
|---|---|
| 6 | 0% |
| 0 | 10-25% |
| 1 | 28-45% |
| 1 | 50-65% |
| 0 | 66-85% |
| 0 | > 86 % |

**[78]** Example 8: Chronic Diarrhea Treatment Study

**[79]** The study population age was 21 to 70, with patients diagnosed with chronic diarrhea, who gave consent for treatment. Patients were excluded if there was a sensitivity or allergy to H1 receptor antagonists or H2 receptor antagonists, renal impairment or a history of renal failure, a diagnosis of inflammatory bowel disease (Crohn's disease or ulcerative colitis), a known active infection of the colon (such as *Clostridium difficile*, giardia, or *Salmonella*), biopsy proven microscopic colitis (collagenous or lymphocytic colitis), or an inability to discontinue other anti-diarrheal agents during the study. Patients were also excluded if they were pregnant or



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lactating women, or if the patient was taking atazanavir, itraconazole, or ketoconazole. The study was initiated after IRB approval.

**[80]** The study was a 4-week randomized, double-blind, controlled trial, with crossover. After informed consent was obtained, patients were randomly assigned to one of the two groups (active or placebo), with neither the patients nor the physicians knowing to which group each patient was assigned. Each patient was provided the treatment method that was randomly assigned and given a diary to document symptoms. After 7 days of treatment, subjects participated in a telephone interview with a blinded member of the research team. Crossover was allowed after one week of treatment for non-responders. At the end of the 28 day study, the patients completed a detailed questionnaire. Stool quality was evaluated using the 7 point Bristol Stool Scale.

**[81]** The "active" group received famotidine (24 mg) and cetirizine (9 mg), once per day, with both drugs combined in the form of a single capsule. The "placebo" group received a capsule once per day, which contained no active ingredients.

**[82]** The results of the study are shown in Table 6. The table shows the results of 27 patients, 12 in the placebo group and 15 in the active group. The average value for percent change is stools per day (SPD) was 25.08 for the placebo group, while the average value for percent change in SPD was 46.00 for the active group. Only 3 of the active group patients agreed to crossover, while 9 of the placebo group patients agreed to crossover. The data demonstrate a clinical significance between the placebo group and the active group, and demonstrate a significant improvement in the quality of life of the patients in the active group.



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**[83]** Table 6: Results of Chronic Diarrhea Treatment Study

| Group | Number of Patients | Mean Δ% SPD |
|---|---|---|
| Placebo | 12 | 25.08 |
| Active | 15 | 46.00 |



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WHAT IS CLAIMED IS:

1. Use, in the treatment of diarrhea in a patient who does not have mastocytic enterocolitis, of:

an H1 receptor antagonist that is one of cetirizine, levocetirizine or a mixture thereof; and

famotidine.

2. The use of claim 1, wherein the patient has chemotherapy-induced diarrhea.

3. The use of claim 1, wherein the patient has chronic idiopathic diarrhea.

4. The use of claim 1, wherein the patient has irritable bowel syndrome-diarrhea predominate (IBS-D).

5. The use of claim 1, wherein the diarrhea is chronic.

6. The use of claim 1, wherein the diarrhea is acute.

7. The use of any one of claims 1 - 6, wherein the H1 receptor antagonist is cetirizine.

8. The use of any one of claims 1 - 7, wherein the H1 receptor antagonist and the famotidine are together in a unit dosage form.

9. The use of claim 8, wherein the H1 receptor antagonist is cetirizine and is in an amount of 5 to 20 mg in each unit of the unit dosage form.

10. The use of claim 8 or 9, wherein the famotidine is in an amount of 10 to 40 mg in each unit of the unit dosage form.



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11. The use of claim 8, 9 or 10, wherein the unit dosage form is an oral dosage form.

12. The use of claim 11, wherein the oral dosage form further comprises an oral rehydration solution.

13. The use of claim 11, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

14. The use of any one of claims 1 - 7, wherein the H1 receptor antagonist and the famotidine are together in an oral dosage form.

15. The use of claim 14, wherein the oral dosage form further comprises an oral rehydration solution.

16. The use of claim 14, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

17. Use, in the treatment of a patient having chemotherapy-induced diarrhea, of:

an H1 receptor antagonist that is one of cetirizine, levocetirizine or a mixture thereof; and

famotidine.

18. The use of claim 17, wherein the H1 receptor antagonist is cetirizine.

19. The use of claim 17, wherein the H1 receptor antagonist and the famotidine are together in a unit dosage form.

20. The use of claim 19, wherein the H1 receptor antagonist is cetirizine and is in an amount of 5 to 20 mg in each unit of the unit dosage form.

21. The use of claim 19 or 20, wherein the famotidine is in an amount of 10 to 40 mg in each unit of the unit dosage form.



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22. The use of claim 19, 20 or 21, wherein the unit dosage form is an oral dosage form.

23. The use of claim 22, wherein the oral dosage form further comprises an oral rehydration solution.

24. The use of claim 22, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

25. The use of claim 17 or 18, wherein the H1 receptor antagonist and the famotidine are together in an oral dosage form.

26. The use of claim 25, wherein the oral dosage form further comprises an oral rehydration solution.

27. The use of claim 25, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

28. Use, in the treatment of a patient having chronic idiopathic diarrhea, of:

an H1 receptor antagonist that is one of cetirizine, levocetirizine or a mixture thereof; and

famotidine.

29. The use of claim 28, wherein the H1 receptor antagonist is cetirizine.

30. The use of claim 28, wherein the H1 receptor antagonist and the famotidine are together in a unit dosage form.

31. The use of claim 30, wherein the H1 receptor antagonist is cetirizine and is in an amount of 5 to 20 mg in each unit of the unit dosage form.



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32. The use of claim 30 or 31, wherein the famotidine is in an amount of 10 to 40 mg in each unit of the unit dosage form.

33. The use of claim 30, 31 or 32, wherein the unit dosage form is an oral dosage form.

34. The use of claim 33, wherein the oral dosage form further comprises an oral rehydration solution.

35. The use of claim 33, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

36. The use of claim 28 or 29, wherein the H1 receptor antagonist and the famotidine are together in an oral dosage form.

37. The use of claim 36, wherein the oral dosage form further comprises an oral rehydration solution.

38. The use of claim 36, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

39. Use, in the treatment of a patient having irritable bowel syndrome-diarrhea predominate (IBS-D), who does not have mastocytic enterocolitis, of:

an H1 receptor antagonist that is one of cetirizine, levocetirizine or a mixture thereof; and

famotidine.

40. The use of claim 39, wherein the H1 receptor antagonist is cetirizine.

41. The use of claim 39, wherein the H1 receptor antagonist and the famotidine are together in a unit dosage form.



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42. The use of claim 41, wherein the H1 receptor antagonist is cetirizine and is in an amount of 5 to 20 mg in each unit of the unit dosage form.

43. The use of claim 41 or 42, wherein the famotidine is in an amount of 10 to 40 mg in each unit of the unit dosage form.

44. The use of claim 41, 42 or 43, wherein the unit dosage form is an oral dosage form.

45. The use of claim 44, wherein the oral dosage form further comprises an oral rehydration solution.

46. The use of claim 44, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

47. The use of claim 39 or 40, wherein the H1 receptor antagonist and the famotidine are together in an oral dosage form.

48. The use of claim 47, wherein the oral dosage form further comprises an oral rehydration solution.

49. The use of claim 47, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

50. Use, in the treatment of diarrhea in a patient having irritable bowel syndrome-diarrhea predominate (IBS-D), who does not have mastocytic enterocolitis, of:

an H1 receptor antagonist that is one of cetirizine, levocetirizine or a mixture thereof; and

famotidine.

51. The use of claim 50, wherein the H1 receptor antagonist is cetirizine.



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52. The use of claim 50, wherein the H1 receptor antagonist and the famotidine are together in a unit dosage form.

53. The use of claim 52, wherein the H1 receptor antagonist is cetirizine and is in an amount of 5 to 20 mg in each unit of the unit dosage form.

54. The use of claim 52 or 53, wherein the famotidine is in an amount of 10 to 40 mg in each unit of the unit dosage form.

55. The use of claim 52, 53 or 54, wherein the unit dosage form is an oral dosage form.

56. The use of claim 55, wherein the oral dosage form further comprises an oral rehydration solution.

57. The use of claim 55, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

58. The use of claim 50 or 51, wherein the H1 receptor antagonist and the famotidine are together in an oral dosage form.

59. The use of claim 58, wherein the oral dosage form further comprises an oral rehydration solution.

60. The use of claim 58, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

61. Use, in the treatment of diarrhea in a patient in need thereof, of:

an H1 receptor antagonist that is one of cetirizine, levocetirizine or a mixture thereof; and

famotidine.

62. The use of claim 61, wherein the H1 receptor antagonist is cetirizine.



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63. The use of claim 61, wherein the H1 receptor antagonist and the famotidine are together in a unit dosage form.

64. The use of claim 63, wherein the H1 receptor antagonist is cetirizine and is in an amount of 5 to 20 mg in each unit of the unit dosage form.

65. The use of claim 63 or 64, wherein the famotidine is in an amount of 10 to 40 mg in each unit of the unit dosage form.

66. The use of claim 63, 64 or 65, wherein the unit dosage form is an oral dosage form.

67. The use of claim 66, wherein the oral dosage form further comprises an oral rehydration solution.

68. The use of claim 66, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

69. The use of claim 61 or 62, wherein the H1 receptor antagonist and the famotidine are together in an oral dosage form.

70. The use of claim 69, wherein the oral dosage form further comprises an oral rehydration solution.

71. The use of claim 69, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

72. Use, in the treatment of acute diarrhea in a patient in need thereof, of:

an H1 receptor antagonist that is one of cetirizine, levocetirizine or a mixture thereof; and

famotidine.



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73. The use of claim 72, wherein the H1 receptor antagonist is cetirizine.

74. The use of claim 72, wherein the H1 receptor antagonist and the famotidine are together in a unit dosage form.

75. The use of claim 74, wherein the H1 receptor antagonist is cetirizine and is in an amount of 5 to 20 mg in each unit of the unit dosage form.

76. The use of claim 74 or 75, wherein the famotidine is in an amount of 10 to 40 mg in each unit of the unit dosage form.

77. The use of claim 74, 75 or 76, wherein the unit dosage form is an oral dosage form.

78. The use of claim 77, wherein the oral dosage form further comprises an oral rehydration solution.

79. The use of claim 77, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

80. The use of 72 or 73, wherein the H1 receptor antagonist and the famotidine are together in an oral dosage form.

81. The use of claim 80, wherein the oral dosage form further comprises an oral rehydration solution.

82. The use of claim 80, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

83. A pharmaceutical composition comprising:

one of cetirizine, levocetirizine or a mixture thereof; and

famotidine,



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wherein the pharmaceutical composition is in a unit dosage form that is an oral dosage form; and

the one of cetirizine, levocetirizine or mixture thereof is in an amount of 5 to 20 mg in each unit of the unit dosage form.

84. The pharmaceutical composition of claim 83, wherein the one of cetirizine, levocetirizine or mixture thereof is cetirizine.

85. The pharmaceutical composition of claim 84, wherein the famotidine is in an amount of 10 to 40 mg in each unit of the unit dosage form.

86. The pharmaceutical composition of claim 84 or 85, wherein the unit dosage form is a capsule.

87. The pharmaceutical composition of claim 84 or 85, wherein the unit dosage form is a tablet.

88. A pharmaceutical composition for use in treating diarrhea in a patient who does not have mastocytic enterocolitis, the pharmaceutical composition comprising:

an H1 receptor antagonist that is one of cetirizine, levocetirizine or a mixture thereof; and

famotidine.

89. The pharmaceutical composition of claim 88, wherein the H1 receptor antagonist is cetirizine.

90. The pharmaceutical composition of claim 88, wherein the H1 receptor antagonist and the famotidine are together in a unit dosage form.

91. The pharmaceutical composition of claim 90, wherein the H1 receptor antagonist is cetirizine and is in an amount of 5 to 20 mg in each unit of the unit dosage form.



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92. The pharmaceutical composition of claim 90 or 91, wherein the famotidine is in an amount of 10 to 40 mg in each unit of the unit dosage form.

93. The pharmaceutical composition of claim 90, 91 or 92, wherein the unit dosage form is an oral dosage form.

94. The pharmaceutical composition of claim 93, wherein the oral dosage form further comprises an oral rehydration solution.

95. The pharmaceutical composition of claim 93, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

96. The pharmaceutical composition of claim 88 or 89, wherein the H1 receptor antagonist and the famotidine are together in an oral dosage form.

97. The pharmaceutical composition of claim 96, wherein the oral dosage form further comprises an oral rehydration solution.

98. The pharmaceutical composition of claim 96, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

99. A pharmaceutical composition for use in treating chemotherapy-induced diarrhea, the pharmaceutical composition comprising:

an H1 receptor antagonist that is one of cetirizine, levocetirizine or a mixture thereof; and

famotidine.

100. The pharmaceutical composition of claim 99, wherein the H1 receptor antagonist is cetirizine.

101. The pharmaceutical composition of claim 99, wherein the H1 receptor antagonist and the famotidine are together in a unit dosage form.



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102. The pharmaceutical composition of claim 101, wherein the H1 receptor antagonist is cetirizine and is in an amount of 5 to 20 mg in each unit of the unit dosage form.

103. The pharmaceutical composition of claim 101 or 102, wherein the famotidine is in an amount of 10 to 40 mg in each unit of the unit dosage form.

104. The pharmaceutical composition of claim 101, 102 or 103, wherein the unit dosage form is an oral dosage form.

105. The pharmaceutical composition of claim 104, wherein the oral dosage form further comprises an oral rehydration solution.

106. The pharmaceutical composition of claim 104, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

107. The pharmaceutical composition of claim 99 or 100, wherein the H1 receptor antagonist and the famotidine are together in an oral dosage form.

108. The pharmaceutical composition of claim 107, wherein the oral dosage form further comprises an oral rehydration solution.

109. The pharmaceutical composition of claim 107, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

110. A pharmaceutical composition for use in treating diarrhea in a patient having irritable bowel syndrome-diarrhea predominate (IBS-D), who does not have mastocytic enterocolitis, the pharmaceutical composition comprising:

an H1 receptor antagonist that is one of cetirizine, levocetirizine or a mixture thereof; and

famotidine.

111. The pharmaceutical composition of claim 110, wherein the H1 receptor antagonist is cetirizine.



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112. The pharmaceutical composition of claim 110, wherein the H1 receptor antagonist and the famotidine are together in a unit dosage form.

113. The pharmaceutical composition of claim 112, wherein the H1 receptor antagonist is cetirizine and is in an amount of 5 to 20 mg in each unit of the unit dosage form.

114. The pharmaceutical composition of claim 112 or 113, wherein the famotidine is in an amount of 10 to 40 mg in each unit of the unit dosage form.

115. The pharmaceutical composition of claim 112, 113 or 114, wherein the unit dosage form is an oral dosage form.

116. The pharmaceutical composition of claim 115, wherein the oral dosage form further comprises an oral rehydration solution.

117. The pharmaceutical composition of claim 115, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

118. The pharmaceutical composition of claim 110 or 111, wherein the H1 receptor antagonist and the famotidine are together in an oral dosage form.

119. The pharmaceutical composition of claim 118, wherein the oral dosage form further comprises an oral rehydration solution.

120. The pharmaceutical composition of claim 118, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

121. A pharmaceutical composition for use in treating a patient having irritable bowel syndrome-diarrhea predominate (IBS-D), who does not have mastocytic enterocolitis, the pharmaceutical composition comprising:

an H1 receptor antagonist that is one of cetirizine, levocetirizine or a mixture thereof; and



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famotidine.

122. The pharmaceutical composition of claim 121, wherein the H1 receptor antagonist is cetirizine.

123. The pharmaceutical composition of claim 121, wherein the H1 receptor antagonist and the famotidine are together in a unit dosage form.

124. The pharmaceutical composition of claim 123, wherein the H1 receptor antagonist is cetirizine and is in an amount of 5 to 20 mg in each unit of the unit dosage form.

125. The pharmaceutical composition of claim 123 or 124, wherein the famotidine is in an amount of 10 to 40 mg in each unit of the unit dosage form.

126. The pharmaceutical composition of claim 123, 124 or 125, wherein the unit dosage form is an oral dosage form.

127. The pharmaceutical composition of claim 126, wherein the oral dosage form further comprises an oral rehydration solution.

128. The pharmaceutical composition of claim 126, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

129. The pharmaceutical composition of claim 121 or 122, wherein the H1 receptor antagonist and the famotidine are together in an oral dosage form.

130. The pharmaceutical composition of claim 129, wherein the oral dosage form further comprises an oral rehydration solution.

131. The pharmaceutical composition of claim 129, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.



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132. A pharmaceutical composition for use in treating chronic idiopathic diarrhea, the pharmaceutical composition comprising:

an H1 receptor antagonist that is one of cetirizine, levocetirizine or a mixture thereof; and

famotidine.

133. The pharmaceutical composition of claim 132, wherein the H1 receptor antagonist is cetirizine.

134. The pharmaceutical composition of claim 132, wherein the H1 receptor antagonist and the famotidine are together in a unit dosage form.

135. The pharmaceutical composition of claim 134, wherein the H1 receptor antagonist is cetirizine and is in an amount of 5 to 20 mg in each unit of the unit dosage form.

136. The pharmaceutical composition of claim 134 or 135, wherein the famotidine is in an amount of 10 to 40 mg in each unit of the unit dosage form.

137. The pharmaceutical composition of claim 134, 135 or 136, wherein the unit dosage form is an oral dosage form.

138. The pharmaceutical composition of claim 137, wherein the oral dosage form further comprises an oral rehydration solution.

139. The pharmaceutical composition of claim 139, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

140. The pharmaceutical composition of claim 132 or 133, wherein the H1 receptor antagonist and the famotidine are together in an oral dosage form.

141. The pharmaceutical composition of claim 140, wherein the oral dosage form further comprises an oral rehydration solution.



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142. The pharmaceutical composition of claim 140, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

143. A pharmaceutical composition for use in treating diarrhea in a patient in need thereof, the pharmaceutical composition comprising:

an H1 receptor antagonist that is one of cetirizine, levocetirizine or a mixture thereof; and

famotidine.

144. The pharmaceutical composition of claim 143, wherein the H1 receptor antagonist is cetirizine.

145. The pharmaceutical composition of claim 143, wherein the H1 receptor antagonist and the famotidine are together in a unit dosage form.

146. The pharmaceutical composition of claim 145, wherein the H1 receptor antagonist is cetirizine and is in an amount of 5 to 20 mg in each unit of the unit dosage form.

147. The pharmaceutical composition of claim 145 or 146, wherein the famotidine is in an amount of 10 to 40 mg in each unit of the unit dosage form.

148. The pharmaceutical composition of claim 145, 146 or 147, wherein the unit dosage form is an oral dosage form.

149. The pharmaceutical composition of claim 148, wherein the oral dosage form further comprises an oral rehydration solution.

150. The pharmaceutical composition of claim 148, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

151. The pharmaceutical composition of claim 143 or 144, wherein the H1 receptor antagonist and the famotidine are together in an oral dosage form.



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152. The pharmaceutical composition of claim 151, wherein the oral dosage form further comprises an oral rehydration solution.

153. The pharmaceutical composition of claim 151, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.

154. A pharmaceutical composition for use in treating acute diarrhea in a patient in need thereof, the pharmaceutical composition comprising:

an H1 receptor antagonist that is one of cetirizine, levocetirizine or a mixture thereof; and

famotidine.

155. The pharmaceutical composition of claim 154, wherein the H1 receptor antagonist is cetirizine.

156. The pharmaceutical composition of claim 154, wherein the H1 receptor antagonist and the famotidine are together in a unit dosage form.

157. The pharmaceutical composition of claim 156, wherein the H1 receptor antagonist is cetirizine and is in an amount of 5 to 20 mg in each unit of the unit dosage form.

158. The pharmaceutical composition of claim 156 or 157, wherein the famotidine is in an amount of 10 to 40 mg in each unit of the unit dosage form.

159. The pharmaceutical composition of claim 156, 157 or 158, wherein the unit dosage form is an oral dosage form.

160. The pharmaceutical composition of claim 159, wherein the oral dosage form further comprises an oral rehydration solution.

161. The pharmaceutical composition of claim 159, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.



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162. The pharmaceutical composition of claim 154 or 155, wherein the H1 receptor antagonist and the famotidine are together in an oral dosage form.

163. The pharmaceutical composition of claim 162, wherein the oral dosage form further comprises an oral rehydration solution.

164. The pharmaceutical composition of claim 162, wherein the oral dosage form further comprises sodium, and glucose or a glucose-containing saccharide.



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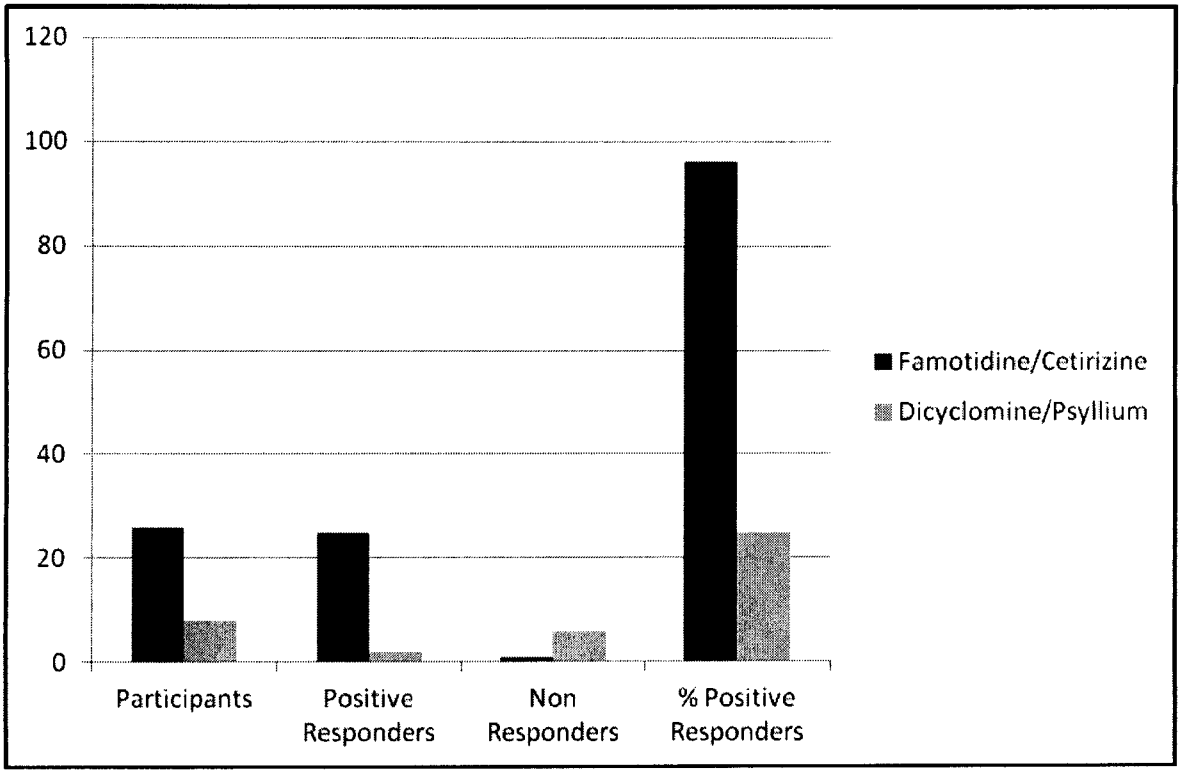
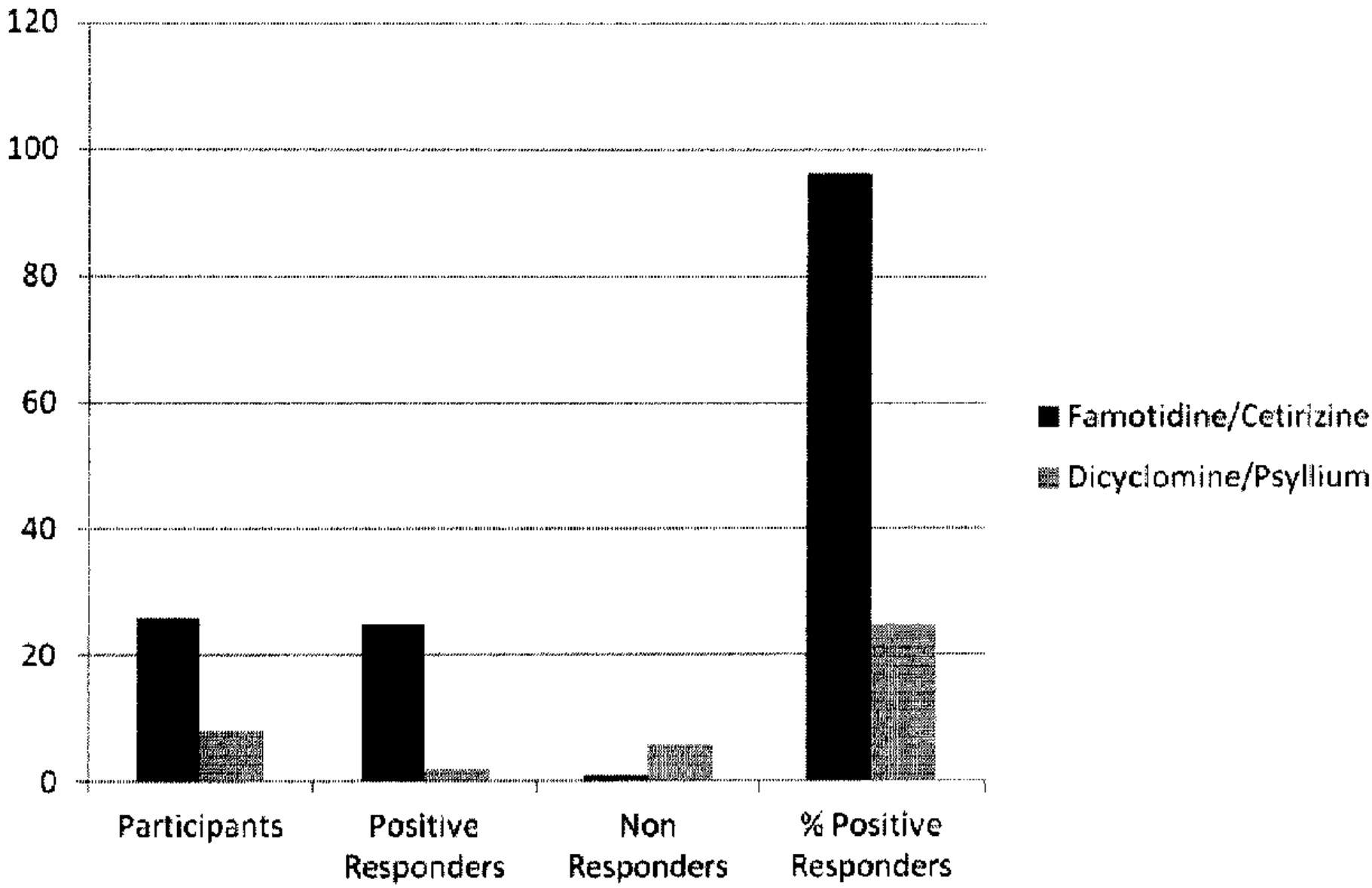

120
100
80
60
40
20
0
Participants
Positive Responders
Non Responders
% Positive Responders
Famotidine/Cetirizine
Dicyclomine/Psyllium

FIG. 1


120
100
80
60
40
20
0
Participants
Positive Responders
Non Responders
% Positive Responders
Famotidine/Cetirizine
Dicyclomine/Psyllium