Title: SYSTEM AND METHOD OF TREATMENT WITH NIZATIDINE

Abstract: This invention relates to a nizatidine composition and a method for treating gastric and intestinal disorders by administering a composition containing about 175 to about 300 mg of nizatidine or salt thereof and one or more pharmaceutically acceptable excipients twice daily. Nizatidine is preferably administered before and after meals to effectively inhibit and control gastric acid secretions, which are typically associated with heartburn and gastric ulcers. The oral administration may be immediate release, time-sustained release, time-delayed release or a combination thereof.
SYSTEM AND METHOD OF TREATMENT WITH NIZATIDINE

FIELD OF THE INVENTION

[0001] This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/624,525 of George Bobotas, Keith Rotenberg, and Abdel Fawzy, titled "System and Method of Treatment with Nizatidine" filed November 4, 2004. The entirety of the provisional patent application is incorporated herein by reference.

[0001] The present invention relates to a method of treating patients with about 175 to about 300 milligrams of nizatidine twice daily.

BACKGROUND OF THE INVENTION

[0002] Nizatidine is generally used to treat stomach or intestinal disorders. For example, nizatidine is typically orally administered to treat and prevent ulcers in the stomach and the intestines. Nizatidine basically works by decreasing the amount of acid the stomach produces. Nizatidine is also used to treat conditions in which the stomach produces too much acid and conditions in which acid comes up into the esophagus and causes heartburn, such as gastroesophageal reflux disease (GERD). Nizatidine has also been used to treat hyperacidity and Zollinger-Ellison Syndrome, which is a condition where large amounts of acid pour from the stomach.

[0003] Heartburn is most frequently associated with food and beverage ingestion and is the most common symptom of gastroesophageal reflux disease. Studies indicate that as many as 45% of otherwise healthy people experience heartburn at least twice a month and 7% experience heartburn
daily. Heartburn is often associated with meal-stimulated gastric acid secretion and gastroesophageal reflux with a pH of 4 or higher. Stomach acid is produced as a normal part of the digestive process. However, if large amounts of stomach acid are produced, the excess acid may flow back into the food pipe (esophagus), causing pain and a burning sensation known as heartburn. Excess stomach acid can also irritate the lining of the stomach and duodenum. This lining normally resists attack from the stomach acid, but if the lining is damaged, for example due to treatment with non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen), or large amounts of stomach acid are produced, a peptic ulcer can develop.

[0004] Nizatidine is in a class of drugs called histamine receptor antagonists. Nizatidine is generally a water-soluble competitive, reversible inhibitor of histamine at the histamine H2-receptors, particularly those in the gastric parietal cells. Generally, as nizatidine blocks the H2 receptors on the cells in the stomach, nizatidine prevents histamine from binding to the cells of the stomach. This prevention thereby decreases the amount of stomach acid produced by stomach cells and lowers the amount of acid in the stomach and duodenum. This action helps to relieve the pain of heartburn, and helps ulcers to heal, including those caused by NSAIDs. By decreasing the production of stomach acid, nizatidine can also be used to prevent ulcers from recurring.

Nizatidine has the molecular formula $C_{12}H_{21}N_6O_2S_2$ representing a molecular weight of 331.46. The structural formula is as follows:

![Nizatidine structural formula]

[0006] Generally, nizatidine is administered in doses of 300 mg once a day or 150 mg twice per day. Nizatidine is also administered at 150 mg once per day. Indications for use typically recommend these amounts. At 300 mg, nizatidine has been shown in some studies to reduce gastric secretions and treat gastric ulcers. However, as evident by Table 1 below, 300 mg of nizatidine once per day is not absolutely effective in achieving these goals.

Table 1

<table>
<thead>
<tr>
<th>Effect of Oral Acid on Gastric Acid Secretion</th>
<th>Time After Dose (h)</th>
<th>% Inhibition of Gastric Acid Output by Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20-60</td>
<td>75</td>
</tr>
<tr>
<td>Nocturnal</td>
<td>Up to 10</td>
<td>57</td>
</tr>
<tr>
<td>Betazole</td>
<td>Up to 3</td>
<td>93</td>
</tr>
<tr>
<td>Pentagastrin</td>
<td>Up to 6</td>
<td>25</td>
</tr>
<tr>
<td>Meal</td>
<td>Up to 4</td>
<td>41</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Up to 3</td>
<td>73</td>
</tr>
</tbody>
</table>

[0007] It is unknown in the conventional art whether increasing dosages of nizatidine significantly increases the benefits observed through nizatidine use. Moreover, the conventional art has not researched the efficacy and safety of nizatidine dosages more than 300 mg, and administrations thereof more than once a day. Specifically, researchers have not found an amount of nizatidine that increases the percent inhibition of gastric acid output, while maintaining
the safety, i.e., maintaining or reducing the side effects or adverse reactions, associated with the use of nizatidine.

[0008] A limited number of studies have examined dosages other than 150 mg and 300 mg. For example, in Spiegel, Jill E. et al, A double-blind placebo controlled study of the effectiveness and safety of nizatidine in the prevention of postprandial heartburn, Archives of Internal Medicine (1997), 157(14), 1594-1599, the researchers examined the effectiveness of three does levels, 225 mg, 75 mg, and 25 mg, in preventing postprandial heartburn. Subjects were given a dosage of nizatidine or a placebo thirty minutes before eating a meal. The presence and severity of heartburn was assessed before the meal and multiple times thereafter. Researchers determined that single doses of 225 mg and 75 mg of nizatidine administered 30 minutes before a standard meal, which is intended to provoke heartburn, acted at a significantly more effective level than placebo for the prevention and/or reduction of postprandial heartburn. However, this study did not examine dosages greater than 300 mg day. Moreover, while this study examined dosages other than 150 mg and 300 mg, the study did not examine administration more than once, e.g., twice, a day.

[0009] There is an unmet need in the art for an effective amount of nizatidine to treat gastric and intestinal disorders without occurrence or manifestation of the side effects or potential adverse reactions associated with conventional dosages of nizatidine. In particular, there is an unmet need in the art for a total dosage above 300 mg per day of nizatidine that is also safe for human administration. Additionally, there is an unmet need in the art for
administration of dosages of nizatidine that can be given multiple times a day, while being effective in each use.

SUMMARY OF THE INVENTION

[0010] The present invention overcomes the above-mentioned problems, as well as others, by administering a safe and effective amount of nizatidine to treat gastric and intestinal disorders. In particular, the present invention is related to orally administering to humans nizatidine at about 175 to about 300 mg, preferably about 200 to about 250 mg, most preferably about 225 mg, twice daily to treat gastric and intestinal disorders. The present invention provides an effective single dosage, as part of a single or bi-daily dose regimen, to address gastric and intestinal disorders. The invention provides that single or bi-daily administration of nizatidine effectively inhibits and controls gastric secretions. Moreover, the total daily dosage of about 175 to about 600 mg, preferably about 400 to about 500 mg, most preferably about 450 mg, effectively inhibits and controls gastric secretions associated with gastric and intestinal disorders.

[0011] Nizatidine is desirably provided using a delayed and sustained release composition suitable for oral administration. This ensures that nizatidine can be taken after meal intake or before nightly sleep, and the active composition is continuously released to the intended sites for a duration of time corresponding to the duration of time gastric secretions are prevalent.

[0012] Other features of the present invention will become apparent to those skilled in the art upon examination of the following or upon learning by practice of the invention.
DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0013] The present invention provides a safe and effective administration of nizatidine to treat gastric and intestinal disorders. The present invention provides an administration of nizatidine of about 175 to about 300 mg, preferably about 200 to about 250 mg, most preferably about 225 mg, twice daily, or a total daily dosage of about 350 to about 600 mg, preferably about 400 to about 500 mg, most preferably about 450 mg, administered once or in two divided doses. Thus, the administration is effective in treating gastrointestinal disorders, such as GERD, heartburn, impaired gastric motility and peptic ulcers, specifically inhibiting gastric secretions to an extent not before seen in the art. The present invention also is useful in minimizing weight gain, or promoting weight loss, in subjects engaged in a dietary regimen.

[0014] Nizatidine is administered once or twice daily, in accordance with the present invention. In the prevention of heartburn or daily gastric secretions, the first administration of nizatidine is preferably taken prior to consumption of a meal which is likely to induce gastric secretions. Accordingly, under twice daily administration, the first administration of nizatidine is preferably administered about 15 to about 90 minutes before the meal is consumed by the user. Preferably, the administration of nizatidine occurs about 15 to about 45 minutes, more preferably about 30 minutes before the meal.

[0015] The second administration of nizatidine is preferably taken by the user after a meal, typically 6-14 hours after the first administration. In one
variation, the second administration is taken immediately after a meal. In another variation, the second administration is taken between about 30 minutes after the meal to about 180 minutes after the meal. Preferably, the second administration is taken about 60 minutes to about 120 minutes after the meal. Alternatively, if the meal is consumed in the evening, i.e., dinner, the second administration may be taken prior to overnight sleep, e.g. about 10 pm. It is generally known in the art that nizatidine is effectively inhibits nocturnal gastric acid secretions.

[0016] In treatment of more long-term ailments, such as gastric ulcers, bidaily administrations of nizatidine can be scheduled on a more fixed basis, i.e., not dependent on meal intake. For example, nizatidine is first administered in the morning hours, prior to ingestion of food. In one variation, the first administration is before breakfast, and the second administration is taken at a predetermined evening hour or prior to nightly sleep. It is noted that exact times of administration of nizatidine may be variable. In accordance with this aspect of present invention, however, it is constant that nizatidine is administered twice daily. Under once daily administration, the nizatidine can be taken in the morning, or in the evening to treat nocturnal gastric acid secretions.

[0017] A delivery system of the present invention can comprise a combination of active and non-active pharmaceutical ingredients (also known generally herein as "excipients"). Non-active ingredients, for example, serve to solubilize, suspend, emulsify, stabilize, preserve, protect, color, flavor, and fashion the active ingredients into an applicable and efficacious preparation.
that is safe, convenient, and otherwise acceptable for use. The active ingredient, i.e., nizatidine or a suitably acceptable salt thereof, can constitute about 1 to 60% of the total weight percent of the delivery system, for example.

[0018] The delivery system of the present invention is of any type that allows oral administration. Accordingly, the pharmaceutical compositions may be in a form suitable for oral use, for example, as tablets, lozenges, aqueous or oily suspensions, dispersible powders or granules, liquids, emulsions, hard or soft capsules, syrups, elixirs or oral solutions.

[0019] Generally, excipients and non-active ingredients of orally administered nizatidine are of any type generally known in the art. Compositions intended for oral use may contain one or more agents, such as sweetening agents, flavoring agents, coloring agents and the like, in order to provide a pharmaceutically elegant and palatable preparation. Syrups and elixirs may be formulated with suitable sweetening agents, for example, glycerol, sorbitol, or sucrose. Such formulations may also contain suitable demulcients, preservatives and flavoring and coloring agents.

[0020] Minor amounts of other ingredients such as tonicity agents (e.g. NaCl), pH adjusters (e.g., a base such as NaOH, acids such as citric), emulsifiers or dispersing agents, buffering agents, preservatives, wetting agents, thickening agents (e.g. polyvinyl alcohol) and gelling agents (e.g. poloxamer) may also be present. Particularly preferred compositions contain sufficient amounts of the foregoing and/or other ingredients to be a substantially isotonic and/or buffered to a physiologically acceptable pH.
[0021] For example, in one tablet variation of the present invention, nontoxic, pharmaceutically acceptable excipients, which are suitable for manufacture of tablets, include inert diluents (e.g., calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate), granulating and disintegrating agent (e.g., maize starch or alginic acid), binding agents (e.g., starch, gelatin or acacia), and/or lubricating agents (e.g., magnesium stearate or stearic acid). As further discussed in this description, the tablets may be uncoated or they may be coated by known techniques to delay disintegration (also interchangeably referred to herein as “time-sustained release”) and absorption in the gastrointestinal tract and therefore provide an even longer sustained action over a period of time.

[0022] In another variation of the present invention, the oral use formulation includes hard gelatin capsules, wherein nizatidine is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with either a suitable oil medium, for example, arachis oil, liquid paraffin, olive oil or an aqueous medium.

[0023] In one more variation of the present invention, the oral use formulation includes aqueous suspensions. Nizatidine is admixed with excipients, including suspending agents (e.g., sodium carboxymethyl cellulose, methyl cellulose, hydroxy propyl methyl cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia) and wetting agents (e.g., lecithin, polyoxyethylene stearate, heptadecaethyleneoxycetanol, polyoxyethylene sorbitol monooleate, or polyoxethylene sobirtan.
monooleate). The aqueous suspensions may also contain one or more suitable preservatives (e.g., ethyl, or n-propyl, p-hydroxy benzoate), one or more suitable coloring agents, one or more suitable flavoring agents and one or more suitable sweetening agents (e.g., sucrose, saccharin, or sodium or calcium cyclamate).

[0024] It is also conceived that the present invention can be delivered in chewable form, i.e. a tablet intended to disintegrate in the mouth under the action of chewing or sucking and where, in consequence, the unpleasant-tasting active ingredient has ample opportunity to come into contact with the bitter-taste receptors on the tongue. Accordingly, the drug with a coating agent, which prevents the active ingredient, which is characterized with a bitter taste from coming into contact with the tastebuds.

[0025] In one more example, one variation an oral administration of nizatidine includes a gelatin, pregelatinized starch, dimethicone, starch, titanium dioxide, yellow iron oxide, and 225 mg (0.68mmol) nizatidine. The oral administration may also include magnesium stearate, croscarmellose sodium, povidone, red iron oxide, and talc.

[0026] To maximize the efficacy of nizatidine to treat gastric and intestinal disorders, it is desirable that the presence of nizatidine be maintained over a substantial period of time. Accordingly, in another variation of the present invention, the active ingredient nizatidine is formulated to be released in a controlled manner, i.e., time sustained release. Thus, it is preferred to sustain an appropriate blood concentration of nizatidine for at least one hour, and
preferably at least two, three, or four hours before and after meal intake. This may be ensured by using a delayed and/or controlled release formulation.

[0027] Any effective controlled and/or delayed release enhancing compounds can be utilized in the formulation. Also, the delayed release mechanism and/or components are preferably in the form of a coating but can take the form of any other effective vehicle, while the controlled release mechanism and/or components are preferably in the form or a coating or a matrix, but can also be in the form of an any other effective vehicle.

[0028] The controlled and delayed release formulations can be generally made of two or three (or more) parts. The first part is a central core, which either includes the nizatidine (the two part formulation) or can be coated with a coating (the second part in the three part formulation) that contains nizatidine, for example in association with conventional excipients. The second part (or third part in the three part formulation) can be a coating, for example, a polymeric coating that envelops or substantially envelops the central core. This coating is responsible for giving the blocking agent its particular controlled and/or delayed release characteristics. The central core (or the second part of the three part formulation) may be prepared by a number of techniques known in the art. Typically the nizatidine is bound to an inert carrier, typically a starch or sugar sphere, with a conventional binding agent. Sugar spheres are preferred but any pharmaceutically acceptable inert carrier may be utilized.

[0029] The binding agent that is used to secure the nizatidine can be any of the known binding agents. Examples of suitable lubricants that can be
used include white wax, castor oil, palmitic acid, stearic acid, mineral oil, polyethylene glycol, etc. Examples of suitable coating agents that can be used include ethyl cellulose, methylcellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, polymerized acrylates, etc. Other conventional pharmaceutical excipients may be incorporated into the binding agent.

[0030] The second (or third) component is the coating, for example, a polymeric coating. The coating is responsible for giving the nizatidine its particular release characteristics. The coating may be produced, for example, from polymerized acrylates or copolymers of acrylic acid and methacrylic acid or esters of either monomer (hereinafter polymerized acrylates). The polymeric coating of the delayed release pellet may also be prepared from one of the organosiloxane oral coating materials known in the art such as polydimethylsiloxane, polydiethyilsiloxane, etc.

[0031] Polymerized acrylates as well as copolymers of acrylic acid and methacrylic acid or esters of either monomer are known in the art and are available from many commercial sources. Examples of such copolymers include poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(isobutyl methacrylate), poly(phenyl methacrylate) etc. The polymeric coating may optionally contain a sufficient quantity of a suitable plasticizer. Examples of such plasticizers include acetyl triethyl citrate, dibutyl phthalate, tributyl citrate, triethyl citrate, acetyl tributyl citrate, propylene glycol, triacetin, polyethylene glycol and diethyl phthalate.
[0032] The polymeric coating may also be made from a variety of coating materials that are typically utilized in the pharmaceutical arts. The coating may be manufactured from a variety of water insoluble polymers such as, for example, ethylcellulose, hypromellose phthalate, cellulose acetate, cellulose propionate, cellulose acetate butyrate, polyethylene, polypropylene, polyethylene oxide, polyvinyl acetate, polyvinyl chloride, etc. A minor proportion of a water-soluble polymer may also be included in the polymeric coating. Examples of such polymers include methyl cellulose, hydroxypropyl cellulose, polyethylene glycol, polyvinyl pyrrolidone, etc. These coatings may also include conventional excipients such as plasticizers, antifoaming agents, antiadherants, etc.

[0033] The polymeric coating may be applied to the central core using methods and techniques known in the art. Typically a suspension, emulsion, or solution of the polymeric coating is prepared as is known in the art. The amount of fluidized polymeric coating required in the coating process may be readily calculated depending upon the amount of polymeric coating desired. The fluid polymeric coating may be applied to the central core by a number of coating techniques known in the art. Examples of suitable coating devices include fluid bed coaters, pan coaters, etc.

[0034] It is also suitable to prepare sustained release forms by extrusion/spheronization of a mixture comprising the blocking agent and pharmaceutically acceptable excipients, as known in the art. See, e.g., J. W. Conine et al., Drug & Cosmetic Ind. 106, 38-41 (1970), hereby incorporated by reference.
The sustained-release forms of administration according to the invention can also contain the blocking agent in a sustained-release matrix, preferably as a uniform distribution.

Matrix materials, which can be used, are physiologically compatible, hydrophilic materials known to those skilled in the art. The hydrophilic matrix materials used are preferably polymers and particularly preferably cellulose ethers, cellulose esters and/or acrylic resins. The matrix materials used are very particularly preferably ethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, hydroxymethyl cellulose, poly(meth)acrylic acid and/or derivatives thereof such as their salts, amides or esters.

Other preferred matrix materials are those consisting of hydrophobic materials such as hydrophobic polymers, waxes, fats, long-chain fatty acids, fatty alcohols or corresponding esters or ethers, or mixtures thereof. The hydrophobic materials used are particularly preferably C_{12} - C_{30} fatty acid mono- or diglycerides and/or C_{12} - C_{30} fatty alcohols and/or waxes, or mixtures thereof.

It is also possible to use mixtures of the above-mentioned hydrophilic and hydrophobic materials as the sustained-release matrix material. The sustained-release matrix can be prepared by the conventional methods known to those skilled in the art.

In one embodiment of this invention, beads are loaded into capsules to contain 225 mg of active ingredient nizatidine along with sugar spheres, ethylcellulose, povidone, hypromellose phthalate, diethyl phthalate,
hypromellose, polyethylene glycol, gelatin, titanium dioxide and black iron oxide.

[0040] The most preferred embodiment of the immediate release (IR) form of the present invention comprises a two-step process: 1) first the drug layering process 2) followed by the seal coating process. The drug layering solution preparation preferably comprises suspending nizatidine and the binder (e.g. hydroxypropyl cellulose) in purified water. This aqueous suspension is sprayed onto the sugar spheres to form drug layered beads. This process is followed by the seal coating process where an aqueous protective coating of, for example, Opadry® Clear YS-1-7006 is sprayed onto the drug layered beads. The beads may then be dried and sieved to separate undersized (<25 mesh) and oversized (>14 mesh) material. These beads may be used as is, or as starting materials in the manufacture of Timed Sustain Release (TSR) beads.

[0041] The most preferred embodiment of the TSR form of the present invention includes manufacture using a solution of 2:1 to 1:2, preferably about 1:1, water-insoluble polymer coating, such as ethylcellulose: hypromellose phthalate, which may be prepared by dissolving both polymers in a solution, such as 98/02 acetone, purified water. This solution containing the blend of ethylcellulose and hypromellose phthalate as the lag time controlling polymeric system, at about 3 to 15%, preferably about 5-10%, most preferably about 7.5 %, w/w solids level is sprayed on the IR beads to form the TSR beads. This solution may also contain diethyl phthalate as a plasticizer. The beads may then be dried and sieved to separate undersized (<25 mesh) and
oversized (>14 mesh) material. The sieved beads may then be placed in
trays and cured in a tray drier at, for example, 140 ± 7°F for 4 hours.

[0042] The most preferred embodiment of the present invention, which is
referred to as “Nizatidine CR Capsules”, contains both forms, Immediate
Release (IR) and Timed Sustained Release (TSR) Beads. The capsules are
filled in a ratio of about 25 to 50%, preferably about 30 to 45%, most
preferably about 38% IR Beads, and about 50 to 75%, preferably about 55 to
70%, most preferably about 62% TSR Beads, such that about 25 to 75%,
preferably about 40 to 60%, most preferably about 50% of the dose is
released from the IR beads, and the remaining dose is released from the TSR
beads.
WE CLAIM:

1. A method for treating a patient with a gastric or intestinal disorder by administering a pharmaceutical composition containing about 175 mg to about 300 mg nizatidine or a salt thereof and one or more pharmaceutically acceptable excipients to the patient twice daily to treat the gastric or intestinal disorder or to inhibit or control gastric secretions associated with the gastric or intestinal disorder.

2. The method of claim 1, wherein the composition contains about 200 mg to about 250 mg of nizatidine or a salt thereof.

3. The method of claim 2, wherein the composition contains about 225 mg of nizatidine or a salt thereof.

4. The method of claim 1, wherein the composition contains about 1 to 60% of nizatidine or a salt thereof.

5. The method of claim 1, wherein the total daily dosage is about 350 mg to about 600 mg of nizatidine or a salt thereof.

6. The method of claim 5, wherein the total daily dosage is about 450 mg of nizatidine or a salt thereof.

7. The method of claim 1, wherein the gastric or intestinal disorder is
gastroesophageal reflux disease, heartburn, impaired gastric motility, ulcers
or related gastric secretions.

8. The method of claim 1, wherein a first administration of the composition is
in the morning.

9. The method of claim 1, wherein a first administration of the composition is
before consumption of a meal.

10. The method of claim 1, wherein a second administration of the
composition is after consumption of a meal.

11. The method of claim 1, wherein a second administration of the
composition is in the evening.

12. The method of claim 1, wherein nizatidine or a salt thereof is
administered in immediate release form, delayed release form, sustained
release form, or combinations thereof.

13. The method of claim 12, wherein nizatidine or a salt thereof is
administered together in an immediate release form and a sustained release
form.
14. The method of claim 1, where the composition is administered orally.

15. The method of claim 14, wherein the composition is administered in the form of a tablet, capsule, or suspension.

16. The method of claim 1, wherein an effective blood concentration of nizatidine or salt thereof is maintained for at least one hour before and after consumption of a meal.

17. A method for treating a patient with a gastric or intestinal disorder by administering a pharmaceutical composition containing about 175 mg to about 600 mg nizatidine or a salt thereof and one or more pharmaceutically acceptable excipients to the patient once daily to treat the gastric or intestinal disorder or to inhibit or control gastric secretions associated with the gastric or intestinal disorder.

18. The method of claim 17, wherein the composition contains about 200 mg to about 500 mg of nizatidine or a salt thereof.

19. The method of claim 17, wherein the composition contains about 450 mg of nizatidine or a salt thereof.

20. The method of claim 17, wherein the gastric or intestinal disorder is gastroesophageal reflux disease, heartburn, impaired gastric motility, ulcers or related gastric secretions.
21. The method of claim 17, wherein the administration of the composition is in the morning.

22. The method of claim 17, wherein the administration of the composition is in the evening.

23. The method of claim 17, wherein nizatidine or a salt thereof is administered in immediate release form, delayed release form, sustained release form, or combinations thereof.

24. The method of claim 23, wherein nizatidine or a salt thereof is administered together in an immediate release form and a sustained release form.

25. The method of claim 17, where the composition is administered orally.

26. The method of claim 25, wherein the composition is administered in the form of a tablet, capsule, or suspension.

27. A method for minimizing weight gain or promoting weight loss in a patient engaged in a dietary regimen by administering a pharmaceutical composition containing about 175 mg to about 300 mg nizatidine or a salt thereof and one or more pharmaceutically acceptable excipients to the patient twice daily to minimize weight gain or promote weight loss.
28. A method for minimizing weight gain or promoting weight loss in a patient engaged in a dietary regimen by administering a pharmaceutical composition containing about 175 mg to about 600 mg nizatidine or a salt thereof and one or more pharmaceutically acceptable excipients to the patient once daily to minimize weight gain or promote weight loss.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(8) : A61K 31/426  
US CL : 514/365  
According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
U.S. : 514/365

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
STN

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category *</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
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</table>

* Further documents are listed in the continuation of Box C.  
See patent family annex.

**Date of the actual completion of the international search**  
01 April 2006 (01.04.2006)

**Date of mailing of the international search report**  
24 APR 2006

**Form PCT/ISA/210 (second sheet) (April 2005)**

**International application No.**  
PCT/US05/40230