LISINOPRIL FORMULATIONS

CROSS-REFERENCE

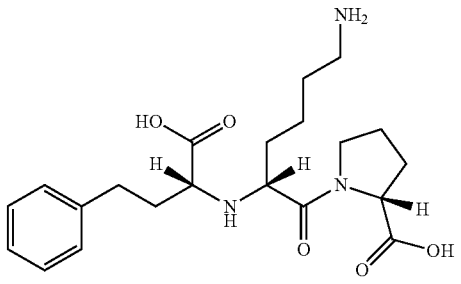
This application is a Continuation Application of U.S. patent application Ser. No. 15/268,095, filed Sep. 16, 2016, which is a Continuation Application of U.S. patent application Ser. No. 14/934,752, filed Nov. 6, 2015, which claims the benefit of U.S. Provisional Patent Application No. 62/249,011, filed Oct. 30, 2015, all of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

Hypertension, or high blood pressure, is a serious health issue in many countries. According to the National Heart Blood and Lung Institute, it is thought that about 1 in 3 adults in the United States alone have hypertension. Left unchecked, hypertension is considered a substantial risk factor for cardiovascular and other diseases including coronary heart disease, myocardial infarction, congestive heart failure, stroke and kidney failure. Hypertension is classified as primary (essential) hypertension or secondary hypertension. Primary hypertension has no known cause and may be related to a number of environmental, lifestyle and genetic factors such as stress, obesity, smoking, inactivity and sodium intake. Secondary hypertension can be caused by drug or surgical interventions or by abnormalities in the renal, cardiovascular or endocrine system.

A number of antihypertensive drugs are available for treating hypertension. Various therapeutic classes of antihypertensive drugs include alpha-adrenergic blockers, beta-adrenergic blockers, calcium-channel blockers, hypotensives, mineralcorticoid antagonists, central alpha-agonists, diuretics and rennin-angiotensin-aldosterone inhibitors which include angiotensin II receptor antagonists (ARB) and angiotensin-converting enzyme (ACE) inhibitors. Angiotensin-converting enzyme (ACE) inhibitors inhibit angiotensin-converting enzyme (ACE), a peptydyl dipeptidase that catalyzes angiotension I to angiotension II, a potent vasoconstrictor involved in regulating blood pressure.

Lisinopril is a drug belonging to the angiotensin-converting enzyme (ACE) inhibitor class of medications. Lisinopril IUPAC name is N^2-[(1S)-1-carboxy-3-phenylpropyl]-L-lysyl-L-proline. Its structural formula is as follows:



Lisinopril

Lisinopril is currently administered in the form of oral tablets, (e.g., Prinivil®, Zestril®). In addition to the treatment of hypertension, lisinopril tablets have been used for the treatment of heart failure and acute myocardial infarction.

SUMMARY OF THE INVENTION

Provided herein are lisinopril oral liquid formulations. In one aspect, the lisinopril oral liquid formulation comprises (i) lisinopril or a pharmaceutically acceptable salt or solvate thereof, (ii) a sweetener that is xylitol, (iii) a buffer comprising citric acid (iv) a preservative that is sodium benzoate, and (v) water; wherein the pH of the formulation is between about 4 and about 5; and wherein the formulation is stable at about 25±5° C. for at least 12 months.

In some embodiments, the lisinopril is lisinopril dihydrate. In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the formulation further comprises a second sweetener. In some embodiments, the second sweetener is sodium saccharin or sucralose. In some embodiments, the pH is about 4.9. In some embodiments, the formulation is stable at about 25±5° C. for at least 18 months. In some embodiments, the formulation is stable at about 25±5° C. for at least 24 months. In some embodiments, the buffer further comprises sodium citrate.

In some embodiments, the amount of lisinopril or a pharmaceutically acceptable salt or solvate thereof is about 0.8 to about 1.2 mg/ml. In some embodiments, the amount of xylitol is about 140 to about 160 mg/ml. In some embodiments, the amount of citric acid in the buffer is about 0.5 to about 1.2 mg/ml. In some embodiments, the amount of sodium citrate in the buffer is about 1.2 to about 1.7 mg/ml. In some embodiments, the amount of the sodium benzoate is about 0.5 to about 1.2 mg/ml.

In one aspect, the lisinopril oral liquid formulation comprises (i) about 1 mg/ml lisinopril or a pharmaceutically acceptable salt or solvate thereof, (ii) about 150 mg/ml of a sweetener that is xylitol, (iii) a buffer comprising about 0.86 mg/ml citric acid, (iv) about 0.8 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is between about 4 and about 5; and wherein the formulation is stable at about 25±5° C. for at least 12 months.

In some embodiments, the lisinopril is lisinopril dihydrate. In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the formulation further comprises a second sweetener. In some embodiments, the second sweetener is sodium saccharin or sucralose. In some embodiments, the pH is about 4.9. In some embodiments, the formulation is stable at about 25±5° C. for at least 18 months. In some embodiments, the formulation is stable at about 25±5° C. for at least 24 months. In some embodiments, the buffer further comprises sodium citrate. In some embodiments, the buffer further comprises about 1.44 mg/ml sodium citrate.

In some embodiments, the amount of lisinopril or a pharmaceutically acceptable salt or solvate thereof is about 0.5 to about 1% (w/w of solids). In some embodiments, the amount of xylitol is about 95 to about 98% (w/w of solids). In some embodiments, the amount of citric acid in the buffer is about 0.3 to about 0.7% (w/w of solids). In some embodiments, the amount of sodium citrate in the buffer is about 0.7 to about 1.3% (w/w of solids). In some embodiments, the amount of sodium benzoate is about 0.4 to about 1.2% (w/w of solids).

In another aspect, the lisinopril oral liquid formulation comprises (i) about 0.7% (w/w of solids) lisinopril or a pharmaceutically acceptable salt or solvate thereof, (ii) about 97.3% (w/w of solids) of a sweetener that is xylitol, (iii) a buffer comprising about 0.01 molar citrate, (iv) about 0.52% (w/w of solids) of a preservative that is sodium