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

(4) a surfactant;

wherein the composition has a pH from 6.9 to 8.1.

[0004b] In another aspect of the present disclosure, there is provided a lyophilized composition which, when reconstituted, comprises the composition as disclosed herein.

[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 in separate chambers.

[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 -5 °C to -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 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 fibrosis associated with NASH, ASH, ALD, or AFL in a subject in need thereof.

[0004g] 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.

[0004h] 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.

[0004i] 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

WHAT IS CLAIMED:

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

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

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

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

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

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

7. The composition of any one of claims 1-3, comprising 20 mM to 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 10 mM to 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 50 to 220 mM.

12. The composition of claim 11, wherein the sucrose concentration is 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 0.004% to 0.1% w/v.

15. The composition of any one of claims 1-14, wherein the composition has a pH of 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) 25-150 mg/mL Efruxifermin (EFX);
(2) 120 mM sucrose;
(3) 120 mM Arginine/Arginine-HCl;
(4) 0.06% weight/volume (w/v) polysorbate-20; and
(5) 20 mM Tris-HCl;
wherein the composition has a pH of 7.3.

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

19. A lyophilized composition which, when reconstituted, comprises the composition of any one of claims 1-17.

20. The composition of claim 19, comprising a residual moisture content of 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 0.05% to 5%, optionally 0.15% to 1.5%.

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

25. The composition of claim 1, comprising 80 mM arginine/ glutamic acid and 80 mM sucrose.

26. A dual chamber device comprising the composition of claim 19 or 20 and a diluent in separate chambers.

27. 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 -5 °C to -20 °C; (c) primary drying the product of step (b); and

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

28. The process of claim 27, wherein freezing in step (a) is conducted at a temperature of between -40 °C to -50 °C.

29. The process of claim 27 or claim 28, wherein annealing in step (b) is conducted for 5 to 20 hours and/or at a temperature of between -5 °C to -10 °C.

30. The process of any one of claims 27-29, wherein primary drying in step (c) is conducted at 0.08 to 0.2 mbar chamber pressure and/or at a temperature from -5 °C to -30 °C.

31. 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).

32. Use of a pharmaceutical composition of any one of claims 1-20 in the manufacture of a medicament for reducing fibrosis associated with NASH, ASH, ALD, or AFL in a subject in need thereof.

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

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

35. The use of any one of claims 31-34, wherein (a) the composition is reconstituted within five minutes to obtain a reconstituted composition and (b) the reconstituted composition is to be administered to a subject.

36. The use of claim 35, wherein the reconstituted composition of step (a) is maintained at room temperature for up to 10 minutes prior to step (b).

37. The use of claim 35 or 36, wherein the reconstituted composition is to be subcutaneously administered to the subject in step (b).

38. 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).

39. Use of a pharmaceutical composition of any one of claims 21-25 in the manufacture of a medicament for reducing fibrosis associated with NASH, ASH, ALD, or AFL.

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

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

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