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(54) Title: LIQUID ALENDRONATE FORMULATIONS

(57) Abstract

A liquid formulation of alendronic acid, or pharmaceutically acceptable salt has enough buffer so that the pH of the formulation is 4–7.5, and 15 ml of the formulation is able to raise the pH of 50 ml of 0.1N HC1 from 1 to at least 3, and preferably 4.

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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.

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