TITLE OF THE INVENTION
LIQUID ALENDRONATE FORMULATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present invention is related to U.S. provisional applications Serial Nos. 60/026,765, filed October 4, 1996, and 60/036,002, filed January 22, 1997, the contents of which are hereby incorporated by reference.

FIELD OF THE INVENTION

This invention relates to liquid pharmaceutical formulations of alendronic acid or a pharmaceutically acceptable salt thereof, and in particular, those containing a buffer which can control gastric pH.

BACKGROUND OF THE INVENTION

Alendronate, sodium (4-amino-1-hydroxy-butylidene-1,1-bisphosphonic acid monosodium salt trihydrate) has been approved by various regulatory agencies, including the Food and Drug Administration in the United States as an oral osteoporosis treatment in post menopausal women. The currently marketed formulation is a tablet, and the patient is instructed to take the tablet with a full glass of water in the morning, at least a half hour prior to eating or drinking.

Many people suffer from heartburn, often due to the reflux of stomach acid into the esophagus. This can cause a burning sensation. There is an overlap between the population of patients who require alendronate therapy and who suffer heartburn or similar symptoms.

Therefore it would be desirable to develop a formulation which would allow a bisphosphonate such as alendronate sodium to be taken orally and which would have the added advantage of relieving heartburn symptoms.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a liquid pharmaceutical formulation comprising:

alendronic acid or a pharmaceutically acceptable salt as an active ingredient;

a sufficient amount of buffer such that:

A) the pH of the formulation is between approximately 3.5 and approximately 7.5; and

B) 15 ml of the formulation is able to raise the pH of 50 ml of 0.1 N HCl (pH approximately 1) to a pH of at least 3.0; and optionally, one or more additional agents including those selected from the group consisting of: preservatives, flavoring agents, colorants, and sweeteners. Another aspect of this invention is a pharmaceutical formulation made by mixing the aforementioned active ingredients, buffer and optional agent(s).

The type of buffer which can be used in this formulation is not critical, as long as its buffering capacity is such that a relatively small volume can raise the pH of an acidic solution sufficiently. Exemplary buffering systems include those selected from the group consisting of citrate, tartrate, fumarate, phosphate, acetate, and mixtures thereof. Typically, 0.2 to 3 g of a salt or free acid and base will be used to make a buffer salt combination (per 15 ml dose). Generally, a 15 ml dose of the formulation of this invention will contain between 0.2 to 3 g of at least one of the following: disodium phosphate, trisodium citrate dihydrate, disodium tartrate dihydrate, or disodium formate. For example a useful buffering system is a citrate buffer comprising anhydrous citric acid and trisodium citrate dihydrate, present in a molar ratio of about 1:1-350, preferably about 1:50-150, and more preferably about 1:81.

In addition to the foregoing buffers, various bases, e.g., sodium hydroxide, potassium hydroxide, ammonium hydroxide and the like can be used to further adjust the buffer system.

Another aspect of this invention is providing a buffered environment for the alendronic acid active ingredient so that while in vivo it is not exposed to a pH less than about 3.0, preferably about 3.5 and more preferably about 4.0. Thus this invention also includes a method of inhibiting bone resorption comprising administering to a patient a pharmaceutical formulation comprising alendronic acid and a buffer such that the alendronic acid is not exposed to a gastro-intestinal environment which has a pH below about 3.0. It is believed that bioavailability of the active ingredient is enhanced at a pH which is greater than about 3.0.

Another aspect of this invention is an aqueous liquid pharmaceutical formulation which prior to mixing comprises:

alendronic acid or a pharmaceutically acceptable salt as an active ingredient;

a sufficient amount of a buffer such that: A) the pH of the formulation is between approximately 3.5 and approximately 7.5; and B) 15 ml of the formulation is able to raise the pH of 50 ml 0.1N HCl to a pH of at least 3; and

optionally, one or more additional agents selected from the group consisting of preservatives, flavoring agents, colorants, and sweeteners.

Another aspect of this invention is an aqueous liquid pharmaceutical formulation prepared by combining:

alendronic acid or a pharmaceutically acceptable salt as an active ingredient;

a sufficient amount of a buffer such that: A) the pH of the formulation is between approximately 3.5 and approximately 7.5; and B) 15 ml of the formulation is able to raise the pH of 50 ml 0.1N HCl to a pH of at least 3; and

optionally, one or more additional agents selected from the group consisting of preservatives, flavoring agents, colorants, and sweeteners.

Another aspect of this invention relates to methods of preparing an aqueous liquid pharmaceutical composition comprising the step of combining alendronic acid or a pharmaceutically acceptable salt as an active ingredient;

a sufficient amount of a buffer such that: A) the pH of the formulation is between approximately 3.5 and approximately 7.5; and B) 15 ml of the formulation is able to raise the pH of 50 ml 0.1N HCl to a pH of at least 3; and

optionally, one or more additional agents selected from the group consisting of preservatives, flavoring agents, colorants, and sweeteners.

As used throughout this specification and claims, the term "alendronic acid" includes the related bisphosphonic acid forms, pharmaceutically acceptable salt forms, and equilibrium mixtures of these. It includes crystalline, hydrated crystalline, and amorphous forms of alendronic acid and pharmaceutically acceptable salts thereof. It specifically includes alendronate sodium, and its hydrate, also known as alendronate monosodium trihydrate.

"Pharmaceutically acceptable salt forms" means those forms which are commonly used in pharmaceutical formulations such as salts with alkali metals (Na^+, Ca^{2+}, K^+, and Mg^{2+}) organic bases (such as N-methylglucamine) and amino acids (such as lysine).

Methods for the preparation of alendronic acid and alendronate sodium salt trihydrate are known. In particular, methods for the preparation of alendronic acid and its pharmaceutically acceptable salts may be found in U.S. Patents 4,922,007, 5,019,651 and 5,510,517, each of which is hereby incorporated by reference.

The concentration of alendronic acid or alendronate sodium or other alendronate salts in this formulation will range from about 0.05 mg/ml to 2 mg/ml, on an alendronic acid basis; and preferably about 0.1 to 0.9 mg/ml., on an alendronic acid basis. Particularly useful

concentrations are 0.13, 0.33, and 0.67 mg/ml, on an alendronic acid basis, as one tablespoon (approximately 15 ml) of such a solution would correspond to a dose of approximately 2, 5 and 10 mg, respectively, on an alendronic acid basis. This would be mixed in water (approximately 60-200 ml) and ingested. Alternatively, if larger daily doses are considered desirable, such as 20 mg, on an alendronic acid basis, the patient may mix two tablespoons (approximately 30 ml) of the solution in water, which provides a 10 mg dose, on an alendronic acid basis per tablespoon. It is envisioned that the diluted solution will be administered once a day, but additional dosing may be provided if desired; or alternatively, doses may be provided which are less than once a day.

In an alternative dosing method, the formulation, which may contain water is not diluted prior to ingestion by the patient. In this embodiment, the patient swallows only a small amount of liquid (approximately 15 ml).

The formulation of this invention has many distinct advantages. The preferred formulation is supplied as a concentrate, which allows for convenience to the manufacturer and pharmacist. For example, a monthly supply (containing for example 31 tablespoon doses) is only approximately one pint of liquid (473 ml). This allows easy handling and storage. It can be easily diluted by the patient prior to ingestion.

Additionally, the liquid formulation is advantageous in that alendronate sodium is often prescribed to elderly patients who may experience difficulty in swallowing tablets or capsules, but can more easily swallow a liquid formulation. The liquid dosage formulation also allows for the inclusion of a flavoring agent which can improve patient compliance. Further, the bioavailability of the active ingredient appears to be enhanced in this formulation when compared to prior art tablet forms.

Also, the buffering agent negates the requirement that the patient also take various additional antacids to combat acid reflux, heartburn or other gastric problem.

The inclusion of a relatively large amount of buffer is a key feature in this invention. The amount of buffer should be enough such that A) the pH of the formulation is between about 3.5 and about .5, preferably between about 4 and about 7, and more preferably between about 4 and about 5.5; and B) 15 ml of formulation can raise the pH of 50 ml 0.1N HCl (pH approximately 1) to a pH of at least 3.5, and preferably to about 4. The pH of the formulation itself is important because at pH 3.5-5.5 there is minimal potential for additional gastric irritation.

The ability of the formulation to buffer about 50 ml of a strong acid is important because it has the ability to buffer gastric acid. Reflux of gastric acid into the esophagus can cause irritation, and even erosion of the esophagus. Typically, a person has about 50 ml of gastric juice in the stomach with a pH of approximately 1. Upon taking the alendronate formulation of this invention, the stomach acid is buffered to at least 3.5, and preferably to about 4. It has been found, in animal models in accordance with this invention, that an alendronate sodium and gastric acid mixture at a pH of at least 3.5 is not irritating to esophageal tissues. Thus, if the patient experiences reflux, esophageal irritation will not result.

Preservatives which may be used to provide multiple dosing may be any of the known pharmaceutically accepted preservatives which are active in a liquid having a pH of 3.5-7.5 which do not adversely interact with the active ingredient. They should be used at their usual concentrations. Preferred preservatives include sodium benzoate, potassium sorbate, benzyl alcohol, butylparaben, ethylparaben, methylparaben, propylparaben, and the like and mixtures thereof. In a typical embodiment, sodium benzoate is used at a concentration of 1.0-2.0 mg/ml.

It may be desired to include taste enhancers such as sweeteners and colorants, although their inclusion in the formulation is

strictly optional. Suitable sweeteners include various sugars, sorbitol, xylitol, sucrose, or the like. A useful concentration of sorbitol or xylitol is between about 100-700 mg/ml, and preferably about 200-500 mg/ml. Sodium saccharin is another useful sweetener and can be used at a concentration of about 0.1-1.0 mg/ml, and preferably about 0.5-0.7 mg/ml. Combinations of one or more sweeteners can also be used.

An additional optional ingredient is a flavoring agent. Flavoring agents which have been found to be suitable (in terms of clarity of formulation) include Orange #782 (Virginia Dare) Tutti-Frutti (Fermenich/51.880-CE), Artificial Berry #491 (Fermenich), and Artificial Strawberry (Fermenich/57.883-C). Other flavors include, but are not limited to, natural and artificial orange, strawberry, all citrus flavors, tomato, apple, and tutti-frutti. Typical concentrations are 10-50 mg/ml, particularly about 10 mg/ml.

The following, non-limiting Examples are presented to better illustrate the invention.

EXAMPLES

EXAMPLE 1

Alendronate monosodium trihydrate	0.87* mg
sodium benzoate	1.3 mg
Orange flavor (Virginia Dare #792)	10 mg
Sodium citrate dihydrate	100 mg
Citric acid anhydrous	0.45 mg
Xylitol	250 mg
Purified Water	qs 1 ml

Total citrate (M) is 0.50 M. The pH of the formulation is 4.8. When 15 ml of formulation is added to 50 ml 0.1N HCl, the pH is 4.04
*Corresponds to 0.67 mg/ml of alendronic acid.

EXAMPLE 2

Alendronate monosodium trihydrate	0.87* mg
Sodium benzoate	1.3 mg
Potassium sorbate	1.3 mg
Xylitol	400 mg
Sodium citrate dihydrate	100 mg
Citric acid anhydrous	0.45 mg
Flavor	10 mg
Purified Water	qs 1 ml

*Corresponds to 0.67 mg/ml of alendronic acid.

EXAMPLE 3

Alendronate monosodium trihydrate	0.87* mg
Potassium sorbate	1.3 mg
Xylitol	400 mg
Sodium citrate dihydrate	100 mg
Citric acid anhydrous	0.45 mg
Purified Water	qs 1 ml

*Corresponds to 0.67 mg/ml of alendronic acid.

EXAMPLE 4

Alendronate monosodium trihydrate	0.87* mg
Sodium citrate dihydrate	100 mg
Citric acid anhydrous	0.45 mg
Xylitol	400 mg
Purified Water	qs 1 ml

*Corresponds to 0.67 mg/ml of alendronic acid.

EXAMPLE 5

Alendronate monosodium trihydrate	0.87* mg
Tartaric acid, NF	75 mg
Sodium hydroxide pellets, NF	38.5 mg
Xylitol	400 mg
Sodium benzoate NF	1.3 mg
Flavor N & A #782 Orange	10 mg
Purified Water	qs 1 ml

*Corresponds to 0.67 mg/ml of alendronic acid.

EXAMPLE 6

Alendronate monosodium trihydrate	0.87* mg
Tartaric acid, NF	70 mg
Sodium hydroxide pellets, NF	36 mg
Xylitol	400 mg
Sodium benzoate, NF	1.3 mg
Flavor N & A #782 Orange	10.0 mg
Purified Water	qs 1 ml

*Corresponds to 0.67 mg/ml of alendronic acid.

EXAMPLE 7

Alendronate sodium	0.87* mg
Tartaric acid, NF	75 mg
Sodium hydroxide pellets, NF	38.5 mg
Xylitol	50 mg
Sodium saccharin	0.7 mg
Sodium methyl paraben	1.3 mg
Flavor N & A #782 Orange	10.0 mg
Purified Water	qs 1 ml

*Corresponds to 0.67 mg/ml of alendronic acid.

EXAMPLE 8

Alendronate sodium	0.87* mg
Citric acid	70.59 mg
Sodium citrate	0.57 mg
Xylitol	50 mg
Sodium saccharin	0.5 mg
Flavor N & A #782 Orange	10.0 mg
Purified Water	qs 1 ml

*Corresponds to 0.67 mg/ml of alendronic acid.

EXAMPLE 9

Alendronate sodium	0.87* mg
Tartaric acid, NF	75 mg
Sodium hydroxide pellets, NF	38.5 mg
Sodium saccharin	0.7 mg
Sodium methyl paraben	1.3 mg
Flavor N & A #782 Orange	10.0 mg
Purified Water	qs 1 ml

*Corresponds to 0.67 mg/ml of alendronic acid.

WHAT IS CLAIMED IS:

1. An aqueous liquid pharmaceutical formulation comprising:

alendronic acid or a pharmaceutically acceptable salt as an active ingredient;

a sufficient amount of a buffer such that: A) the pH of the formulation is between approximately 3.5 and approximately 7.5; and B) 15 ml of the formulation is able to raise the pH of 50 ml 0.1N HCl to a pH of at least 3; and

optionally, one or more additional agents selected from the group consisting of preservatives, flavoring agents, colorants, and sweeteners.

2. A formulation according to Claim 1, wherein the buffer is a citric acid/sodium citrate or a tartaric acid/sodium tartrate buffer system.

3. A formulation according to Claim 2 wherein the concentration of alendronate monosodium trihydrate is 0.1-0.9 mg/ml on an alendronic acid basis.

4. A formulation according to Claim 3 wherein the concentration of alendronate monosodium trihydrate is 0.133 or 0.67 mg/ml on an alendronic acid basis.

5. A formulation according to Claim 2, wherein the concentration of citric acid and sodium citrate present is 0.06-0.65 M, the pH of the formulation is 3.5-7.5, and the pH of 50 ml of 0.1N HCl when 15 ml of the formulation is added is above pH 3.

6. An aqueous liquid pharmaceutical formulation comprising (in mg/ml):

alendronate monosodium trihydrate (on an alendronic acid basis)	0.2-0.9
sodium benzoate	1.0-2.0
sodium citrate dihydrate	75-125
citric acid, anhydrous	0.3-40
xylitol	100-640

wherein the citric acid and sodium citrate present in the invention is 0.06-0.65M, the pH of the formulation is 3.5-7.5 and the pH of 50 ml of 0.1N HCl when 15 ml of the formulation is added is above pH 3.

7. A liquid pharmaceutical formulation according to Claim 6 comprising (in mg/ml):

alendronate monosodium trihydrate (on an alendronic acid basis)	0.1-0.9
sodium benzoate	1.0-2.0
potassium sorbate	1.0-2.0
xylitol	400
artificial flavoring	5-50
sodium citrate dihydrate	75-125
citric acid, anhydrous	0.3-40

8. A pharmaceutical formulation according to Claim 6 wherein the alendronate monosodium trihydrate is present at 0.33 to 0.67 mg/ml on an alendronic acid basis.

9. An aqueous liquid pharmaceutical formulation comprising (in mg/ml):

alendronate monosodium trihydrate (on an alendronic acid basis)	0.1-0.9
tartaric acid, NF	70-140
sodium hydroxide pellets, NF	36-72
xylitol	100-640
sodium benzoate NF	0-3
flavor N & A #782 Orange	0-100

10. A pharmaceutical formulation according to Claim 9 wherein the alendronate monosodium trihydrate is present at a concentration of 0.13 to 0.67 mg/ml on an alendronic acid basis.

11. A pharmaceutical formulation according to Claim 2 wherein the sum total amount of citric acid and sodium citrate present in the formulation is at least about 50 mg/ml.

12. A pharmaceutical formulation according to Claim 8 wherein the sum total amount of citric acid and sodium citrate present in the formulation is at least about 75 mg/ml.

13. A pharmaceutical formulation according to Claim 8 wherein the sum total amount of citric acid and sodium citrate present in the formulation is at least about 100 mg/ml.

14. A method of inhibiting bone resorption comprising administering an aqueous liquid formulation of alendronic acid or pharmaceutically acceptable salt and a buffer so that the alendronic acid is not exposed to a gastro-intestinal environment which has a pH below about 3.5.

15. An aqueous liquid pharmaceutical formulation prior to mixing comprising:

alendronic acid or a pharmaceutically acceptable salt as an active ingredient;

a sufficient amount of a buffer such that: A) the pH of the formulation is between approximately 3.5 and approximately 7.5; and B) 15 ml of the formulation is able to raise the pH of 50 ml 0.1N HCl to a pH of at least 3; and

optionally, one or more additional agents selected from the group consisting of preservatives, flavoring agents, colorants, and sweeteners.

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16. An aqueous liquid pharmaceutical formulation prepared by combining:

alendronic acid or a pharmaceutically acceptable salt as an active ingredient;

a sufficient amount of a buffer such that: A) the pH of the formulation is between approximately 3.5 and approximately 7.5; and B) 15 ml of the formulation is able to raise the pH of 50 ml 0.1N HCl to a pH of at least 3; and

optionally, one or more additional agents selected from the group consisting of preservatives, flavoring agents, colorants, and sweeteners.

17. A method of preparing an aqueous liquid pharmaceutical composition comprising the step of combining alendronic acid or a pharmaceutically acceptable salt as an active ingredient;

a sufficient amount of a buffer such that: A) the pH of the formulation is between approximately 3.5 and approximately 7.5; and B) 15 ml of the formulation is able to raise the pH of 50 ml 0.1N HCl to a pH of at least 3; and

optionally, one or more additional agents selected from the group consisting of preservatives, flavoring agents, colorants, and sweeteners.