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(54) Title: METHODS AND COMPOSITIONS FOR PREVENTING AND TREATING HEARTBURN

(57) **Abrégé/Abstract:**

A method for preventing heartburn episodes in a patient at risk to development of heartburn, comprising administering to the patient, following the heartburn inducing event but prior to development of heartburn, a composition comprising a pharmaceutically effective amount of an H<sub>2</sub> antagonist and an amount of antacid having between about 15 mEq and 46 mEq acid neutralizing capacity.



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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US97/17083 <b>(22) International Filing Date:</b> 30 September 1997 (30.09.97)  <b>(30) Priority Data:</b> 60/027,659                      4 October 1996 (04.10.96)                      US 9624291.2                      22 November 1996 (22.11.96)                      GB  <b>(71) Applicants (for all designated States except US):</b> MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). McNEIL-PPC, INC. [US/US]; Grandville Road, Skillman, NJ 08858 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> KORN, Scott, H. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). McNALLY, Gerard, P. [US/US]; Grandville Road, Skillman, NJ 08558 (US). LUBER, Joseph, R. [US/US]; Grandville Road, Skillman, NJ 08558 (US). ELLS, Tom, S. [US/US]; Grandville Road, Skillman, NJ 08558 (US).  <b>(74) Common Representative:</b> MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		<b>(81) Designated States:</b> AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> METHODS AND COMPOSITIONS FOR PREVENTING AND TREATING HEARTBURN  <b>(57) Abstract</b>  <p>A method for preventing heartburn episodes in a patient at risk to development of heartburn, comprising administering to the patient, following the heartburn inducing event but prior to development of heartburn, a composition comprising a pharmaceutically effective amount of an H<sub>2</sub> antagonist and an amount of antacid having between about 15 mEq and 46 mEq acid neutralizing capacity.</p>		



## TITLE OF THE INVENTION

### METHODS AND COMPOSITIONS FOR PREVENTING AND TREATING HEARTBURN

#### 5 BACKGROUND OF THE INVENTION

Heartburn, or pyrosis, is a sensation of pain or burning located substernally or high in the epigastrium with radiation into the neck and occasionally to the arms, associated with regurgitation of acid-peptic gastric juice into the esophagus. Occasional heartburn is common  
10 in normal persons, but frequent and severe heartburn is generally a manifestation of esophageal dysfunction. Heartburn may result from abnormal motor activity or distention of the esophagus reflux of acid or bile into the esophagus, or direct esophageal mucosa irritation (esophagitis).

15 Heartburn is most often associated with gastroesophageal reflux. In this setting, heartburn typically occurs after a meal, with stooping or bending, or when the patient is supine. It may be accompanied by the spontaneous appearance in the mouth of fluid which may be salty, sour, or bitter and green or yellow. Heartburn may arise  
20 following the ingestion of certain foods (e.g. citrus fruit juices) or drugs (e.g. alcohol or aspirin).

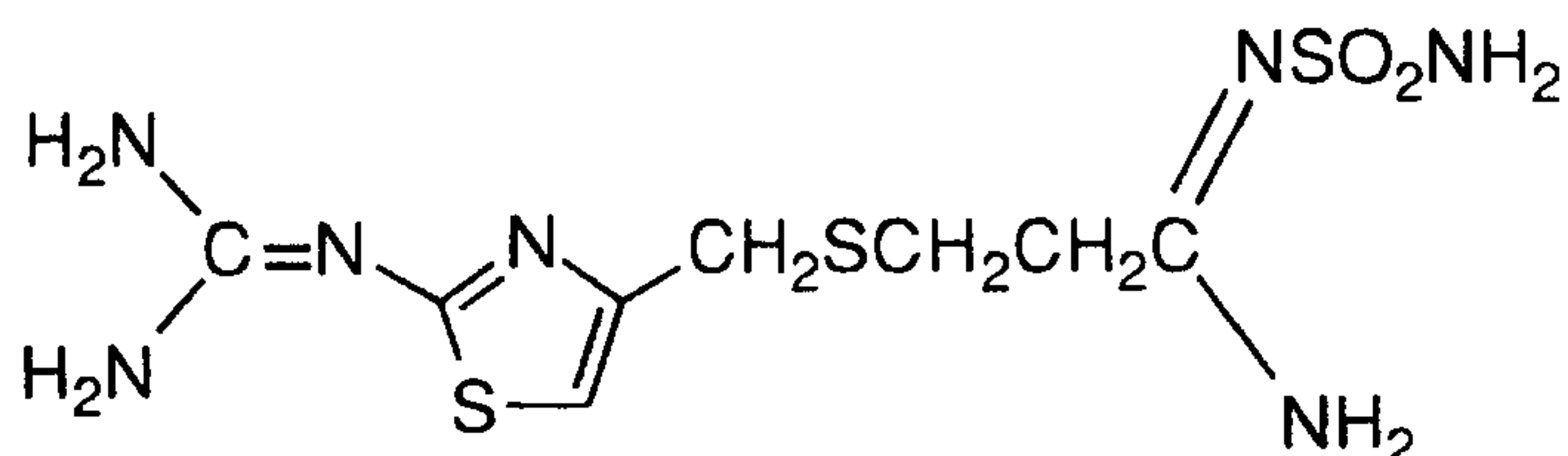
Reflux esophagitis consists of esophageal mucosal damage resulting from reflux of gastric or intestinal contents into the esophagus. Esophagitis, an inflammation of the esophagus from regurgitation of  
25 acid gastric contents, producing substernal pain, develops when the mucosal defenses that normally counteract the effect of injurious agents on the esophageal mucosa succumb to the onslaught of the refluxed acid pepsin or bile. Mild esophagitis shows microscopic changes of mucosal infiltration with granulocytes or eosinophils, hyperplasia of basal cells,  
30 and elongation of dermal pegs. Erosive esophagitis shows endoscopically visible damage to the mucosa in the form of marked redness, friability, bleeding, superficial linear ulcers, and exudates.

Known antagonists of the histamine H<sub>2</sub> receptor include cimetidine, ranitidine, nizatidine, and famotidine. Famotidine (available

- 2 -

from Merck & Co., Inc., Whitehouse Station, NJ, under the name PEPCID<sup>®</sup>), is 3-{{2-[(aminoiminomethyl)amino]-4-thiazolyl)methyl]thio]-N-(aminosulfonyl)propanimidamide, having the structural formula:

5



The primary clinically important pharmacologic activity of famotidine is inhibition of gastric secretion. Both acid concentration and volume of gastric secretion are reduced by famotidine. Famotidine is used to treat acid-related disorders such as gastric and duodenal ulcer, gastroesophageal reflux disease and Zollinger Ellison syndrome. Its safety and efficacy have been well established in controlled clinical studies. It is used by over 31 million patients worldwide.

15               Gitlin et al., Amer. Journal of Gastroenterology (1985) vol. 80 pp. 840 examines famotidine efficacy in the treatment of active duodenal ulcers. 20 mg twice daily, 40 mg twice daily and 40 mg at bedtime were administered over a four week period. Healing rates of 67, 75, 70% , respectively, were seen.

20               Similarly, Miyoshi et al., Naika Hokan (1987) vol. 34 pp. 442-457 demonstrates the efficacy of famotidine as a gastritis therapy. Miyoshi et al. evaluated dosage regimens of 5, 10, or 20 mg twice daily in the treatment of gastritis symptom relief. Patients treated with 10 to 20 mg of famotidine had fewer erosions and mucosal haemorrhages

25               than those treated with 5 mg famotidine.  
                   McCallum et al., Dig. Dis. Sci. (1985) vol. 30 pp. 1139-1144 describes a study of healthy patients demonstrating that 5 mg of famotidine produces has an effect on gastric acid secretion. Laskin et al., J. Clin. Pharmacol. (1993) vol. 33 pp. 636-639 describes a study

30               demonstrating that single doses of 5 and 10 mg of famotidine produces



- 3 -

statistically significant decreases in intragastric acidity, beginning at 90-100 minutes and persisting for approximately 9 hours.

Administration of H<sub>2</sub> antagonists before ingestion of a heartburn inducing meal may reduce the amount of gastric acid produced and prevent heartburn symptoms. However, H<sub>2</sub> antagonists do not neutralize gastric acid, and the onset of the antisecretory effect of H<sub>2</sub> antagonists is not instantaneous. Therefore, administration of an H<sub>2</sub> antagonist following a meal will not substantially prevent heartburn and related symptoms. Antacids are known to neutralize acid in the stomach and may also act locally in the distal esophagus. Antacids are not known to prevent heartburn when taken before food or beverages which may provoke symptoms.

Wolfe, United States Patent 5,229,137, describes compositions and methods which require the simultaneous administration of an H<sub>2</sub> antagonist with an antacid to provide relief from pain, discomfort and symptoms associated with episodic heartburn. EP 138 540 describes oral compositions containing cimetidine and aluminum hydroxide-magnesium carbonate co-dried gel for treating duodenal, gastric, recurrent and stomal ulceration, and reflux esophagitis. EP 233 853 describes effervescent compositions containing cimetidine and sodium bicarbonate for treating duodenal and gastric ulcers. EP 290 229 describes compositions containing cimetidine, aluminum hydroxide gel, and magnesium hydroxide, for treating duodenal, gastric, recurrent and stomal ulceration, and reflux esophagitis. EP 294 933 describes compositions containing cimetidine, aluminum hydroxide gel and magnesium hydroxide, for treating duodenal, gastric, recurrent and stomal ulceration, and reflux esophagitis. The antacid is described as providing rapid relief from the symptoms of excess stomach acidity by neutralizing acid and the cimetidine is described as bringing about more sustained relief by inhibiting secretion of acid. WO 92/00102 describes coadministration of H<sub>2</sub> antagonists with antacids for treating gastric disorders such as hyperacidity. WO 93/12779 describes compositions of H<sub>2</sub> antagonists with antacids for treating gastric disorders such as hyperacidity. EP

- 4 -

600 725 describes compositions of famotidine with antacids for treating gastrointestinal distress.

Applicants have now found that administration to a patient of a composition comprising an H<sub>2</sub> antagonist and antacid, following a heartburn inducing event such as consumption by the patient of heartburn-inducing food or beverage, but prior to development of heartburn, is an effective means for preventing heartburn or reducing the frequency and severity of postprandial heartburn.

Applicants have also found that compositions comprising about 10 mg famotidine and between about 15 and 46 mEq acid neutralizing capacity of antacid are effective for preventing and treating heartburn symptoms.

#### SUMMARY OF THE INVENTION

In accordance with the invention there is provided a pharmaceutical combination comprising: i) a pharmaceutical composition for preventing heartburn episodes in a patient at risk to development of heartburn comprising a pharmaceutically effective amount of a histamine H<sub>2</sub> receptor antagonist and an amount of antacid having between about 15 mEq and 46 mEq acid neutralizing capacity, and ii) directions for administration of said composition following a heartburn inducing event but prior to development of heartburn, to a patient at risk to development of heartburn.

In accordance with another aspect of the invention there is provided a pharmaceutical combination comprising: i) a pharmaceutical composition for reducing the frequency and severity of heartburn episodes in a patient at risk to development of heartburn, comprising a pharmaceutically effective amount of a histamine H<sub>2</sub> receptor antagonist and an amount of antacid having between about 15 mEq and 46 mEq acid neutralizing capacity, and ii) directions for administration of said composition following a heartburn inducing event but prior to development of heartburn.



- 4a -

In accordance with still another aspect of the invention there is provided a pharmaceutical combination comprising: i) a pharmaceutical composition for precluding symptoms associated with heartburn episodes in a patient at risk to development of heartburn, comprising a pharmaceutically effective amount of a histamine H<sub>2</sub> receptor antagonist and an amount of antacid having between about 15 mEq and 46 mEq acid neutralizing capacity, and ii) directions for administration of said composition following a heartburn inducing event but prior to development of heartburn.

10 In accordance with yet another aspect of the invention there is provided a pharmaceutical combination comprising: i) a pharmaceutical composition for reducing the risk of heartburn episodes in a patient at risk to development of heartburn, comprising a pharmaceutically effective amount of a histamine H<sub>2</sub> receptor antagonist and an amount of antacid having between about 15 mEq and 46 mEq acid neutralizing capacity, and ii) directions for administration of said composition following a heartburn inducing event but prior to development of heartburn.

In accordance with still other aspects of the invention there is provided a pharmaceutical composition comprising a pharmaceutically effective amount of a histamine H<sub>2</sub> receptor antagonist and an amount of antacid having between about 15 mEq and 46 mEq acid neutralizing capacity for use in reducing the frequency and severity of heartburn episodes in a patient at risk to development of heartburn, or for use in precluding symptoms associated with heartburn episodes in a patient at risk to development of heartburn, or for use in reducing the risk of heartburn episodes in a patient at risk to development of heartburn,

20 by administration following a heartburn inducing event but prior to development of heartburn.

In yet another aspect of the invention there is provided use of a histamine H<sub>2</sub> receptor antagonist and an antacid having between about 15 mEq and 46 mEq acid

- 4b -

neutralizing capacity in the manufacture of a medicament for preventing heartburn episodes, reducing the frequency and severity of heartburn episodes, precluding symptoms associated with heartburn episodes or reducing the risk of heartburn episodes, in a patient at risk to development of heartburn, by administration following a heartburn inducing event but prior to development of heartburn.

The invention includes a method for preventing heartburn episodes in a patient at risk to development of heartburn, comprising administering to the patient, following the heartburn inducing event but prior to development of heartburn, a composition comprising a pharmaceutically effective amount of a histamine H<sub>2</sub> receptor antagonist and an amount of antacid having between about 15 mEq and 46 mEq acid neutralizing capacity (ANC). The invention is also a composition comprising about 10 mg famotidine and an amount of antacid between about 15 mEq and 46 mEq ANC. The invention is also a method for treating heartburn symptoms in a patient which comprises administering to the patient an effective amount of a composition comprising about 10 mg famotidine and an amount of antacid between about 15 mEq and 46 mEq ANC.

## DETAILED DESCRIPTION OF THE INVENTION

The invention includes methods for preventing, reducing the frequency and severity of, precluding symptoms associated with, and reducing the risk of heartburn episodes in a patient at risk to development of heartburn, comprising administering to the patient, following the heartburn inducing event but prior to development of heartburn, a composition comprising a pharmaceutically effective



- 5 -

amount of an H<sub>2</sub> antagonist and an amount of antacid having between about 15 mEq and 46 mEq ANC. These methods are effective for preventing heartburn related symptoms such as acid indigestion and sour stomach.

5                In one class of methods, the heartburn inducing event is ingestion of a meal which stimulates gastric acid secretion. In a subclass of this class, the H<sub>2</sub> antagonist is famotidine. In a group of this subclass, the amount of antacid has between about 21 mEq and 42 ANC. In a subgroup of this group, the amount of antacid has about 21 ANC.  
10    In a family of this subgroup, the amount of famotidine is about 10 mg.

              The invention also includes a method for treating heartburn symptoms in a patient comprising administering to the patient a pharmaceutically effective amount of a composition comprising about 10 mg famotidine and an amount of antacid having between about 15  
15    mEq and 46 mEq ANC.

              The invention also includes compositions comprising about 10 mg famotidine and an amount of antacid having between about 15 mEq and 46 mEq ANC. In a class of these compositions, the amount of antacid has between about 21 mEq and 42 mEq ANC. In a subclass of  
20    this class, the amount of antacid has about 21 mEq ANC.

              In a particular embodiment of the compositions of the invention, the composition is in the form of a chewable tablet, the amount of famotidine is about 10 mg, and the amount of antacid is about 21 mEq ANC.

25                The compositions of the invention, when administered following the heartburn inducing event, show a faster onset of relief than H<sub>2</sub> antagonists alone, and a longer duration of relief than antacid. The duration of action of the H<sub>2</sub> antagonist is at least equal to that of a comparable amount of H<sub>2</sub> antagonist administered without antacid.

30                The term "preventing heartburn episodes" means precluding symptoms, or reducing the severity of symptoms, associated with heartburn in patients susceptible to heartburn following ingestion of heartburn-inducing food or beverage.

- 6 -

The term "precluding symptoms" means making the experience of symptoms impossible or largely ineffectual by removing the conditions needed for them.

5 The term "reducing the frequency and severity of postprandial heartburn" means substantially lowering the degree of pain associated with heartburn symptoms that would ordinarily occur in patients susceptible to heartburn following ingestion of heartburn-inducing food or beverage.

10 The term "reducing the risk of heartburn episodes" means substantially lowering the tendency of patients susceptible to heartburn, following ingestion of heartburn-inducing food or beverage, to experience symptoms associated with heartburn following ingestion of heartburn-inducing food or beverage.

15 The term "heartburn inducing event" includes experience by the patient associated with stimulation of gastric acid secretion and development of heartburn symptoms, such as stress or ingestion of a meal which stimulates gastric acid secretion.

20 The term "heartburn-inducing food or beverage" includes foods and beverages commonly associated with heartburn in patients susceptible to food- or beverage-induced heartburn episodes, e.g. tomatoes, chili, coffee, red wine, citrus juice, etc. For purposes of describing the invention, the term "meal" is hereinafter to be understood to mean heartburn-inducing food and/or beverage.

25 The degree of heartburn pain associated with ingestion of such foods varies among individuals and with food types. Thus, some individuals may be more sensitive to certain heartburn-inducing foods than are other individuals. The tendency for a given individual to experience heartburn in response to ingestion of a particular food or beverage is predictable, however, and the individual is able to  
30 determine, prior to ingestion, which food or beverage will induce heartburn symptoms.

A "patient susceptible to suffering heartburn episodes following ingestion of heartburn-inducing food or beverage" means any



- 7 -

patient who ordinarily experiences symptoms of heartburn caused by ingestion of heartburn-inducing food or beverage.

The antacids suitable for the present invention typically are selected from, but are not limited to, magnesium hydroxide, magnesium carbonate, calcium carbonate and co-dried gels. Calcium and magnesium antacids are preferred antacids.

The H<sub>2</sub> antagonists suitable for the methods of the invention for preventing heartburn include, but are not limited to, famotidine, cimetidine, ranitidine, and nizatidine. Preferable, the H<sub>2</sub> antagonist is famotidine. Suitable amounts of famotidine are in the range between about 5 mg and 160 mg, preferable between about 5 mg and 80 mg, e.g. 5 mg, 10 mg, 20 mg, and 40 mg.

In compositions of the invention, amounts of antacid between about 15 and 46 mEq ANC provide immediate preventative and therapeutic relief necessary for effective prevention and treatment of heartburn symptoms. Antacids have known theoretical ANC values (e.g. the ANC of calcium carbonate is 0.020 mEq/mg, and of magnesium hydroxide is 0.0343 mEq/mg - see The United States Pharmacopeia USP 23 NF 18, page 1732 which describes an assay for measuring acid-neutralizing capacity of test substances), and determination of the amount of a specified antacid required to provide a specified ANC can be readily done by persons skilled in the art.

The compositions may also contain pharmaceutically acceptable carriers. Compositions may be formulated for oral administration in solid or liquid form, for example as effervescent or non-effervescent powders or tablets (including chewable and non-chewable tablets), capsules, lozenges, suspensions or dispersions. Compositions may thus be formulated by admixture with pharmaceutically acceptable vehicles additionally containing, as desired, pharmaceutically acceptable adjuvants including thickeners, preservatives, coloring agents, flavoring agents and sweeteners, e.g. aspartame, cyclamate and saccharin.

Powder formulations can be prepared by dry blending ingredients under conditions of controlled temperature and humidity

using conventional equipment. Tablet formulations can be prepared by combining the active components with tableting aids, fillers and palatability aids in a conventional manner and tableting on a conventional machine.

The compositions can be in the form of chewable tablets that  
5 disintegrate readily in the mouth when chewed. Such tablets can be prepared by technology known in the art, including, for example, methods for preparing tablets with barrier layers, such as those described in European Patent Publication 600 725. Such technology is effective for masking the bitter taste associated with H<sub>2</sub> antagonists.

10 In the example shown below, tablets comprising famotidine and antacid, and amounts of inactive ingredients such as binders, e.g. dextrates and pregelatinized starch, flavors, lubricants e.g. magnesium stearate, colorants, e.g. red ferric oxide, sweetener, e.g. confectioner's sugar, granulating excipient, e.g. lactose hydrous and hydroxy methylcellulose, particle coating such as  
15 cellulose acetate and hydroxypropyl cellulose, and wetting agents, e.g. sodium lauryl sulfate sufficient to prepare a pharmaceutically acceptable tablet for delivery of the active famotidine and antacid, were prepared.

#### EXAMPLE 1

A chewable tablet which includes 10 mg famotidine, 800 mg  
20 calcium carbonate and 165 mg magnesium hydroxide (which amounts of calcium carbonate and magnesium hydroxide provide 21 mEq ANC) was prepared in the following manner.

An uncoated famotidine rotorgranulation was prepared by dry blending famotidine with various granulating excipients according to the  
25 procedure outlined in European Patent Publication 600 725.

A rotorgranulated and coated famotidine granulation intermediate was blended with a directly compressible grade of calcium carbonate (DESTAB 95S, available from Particle Dynamics) and a directly compressible magnesium hydroxide powder, dextrates,



- 9 -

confectioner's sugar granulation, color, flavors, and then blended. Magnesium stearate was then added to the blender to form the final blend. The lubricated mixture was compressed into single-layer, round pale rose colored tablets on appropriate tooling.

5 The following table lists specific ingredients and amounts which were used to prepare, according to the above process, a pharmaceutical composition comprising famotidine and antacid.

	<u>Ingredient</u>	<u>% Dry</u>	<u>mg/tablet</u>	<u>mg/tablet</u>
10	Confectioner's Sugar .....			136.7
	Dextrates .....			500.00
	Coated Famotidine .....			86.4
	Granulation			
15	Famotidine	11.57	10.00	
	Excipients		76.4	
	Peppermint .....			11.0
	N&A International Creme .....			2.50
	Magnesium Hydroxide .....			168.4
20	Powder DC			
	Rose Colorant.....			27.7
	Calcium Carbonate (DESTAB 95S, Particle Dynamics) .....			842.1
	Magnesium Stearate .....			5.15
25	Total Tablet Weight			1780 mg

### EXAMPLE 2

30 The procedure of Example 1 is followed, using 330 mg magnesium hydroxide and 1600 mg calcium carbonate, to provide a famotidine/antacid chewable tablet having 42 ANC.

- 10 -

EXAMPLE 3

A non-chewable tablet having the following composition is prepared:

5		
	<u>Ingredient</u>	<u>mg</u>
	Famotidine	10.0
	Magnesium hydroxide	165.0
	Calcium carbonate	800.0
10	Magnesium stearate	5.0
	Pregelatinized starch	40.0
	Carboxymethylcellulose	100.0

15 Famotidine, magnesium hydroxide, calcium carbonate, carboxymethylcellulose, and a portion of the starch are mixed and granulated. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets.

20 EXAMPLE 4

A non-chewable tablet having the following composition is prepared:

25	<u>Ingredient</u>	<u>mg</u>
	Coated famotidine granulation	86.4
	Magnesium hydroxide	165.0
	Calcium carbonate	800.0
30	Magnesium stearate	5.0
	Pregelatinized starch	40.0
	Carboxymethylcellulose	100.0



- 11 -

Coated famotidine granulation (used in Example 1), magnesium hydroxide, calcium carbonate, carboxymethylcellulose, and a portion of the starch are mixed and granulated. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets.

### EXAMPLE 5

A non-chewable tablet having the following composition is prepared:

	<u>Ingredient</u>	<u>mg</u>
	Famotidine	10.0
15	Magnesium hydroxide	330.0
	Calcium carbonate	1600.0
	Magnesium stearate	5.0
	Pregelatinized starch	40.0
	Carboxymethylcellulose	100.0

Famotidine, magnesium hydroxide, calcium carbonate, carboxymethylcellulose, and a portion of the starch are mixed and granulated. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets.

### EXAMPLE 6

Adult male and female patients having a history of heartburn, acid indigestion, or sour/upset stomach are given a meal of chili and burgundy wine. Tablets prepared according to Example 1 are administered to the patients after consumption of the meal but prior to development of heartburn symptoms, decreasing the likelihood of heartburn.

- 12 -

EXAMPLE 7

Adult male and female patients having a history of heartburn, acid indigestion, or sour/upset stomach are given a meal of chili and burgundy wine. Tablets prepared according to Example 1 are administered to the patients after development of heartburn symptoms induced by the meal, relieving pain associated with heartburn.



**CLAIMS**

1. A pharmaceutical combination comprising:
  - i) a pharmaceutical composition for preventing heartburn episodes in a patient at risk to development of heartburn comprising a pharmaceutically effective amount of a histamine H<sub>2</sub> receptor antagonist and an amount of antacid having between about 15 mEq and 46 mEq acid neutralizing capacity, and
  - ii) directions for administration of said composition following a heartburn inducing event but prior to development of heartburn, to a patient at risk to development of heartburn.
2. A combination according to claim 1, wherein said H<sub>2</sub> antagonist is famotidine.
3. A composition of claim 1 or 2, wherein the amount of antacid has between about 21 mEq and 42 mEq acid neutralizing capacity.
4. A composition of claim 3, wherein the amount of antacid has about 21 mEq acid neutralizing capacity.
5. A pharmaceutical combination comprising:
  - i) a pharmaceutical composition for reducing the frequency and severity of heartburn episodes in a patient at risk to development of heartburn, comprising a pharmaceutically effective amount of a histamine H<sub>2</sub> receptor antagonist and an amount of antacid having between about 15 mEq and 46 mEq acid neutralizing capacity, and
  - ii) directions for administration of said composition following a heartburn inducing event but prior to development of heartburn.

- 14 -

6. A combination of claim 5, wherein the H<sub>2</sub> antagonist is famotidine.

7. A combination of claim 5 or 6, wherein the amount of antacid has between about 21 mEq and 42 mEq acid neutralizing capacity.

8. A combination of claim 7, wherein the amount of antacid has about 21 mEq acid neutralizing capacity.

9. A pharmaceutical combination comprising:

i) a pharmaceutical composition for precluding symptoms associated with heartburn episodes in a patient at risk to development of heartburn, comprising a pharmaceutically effective amount of a histamine H<sub>2</sub> receptor antagonist and an amount of antacid having between about 15 mEq and 46 mEq acid neutralizing capacity, and

ii) directions for administration of said composition following a heartburn inducing event but prior to development of heartburn.

10. A combination of claim 9, wherein the H<sub>2</sub> antagonist is famotidine.

11. A combination of claim 9 or 10, wherein the amount of antacid has between about 21 mEq and 42 mEq acid neutralizing capacity.

12. A combination of claim 11, wherein the amount of antacid has about 21 mEq acid neutralizing capacity.

13. A pharmaceutical combination comprising:



- 15 -

i) a pharmaceutical composition for reducing the risk of heartburn episodes in a patient at risk to development of heartburn, comprising a pharmaceutically effective amount of a histamine H<sub>2</sub> receptor antagonist and an amount of antacid having between about 15 mEq and 46 mEq acid neutralizing capacity, and

ii) directions for administration of said composition following a heartburn inducing event but prior to development of heartburn.

14. A combination of claim 13, wherein the H<sub>2</sub> antagonist is famotidine.

15. A combination of claim 13 or 14, wherein the amount of antacid has between about 21 mEq and 42 mEq acid neutralizing capacity.

16. A combination of claim 15, wherein the amount of antacid has about 21 mEq acid neutralizing capacity.

17. A composition comprising about 10 mg famotidine and an amount of antacid between about 15 mEq and 46 mEq acid neutralizing capacity.

18. A composition of claim 17, wherein the amount of antacid having between about 21 mEq and 42 mEq acid neutralizing capacity.

19. A composition of claim 18, wherein the amount of antacid having about 21 mEq acid neutralizing capacity.

20. A composition of claim 17, 18 or 19, wherein the composition is in the form of a chewable tablet.

- 16 -

21. A pharmaceutical composition comprising a pharmaceutically effective amount of a histamine H<sub>2</sub> receptor antagonist and an amount of antacid having between about 15 mEq and 46 mEq acid neutralizing capacity for use in reducing the frequency and severity of heartburn episodes in a patient at risk to development of heartburn, by administration following a heartburn inducing event but prior to development of heartburn.

22. A pharmaceutical composition comprising a pharmaceutically effective amount of a histamine H<sub>2</sub> receptor antagonist and an amount of antacid having between about 15 mEq and 46 mEq acid neutralizing capacity for use in precluding symptoms associated with heartburn episodes in a patient at risk to development of heartburn, by administration following a heartburn inducing event but prior to development of heartburn.

23. A pharmaceutical composition comprising a pharmaceutically effective amount of a histamine H<sub>2</sub> receptor antagonist and an amount of antacid having between about 15 mEq and 46 mEq acid neutralizing capacity for use in reducing the risk of heartburn episodes in a patient at risk to development of heartburn, by administration following a heartburn inducing event but prior to development of heartburn.

24. A composition according to claim 21, 22 or 23, wherein said histamine H<sub>2</sub> receptor antagonist is famotidine.

25. A composition of claim 21, 22, 23 or 24, wherein the amount of antacid has between about 21 mEq and 42 mEq acid neutralizing capacity.



- 17 -

26. A composition of claim 25, wherein the amount of antacid has about 21 mEq acid neutralizing capacity.

27. Use of a histamine H<sub>2</sub> receptor antagonist and an antacid having between about 15 mEq and 46 mEq acid neutralizing capacity in the manufacture of a medicament for preventing heartburn episodes, reducing the frequency and severity of heartburn episodes, precluding symptoms associated with heartburn episodes or reducing the risk of heartburn episodes, in a patient at risk to development of heartburn, following a heartburn inducing event but prior to development of heartburn.

28. Use according to claim 27, wherein said H<sub>2</sub> antagonist is famotidine.

29. Use according to claim 27 or 28, wherein the antacid has between about 21 mEq and 42 mEq acid neutralizing capacity.

30. Use according to claim 29, wherein the antacid has about 21 mEq acid neutralizing capacity.

31. A composition comprising about 10 mg famotidine and an amount of antacid between about 15 mEq and 46 mEq acid neutralizing capacity.

32. A composition of claim 31, wherein the amount of antacid has between about 21 mEq and 42 mEq acid neutralizing capacity.

33. A composition of claim 32, wherein the amount of antacid has about 21 mEq acid neutralizing capacity.

- 18 -

34. A composition of claim 31, 32 or 33, wherein the composition is in the form of a chewable tablet.