



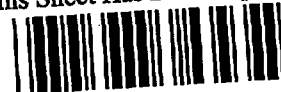
**RANITIDINE AND CALCIUM CARBONATE
PHARMACEUTICAL COMBINATION PRODUCT
BACKGROUND OF THE INVENTION**

5 Ranitidine, chemically identified as N-[2-[[[5-(dimethylamino)methyl-2-furanylmethyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine (see U.S. Patents 4,128,658; 4,521,431; 4,585,790 and 4,672,133 incorporated herein by reference), is an antagonist to histamine H₂ receptors. As used herein the term "ranitidine" refers to the free base and the pharmaceutically acceptable acid
10 addition salts thereof unless otherwise noted. This drug is widely used in the treatment of duodenal ulcers in humans in the form of the hydrochloride salt. While the drug is generally given orally or by injection, the oral route is preferred. Ranitidine HCl is sold under the trademark Zantac® by Glaxo Inc. of Research Triangle Park, North Carolina.

15 Calcium carbonate is used as an antacid for fast relief of acid indigestion, heartburn, sour stomach and upset stomach associated with those symptoms. It is used in antacids sold commercially under the trademark Tums® by SmithKline Beecham Consumer Brands of Pittsburgh, Pennsylvania and is a buffer in
20 Ascriptin® analgesic in combination with aspirin, magnesium hydroxide and aluminum hydroxide as sold by Rorer Consumer Pharmaceuticals of Fort Washington, Pennsylvania. U.S. Patent 4,650,669 to Alexander describes formulations for pharmaceuticals containing calcium carbonate.

25 Pharmaceuticals having both ranitidine or another H₂ receptor antagonist and NaHCO₃ include the effervescent compositions described by Schaeffer in U.S. Patent 5,102,665. An effervescent pharmaceutical comprising an antacid effervescent couple, an antacid and an histamine H₂-antagonist is described in
30 US Patent 4,824, 664 issued to Tarral. Other disclosures of combinations H₂-antagonists and antacids are found in European Patent Specification No. 286,781.

35 PCT Publication WO/92/00102 published 9 January 1992 to Davis describes co-administration of a histamine H₂-receptor antagonist and antacid for the treatment of gastric disorder, e.g., Example 17 thereof listing calcium carbonate.



PCT Publication WO 93/12779 published 8 July 1993 to Davis describes co-administration of a histamine H₂-receptor antagonist and antacid for the treatment of gastric disorder, e.g., Example 14 thereof listing calcium carbonate.

5 US Patent 5,229,137 issued to Wolfe describes the co-administration of a histamine H₂-receptor antagonist and an antacid for the treatment of episodic heartburn, e.g., Example IV thereof relating to the co-administration of ranitidine and Tums[®] tablets.

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SUMMARY OF THE INVENTION

Pharmaceutical compositions such as tablets containing both calcium carbonate and ranitidine. The composition provides relief from many gastrointestinal diseases and symptoms.

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DETAILED DESCRIPTION OF THE INVENTION

The composition of the invention is substantially free of acid, e.g., acid as may be used as part of an acid-base couple to produce effervescence.

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Ranitidine

Preferably, the ranitidine is used in the present invention as its hydrochloride and in the Form 2 crystalline form.

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Calcium Carbonate

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Calcium carbonate, also known as carbonic acid calcium salt, occurs in nature as the minerals aragonite, calcite and vaterite. In the present invention, the calcium carbonate may be used in the calcite form and be essentially free of the aragonite crystal form.



5 The calcium carbonate employed in the present invention can be in the particulate form. Suitable particulate calcium carbonate is Albaglos®, supplied by Pfizer, at its facility in Adams, Massachusetts. Albaglos is a precipitated calcium carbonate made by starting with high quality CaCO_3 and burning it to create CO_2 and CaO (lime). The CaO is dissolved in H_2O to create a milk of lime solution ($\text{CaCOH}/_2$). The CO_2 (which was previously captured) is injected into the solution, causing pure crystals of CaCO_3 to precipitate.

10 Other Ingredients

15 Other known pharmaceutical excipients such as flavorings, taste masking agents, lubricants, surfactants, binders or coloring agents and the like may be optionally added into the tablet composition of the present invention. Typical flavorings include grapefruit, lemon, mint and orange, and/or sweeteners such as aspartame or sodium saccharin. A small amount of dioctylsodium sulfosuccinate (DOSS also known as docusate sodium) solution, for instance, may be added as a surfactant, and/or a small amount of fumaric acid may be added as a lubricant. These excipients are usually added in the amount of 0.001% to 100% weight/weight, more particularly 0.01% to 60% weight/weight, of the CaCO_3 .

25 Taste-masking ingredients and formulation techniques known in the art may be applied in the pharmaceutical composition of the invention. Examples include those in UK Patent Specification Nos 2198352 (liquid preparations), 2219940 (effervescent tablets), 2218333 (ranitidine resinate), 2218336 (film-coated tablets), 2229094 (gelatin capsules), 2262445 (pulsed-release formulation), European Patent Specification Nos 349103, 459695, 473431, 523847 and 538034 (chewable tablets), 542364 (controlled-release formulations), International Patent Specification Nos W092/21328 (chewable compositions), 30 WO94/08560 (chewable tablets), W094/05260 (aqueous compositions), WO94/08576 (lipid-coated granules), Canadian Patent Specification No. 2068366 (taste-masked powder), United States Patent Specification Nos 5169864 and 5304571 (aqueous compositions) which patent specifications are incorporated herein by reference.

35 Suitable binders for use in tablet preparation include methylcellulose, sodium carboxymethylcellulose, hydroxypropyl methylcellulose, alginic acid, ethylcellulose, acacia, gelatin, pregelatinized starch, sucrose syrup,



polyvinylpyrrolidone and guar gum. A particular binder is polyvinylpyrrolidone (povidone).

5 Suitable lubricants for use in tablet preparation include magnesium stearate, zinc stearate, calcium stearate, stearic acid, sodium stearyl fumarate, hydrogenated vegetable oils, glyceryl palmitostearate, glyceryl behenate, sodium benzoate, sodium lauryl sulphate, magnesium lauryl sulphate, mineral oil, talc and mixtures thereof. Magnesium stearate is a particular lubricant.

10 Suitable dessicants for use in tablet preparation include silica gel.

Dose

15 Ranitidine may be used in the composition of the present invention in an amount of 25 to less than 100 mg per dose, e.g., about 30 to 90 mg calculated as ranitidine base. In particular, a dose of about 50 to 80 mg, e.g., 75 mg may be used.

20 Calcium carbonate may be used in the unit dose composition of the present invention in an amount of about 250 mg to 1000 mg to provide an antacid neutralizing capacity of about 5 to 40 mEq. A particular dose is about 500 mg of calcium carbonate.

25 The unit dose may be administered up to, for example, 6 times a day depending upon the unit dose used, the nature and severity of the conditions being treated, and the age and weight of the patient. Thus, for example, in the treatment of minor conditions where there is an advantage in lowering gastric acidity such as, for example, acid indigestion, over-indulgence of food or drink, acid stomach, sour stomach, waterbrash/regurgitation, heartburn, such as episodic heartburn, nocturnal heartburn, and meal-induced heartburn, gastritis and
30 dyspepsia, lower and more frequent doses of ranitidine may be used, for example doses in the range of 25-95 mg, e.g., 40-75 mg ranitidine expressed as the weight of free base, such as 83.7 mg ranitidine hydrochloride, administered up to 6 times a day as and when required.

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It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms.

Pharmaceutical Presentation

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The pharmaceutical composition of the invention may be in the form of a solid particulate, e.g., a powder, with the 2 ingredients present homogeneously so that the unit dose would be a measure such as a teaspoonful. Alternatively, the composition can be used in the form of a liquid where the unit dose would be a liquid measure, e.g., 10 ml. Most conveniently, the composition of the invention is used as a pre-formed unit dose such as a tablet, bi-layer tablet with separate location for the ranitidine and the calcium carbonate, capsule or other particular modification such as a gelcap, caplet, tongue tablet or chewable tablet.

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Tableting

To produce tablets of the composition according to the present invention, the active ingredients and excipients may be subject to dry slugging, wet granulation or dry blending followed by compression into tablets using an appropriate tablet press fitted with suitable punches.

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Capsules

To produce capsules of the composition according to the present invention, the active ingredients and inactive excipients are mixed and filled into gelatin capsules as is conventional in the art.

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In a further or alternative aspect, the present invention provides the use of an oral pharmaceutical composition comprising ranitidine, or a pharmaceutically acceptable salt thereof, and an antacid for the manufacture of a medicament of the treatment of conditions where there is an advantage in lowering gastric acidity, characterized in that the antacid comprises calcium carbonate.

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Example 1

5 The following ingredients are mixed and formulated into tablets in a conventional manner.

	ranitidine hydrochloride	83.7	grams
	calcium carbonate	500	grams
	starch	80	grams
10	powdered lactose	80	grams
	talc	<u>20</u>	grams
		763.7	grams

15 The above ingredients are combined, mixed and then compressed into slugs. The slugs may then be ground to form granules that will pass through a 14 to 16 mesh screen. The granules may then be recompressed into tablets using a suitable compression mold to form 1000 tablets, each weighing about 763.7 mg.

Example 2

20 The following is a bi-layer tablet to cover any incompatibilities between the ingredients.

	Ranitidine Layer	mg/tablet
	Ranitidine hydrochloride	84.0
25	Microcrystalline cellulose USP	64.5
	Magnesium stearate USNF	1.5

The ranitidine hydrochloride (taste-masked if required) is blended with the microcrystalline cellulose and magnesium stearate.

30	Antacid Layer	mg/tablet
	Calcium carbonate precipitated USP	500.0
	Sucrose	346.0
	Flavor/sweetener	qs
35	Magnesium stearate USNF	4.0



The calcium carbonate and sucrose for the antacid layer are granulated together in a conventional manner. The calcium carbonate/sucrose granule is blended with the flavor sweetener and magnesium stearate.

- 5 The ranitidine containing granules and antacid granules are compressed together as a bi-layer tablet on a suitable compression machine.



What is claimed is:

1. A pharmaceutical composition comprising ranitidine in an amount of 25 to less than 100 mg per dose and calcium carbonate.

2. The pharmaceutical composition of Claim 1, wherein the composition is substantially free of acid.

3. The pharmaceutical composition of Claim 1, wherein said ranitidine is in the form of ranitidine hydrochloride salt.

4. The pharmaceutical composition of Claim 1, wherein said ranitidine is present in an amount of about 30 to 90 mg, calculated as ranitidine free base, per unit dose of said pharmaceutical composition.

5. The pharmaceutical composition of Claim 1, wherein said ranitidine is present in an amount of 25 or 75 mg, calculated as ranitidine free base, per unit dose of said pharmaceutical composition.

6. The pharmaceutical composition of Claim 1, wherein said calcium carbonate is present in an amount of about 250 to 1000 mg per unit dose of said pharmaceutical composition.

7. The pharmaceutical composition of Claim 1, in the form of a solid particulate.

8. The pharmaceutical composition of Claim 1, in the form of a liquid.

9. The pharmaceutical composition of Claim 1, in the form of a solid unit dose.

10. The pharmaceutical composition of Claim 9, wherein said solid unit dose is a tablet or capsule.

11. The pharmaceutical composition of Claim 1, further comprising one or more flavoring agents, taste masking agents, binders, lubricants, surfactants or coloring agents.

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12. The pharmaceutical composition of Claim 1, in the form of a bi-layer tablet.

5 13. The pharmaceutical composition of Claim 1, wherein said composition contains only said ranitidine and calcium carbonate as active ingredients.

10 14. A method of treating episodic heartburn, nocturnal heartburn, meal-induced heartburn, gastritis, dyspepsia or gastrointestinal symptoms associated with the overindulgence of food and drink which comprises administering to a human in need thereof, the pharmaceutical composition of Claim 1.

15 15. A method of treating and preventing duodenal ulcers, pathological hypersecretory conditions, gastric ulcers, gastro-esophageal reflux or erosive esophagitis which comprises administering to a human in need thereof, the pharmaceutical composition of Claim 1.