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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	43060-706.201
First Named Inventor	Gerold L. Mosher
Title	Lisinopril Formulations
Express Mail Label No.	Filed Electronically on November 6, 2015

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. [ ] **Fee Transmittal Form** (PTO/SB/17 or equivalent)
2. [ ] **Applicant asserts small entity status.** See 37 CFR 1.27
3. [ ] **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. [✓] **Specification** [*Total Pages* 49] Both the claims and abstract must start on a new page. *(See MPEP § 608.01(a) for information on the preferred arrangement)*
5. [✓] **Drawing(s)** (35 U.S.C. 113) [*Total Sheets* 2]
6. **Inventor's Oath or Declaration** [*Total Pages* 2] *(including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))*
   a. [✓] Newly executed (original or copy)
   b. [ ] A copy from a prior application (37 CFR 1.63(d))
7. [✓] **Application Data Sheet** ** See note below.* See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. **CD-ROM or CD-R** in duplicate, large table, or Computer Program (*Appendix*)
   [ ] Landscape Table on CD
9. **Nucleotide and/or Amino Acid Sequence Submission** *(if applicable, items a. – c. are required)*
   a. [ ] Computer Readable Form (CRF)
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ACCOMPANYING APPLICATION PAPERS

10. [ ] **Assignment Papers** (cover sheet & document(s))
    Name of Assignee: Silvergate Pharmaceuticals, Inc.
11. [✓] **37 CFR 3.73(c) Statement** (*when there is an assignee*) [✓] **Power of Attorney**
12. [ ] **English Translation Document** (*if applicable*)
13. [ ] **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    [ ] Copies of citations attached
14. [ ] **Preliminary Amendment**
15. [ ] **Return Receipt Postcard** (*MPEP § 503*) (*Should be specifically itemized*)
16. [ ] **Certified Copy of Priority Document(s)** (*if foreign priority is claimed*)
17. [ ] **Nonpublication Request** Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
18. [✓] **Other:** Certification and Request for Prioritized Examination Under 37 CFR 1.102(e) (1pp); Request for First Action Interview (1pp); Copy of Assignment from parent application (2 pp)

Note:* (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS

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Name (Print/Type)	Clark Y. Lin	Registration No. (Attorney/Agent)	67024

UNITED STATES PATENT APPLICATION

LISINOPRIL FORMULATIONS

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Filed Electronically on: November 6, 2015

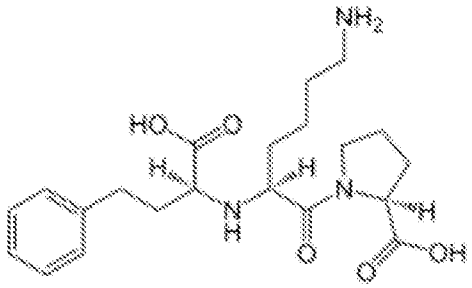
LISINOPRIL FORMULATIONS

BACKGROUND OF THE INVENTION

[0001] 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.

[0002] 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.

[0003] 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

[0004] 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

[0005] 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 ºC for at least 12 months.

[0006] 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 ºC for at least 18 months. In some embodiments, the formulation is stable at about 25±5 ºC for at least 24 months. In some embodiments, the buffer further comprises sodium citrate.

[0007] 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.

[0008] 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 ºC for at least 12 months.

[0009] 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 ºC for at least 18 months. In some embodiments, the formulation is stable at about 25±5 ºC 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.

[0010] 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).

[0011] 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 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 ºC for at least 12 months.

[0012] 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 ºC for at least 18 months. In some embodiments, the formulation is stable at about 25±5 ºC for at least 24 months. In some embodiments, the buffer comprises citric acid and sodium citrate.

[0013] In another aspect, the lisinopril oral liquid formulation consists of (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 and about 1.44 mg/ml sodium citrate, (iv) about 0.8 mg/ml of a preservative that is sodium benzoate, (v) and water; wherein the pH of the formulation is between about 4 and about 5 adjusted by sodium hydroxide or hydrochloric acid; and wherein the formulation is stable at about 25±5 ºC for at least 12 months. In some embodiments, the formulation is stable at about 25±5 ºC for at least 24 months. In some embodiments, the pH is about 4.9.

[0014] Also provided herein are methods of treating hypertension comprising administering to a patient in need thereof a lisinopril oral liquid formulation described herein. In some embodiments, the hypertension is primary (essential) hypertension. In some embodiments, the hypertension is secondary hypertension. In some embodiments, the subject with hypertension has blood pressure values greater than or equal to 140/90 mmm Hg.

[0015] Also provided herein are methods of treating prehypertension comprising administering to a patient in need thereof a lisinopril oral liquid formulation described herein. In some embodiments, the subject with prehypertension has blood pressure values of about 120-139/80-89 mm Hg.

[0016] Also provided herein are methods of treating heart failure or acute myocardial infarction comprising administering to a patient in need thereof a lisinopril oral liquid formulation described herein.

[0017] In some embodiments, the subject is an adult. In some embodiments, the subject is elderly. In some embodiments, the subject is a child. In some embodiments, the lisinopril oral liquid formulation is

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