PHARMACEUTICAL COMPOSITIONS OF EFRUXIFERMIN

CROSS REFERENCE TO RELATED APPLICATIONS AND INCORPORATION BY REFERENCE OF MATERIAL SUBMITTED ELECTRONICALLY

[0001] This application claims priority to U.S. Provisional Patent Application No. 63/255,286, filed October 13, 2021, the disclosure of which is hereby incorporated by reference in its entirety.

[0002] Incorporated by reference in its entirety is a computer-readable nucleotide/amino acid sequence listing submitted concurrently herewith and identified as follows: 50011_Seqlisting.XML; Size: 2,497 bytes; Created: October 9, 2022.

FIELD OF THE INVENTION

[0003] The disclosure is related to a pharmaceutical composition comprising Efruxifermin (EFX), processes for preparing a lyophilized composition, and methods of use.

BACKGROUND

[0004] Fibroblast growth factor 21 (FGF21) is an endocrine hormone that acts on the liver, pancreas, muscle, and adipose tissue to regulate the metabolism of lipids, carbohydrates, and proteins. Acting as a paracrine hormone, human FGF21 also plays a critical role in protecting cells against stress. These attributes make FGF21 agonism a compelling therapeutic mechanism, but native FGF21 is limited by its short half-life in the bloodstream. The Fc-FGF21 fusion protein, Efruxifermin (EFX), has been genetically engineered to increase human FGF21's half-life (Hecht et al, PLoS One 2012; 7(11): e49345; Stanislaus et al., Endocrinology. 2017;158(5):1314-1327). However, formulations of EFX are susceptible to post-translational modifications, including formation of charge and size variants, resulting in stability constraints. There is a need in the art for pharmaceutical formulations that provide enhanced stabilization and reduced post-translational modifications of Fc-FGF21 fusion proteins, such as Efruxifermin (EFX).

SUMMARY

[0004a] In an aspect of the present disclosure, there is provided a pharmaceutical composition comprising:

(1) Efruxifermin (EFX);

(2) a sugar;

(3) about 20 to about 200 mM arginine/arginine-HCl or arginine/glutamic acid; and

(4) a surfactant;

wherein the composition has a pH from about 6.9 to about 8.1.

[0004b] In another aspect of the present disclosure, there is provided a use of a composition as disclosed herein in the manufacture of a medicament, wherein (a) the composition is reconstituted within about five minutes to obtain a reconstituted composition and (b) the reconstituted composition is to be administered to a subject.

[0004c] In a further aspect of the present disclosure, there is provided a dual chamber device comprising the composition as disclosed herein and a diluent.

[0004d] In another aspect of the present disclosure, there is provided a process for preparing a lyophilized composition, the process comprising:

(a) freezing the composition as disclosed herein;

(b) annealing the composition of step (a) at a temperature of about -5 °C to about -20 °C;

(c) primary drying the product of step (b); and

(d) secondary drying the product of step (c).

[0004e] In a further aspect of the present disclosure, there is provided a use of a pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease (NAFL).

[0004f] In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition as disclosed herein in the manufacture of a medicament for reversing NASH with cirrhosis.

[0004g] In a further aspect of the disclosure, there is provided a use of a pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating alcoholic steatohepatitis (ASH), alcoholic liver disease (ALD) or alcoholic fatty liver disease (AFL).

[0004h] In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition as disclosed herein in the manufacture of a medicament for normalizing liver fat content in a subject in need thereof.

[0004i] In a further aspect of the present disclosure, there is provided a use of a pharmaceutical composition as disclosed herein in the manufacture of a medicament for reversing liver cirrhosis or reducing fibrosis associated with NASH, ASH, ALD, AFL, or protein misfolding disease in a subject in need thereof.

[0004j] In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition as disclosed herein in the manufacture of a medicament for lowering blood glucose.

[0004k] In a further aspect of the present disclosure, there is provided a use of a pharmaceutical composition as disclosed herein in the manufacture of a medicament for reducing uric acid.

[0004l] In another aspect of the present disclosure, there is provided a pharmaceutical composition as disclosed herein for use in therapy.

[0005] The disclosure provides a pharmaceutical composition comprising Efruxifermin (EFX), a sugar, about 20 to about 200 mM arginine/arginine-HCl or arginine/glutamic acid, and a surfactant. In various examples, the composition has a pH from about 6.9 to about 8.1. In various examples, the sugar of the composition is sucrose, glucose, fructose, or maltose. Optionally, the surfactant of the composition is polysorbate-20 or polysorbate-80. In various

examples, the pharmaceutical composition comprises about 25-150 mg/mL EFX; about 120 mM sucrose; about 120 mM Arginine/Arginine-HCl; about 0.06% weight/volume (w/v) polysorbate-20; and about 20 mM Tris-HCl. Optionally, the composition pH is about 7.3.

[0006] The composition of the disclosure is, in various instances, lyophilized, although this is not required. In this respect, the disclosure provides a method for reconstituting a lyophilized composition disclosed herein within five minutes, and administering the reconstituted composition to a subject. In various examples, the reconstituted composition is maintained at room temperature for up to 10 minutes. The disclosure also provides a dual chamber device comprising any of the compositions disclosed herein and a diluent. In certain examples, the diluent is water for injection or a buffering agent (e.g., compounded buffer based on the formulations disclosed herein).

[0007] The disclosure also provides a pharmaceutical composition comprising EFX, 2.9% L-Lysine, 0.008% weight/volume (w/v) polysorbate-20, and 10 mM Tris. In various examples, the composition has a pH of 7.8± 0.3.

[0008] The disclosure also provides a process for preparing lyophilized compositions. In various examples, the process comprises the following steps: (a) freezing a composition disclosed herein; (b) annealing the composition of step (a) at a temperature of about -5 °C to about -15 °C; (c) primary drying the product of step (b) and d) secondary drying the product of step (c).

[0009] The disclosure further provides (a) a method of treating nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease (NAFL), alcoholic steatohepatitis (ASH), alcoholic liver disease (ALD) or alcoholic fatty liver disease (AFL), type 2 diabetes, obesity, dyslipidemia, alcohol-related and other cravings or addictions, or protein misfolding diseases in a subject in need thereof; (b) a method of normalizing liver fat content in a subject; (c) a method of reversing liver cirrhosis or reducing fibrosis associated with NASH, ASH, ALD, AFL, or protein misfolding disease; (d) a method of reducing blood glucose and/or increasing insulin sensitivity in a subject; and (e) a method of reducing uric acid levels in a subject. The method comprises administering a pharmaceutical composition disclosed herein to a subject in need thereof.

[0010] The foregoing summary is not intended to define every aspect of the invention, and additional aspects are described in other sections, such as the Detailed Description. The entire document is intended to be related as an unified disclosure, and it should be understood that all combinations of features described herein are contemplated, even if the combination of features are not found together in the same sentence, or paragraph, or section of this document. In

WHAT IS CLAIMED:

1. A pharmaceutical composition comprising:
(1) Efruxifermin (EFX);
(2) a sugar;
(3) about 20 to about 200 mM arginine/arginine-HCl or arginine/glutamic acid; and
(4) a surfactant;
wherein the composition has a pH from about 6.9 to about 8.1.

2. The composition of claim 1, wherein the EFX concentration is about 25 to about 150 mg/ml.

3. The composition of claims 1 or 2, wherein the EFX concentration is about 28 mg/ml, about 50 mg/ml, about 70 mg/ml or about 100 mg/ml.

4. The composition of any one of claims 1-3, comprising about 20 mM to about 200 mM arginine/arginine-HCl.

5. The composition of claim 4, comprising about 120 mM arginine/arginine-HCl.

6. The composition of any one of claims 1-5, comprising arginine/arginine-HCl at a ratio of about 1:30 arginine/arginine-HCl to about 1:50 arginine/arginine-HCl.

7. The composition of any one of claims 1-3, comprising about 20 mM to about 200 mM arginine/ glutamic acid.

8. The composition of any one of claims 1-7, further comprising Tris-HCl, sodium phosphate, sodium succinate/succinic acid, sodium glutamate/glutamic acid, sodium acetate/acetic acid, glycylglycine/glycylglycine-HCl, histidine, or citrate buffer.

9. The composition of claim 8, comprising Tris-HCl at a concentration of about 10 mM to about 50 mM.

10. The composition of any one of claims 1-9, wherein the sugar is sucrose, glucose, fructose, or maltose.

11. The composition of any one of claims 1-9, wherein the sugar is sucrose present at a concentration of about 50 to about 220 mM.

12. The composition of claim 11, wherein the sucrose concentration is about 120 mM.

13. The composition of any one of claims 1-12, wherein the surfactant is polysorbate-20 or polysorbate-80.

14. The composition of any one of claims 1-13, wherein the surfactant concentration is about 0.004% to about 0.1% w/v.

15. The composition of any one of claims 1-14, wherein the composition has a pH of about 7.3.

16. The composition of any one of claims 1-15, wherein the composition has a viscosity of ≤5 cP at room temperature.

17. The composition of claim 1 comprising:
(1) about 25-150 mg/mL Efruxifermin (EFX);
(2) about 120 mM sucrose;
(3) about 120 mM Arginine/Arginine-HCl;
(4) about 0.06% weight/volume (w/v) polysorbate-20; and
(5) about 20 mM Tris-HCl;
wherein the composition has a pH of about 7.3.

18. The composition of any one of claims 1-17, wherein (a) the composition is stable at a temperature of about 2-8 °C for at least 21 months as a liquid, (b) the composition comprises no more than about 40% EFX acidic charged variant species when stored between -30 °C to -20 °C for up to 24 months, (c) the composition comprises no more than about 40% EFX acidic charged variant species when stored at about 2-8 °C for up to 9 months, (d) the composition comprises no more than about 40% EFX acidic charged variant species when stored at about 25 °C for up to 4 weeks, (e) the composition comprises no more than about 20% EFX size variant species at about 25 °C for up to 4 weeks, or (f) the composition comprises no more than about 10% EFX size variant species when stored at about 2-8 °C for up to 14 months.

19. The composition of any one of claims 1-17, which is a lyophilized composition.

20. The composition of claim 19, comprising a residual moisture content of about 1% or less.

21. The composition of any one of claims 1-20, wherein the composition further comprises carboxymethyl cellulose or hydroxypropyl methylcellulose.

22. The composition of claim 21, wherein (i) the carboxymethyl cellulose is sodium carboxymethyl cellulose or (ii) the hydroxypropyl methylcellulose is sodium hydroxypropyl methylcellulose.

23. The composition of claim 22, wherein the sodium carboxymethyl cellulose is present in a concentration of about 0.05% to about 5%, optionally about 0.15% to about 1.5%.

24. The composition of claim 23, wherein the sodium carboxymethyl cellulose is present in a concentration of about 0.5%.

25. The composition of claim 18, comprising about 80 mM arginine/ glutamic acid and about 80 mM sucrose.

26. Use of a composition of claim 19 or 20 in the manufacture of a medicament, wherein (a) the composition is reconstituted within about five minutes to obtain a reconstituted composition and (b) the reconstituted composition is to be administered to a subject.

27. The use of claim 26, wherein the reconstituted composition of step (a) is maintained at room temperature for up to 10 minutes prior to step (b).

28. The use of claim 26 or 27, wherein the reconstituted composition is to be subcutaneously administered to the subject in step (b).

29. A dual chamber device comprising the composition of claim 19 or 20 and a diluent.

30. A process for preparing a lyophilized composition, the process comprising:
(a) freezing the composition of any one of claims 1-17;
(b) annealing the composition of step (a) at a temperature of about -5 °C to about -20 °C;
(c) primary drying the product of step (b); and
(d) secondary drying the product of step (c).

31. The process of claim 30, wherein freezing in step (a) is conducted at a temperature of between about -40 °C to about -50 °C.

32. The process of claim 30 or claim 31, wherein annealing in step (b) is conducted for about 5 to about 20 hours and/or at a temperature of between about -5 °C to about -10 °C.

33. The process of any one of claims 30-32, wherein primary drying in step (c) is conducted at about 0.08 to 0.2 mbar chamber pressure and/or at a temperature from about -5 °C to -30 °C.

34. Use of a pharmaceutical composition of any one of claims 1-20 in the manufacture of a medicament for treating nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease (NAFL).

35. Use of a pharmaceutical composition of any one of claims 1-20 in the manufacture of a medicament for reversing NASH with cirrhosis.

36. Use of a pharmaceutical composition of any one of claims 1-20 in the manufacture of a medicament for treating alcoholic steatohepatitis (ASH), alcoholic liver disease (ALD) or alcoholic fatty liver disease (AFL).

37. Use of a pharmaceutical composition of any one of claims 1-20 in the manufacture of a medicament for normalizing liver fat content in a subject in need thereof.

38. Use of a pharmaceutical composition of any one of claims 1-20 in the manufacture of a medicament for reversing liver cirrhosis or reducing fibrosis associated with NASH, ASH, ALD, AFL, or protein misfolding disease in a subject in need thereof.

39. Use of a pharmaceutical composition of any one of claims 1-20 in the manufacture of a medicament for lowering blood glucose.

40. Use of a pharmaceutical composition of any one of claims 1-20 in the manufacture of a medicament for reducing uric acid.

41. The use of claim 38, wherein the protein misfolding disease is cystic fibrosis, alpha-1 antitrypsin deficiency, or transthyretin amyloid cardiomyopathy.

42. The use of claim 41, wherein the pharmaceutical composition is to be administered to the subject, and wherein a misfolded protein corrector molecule is to be further administered to the subject.

43. Use of a pharmaceutical composition of any one of claims 21-25 in the manufacture of a medicament for treating nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease (NAFL).

44. Use of a pharmaceutical composition of any one of claims 21-25 in the manufacture of a medicament for reversing NASH with cirrhosis.

45. Use of a pharmaceutical composition of any one of claims 21-25 in the manufacture of a medicament for treating alcoholic steatohepatitis (ASH), alcoholic liver disease (ALD) or alcoholic fatty liver disease (AFL).

46. Use of a pharmaceutical composition of any one of claims 21-25 in the manufacture of a medicament for normalizing liver fat content in a subject in need thereof.

47. Use of a pharmaceutical composition of any one of claims 21-25 in the manufacture of a medicament for reversing liver cirrhosis or reducing fibrosis associated with NASH, ASH, ALD, AFL, or protein misfolding disease.

48. Use of a pharmaceutical composition of any one of claims 21-25 in the manufacture of a medicament for lowering blood glucose.

49. Use of a pharmaceutical composition of any one of claims 21-25 in the manufacture of a medicament for reducing uric acid.

50. A pharmaceutical composition of any one of claims 1-25 for use in therapy.