

obeticholic acid
(also known as INT-747)

[0004] The present disclosure relates to a composition comprising obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, wherein obeticholic acid or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof is in the form of particles, and wherein at least 50% of the particles have a diameter of less than 200 μm. Such compositions include all those described herein.

[0004a] In one aspect of the present disclosure, there is provided a composition comprising obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, wherein obeticholic acid or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof is in the form of particles, and wherein at least 50% of the particles have a diameter of 200 μm or less.

[0005] The present disclosure also relates to treating a disease or condition described herein in a patient in need thereof by administering a composition that includes obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, where the obeticholic acid or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof is in the form of particles.

[0006] The present disclosure also relates to treating a disease or condition described herein in a patient in need thereof by administering a composition that includes obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, where the obeticholic acid or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof is in the form of particles, and wherein at least 50% of the particles have a diameter of 200 μm or less.

[0007] The present disclosure also relates to treating primary biliary cirrhosis (PBC) in a patient in need thereof by administering a composition that includes obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, optionally in a titration period, where the obeticholic acid or a pharmaceutically acceptable salt, ester, or

amino acid conjugate thereof is in the form of particles, and wherein at least 50% of the particles have a diameter of 200 μm or less.

[0007a] In a further aspect of the present disclosure, there is provided a composition comprising obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, wherein obeticholic acid or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof is in the form of particles, and wherein at least 50% of the particles have a diameter of 200 μm or less, for use in treating primary biliary cirrhosis (PBC) in a patient in need thereof.

[0007b] In another aspect of the present disclosure, there is provided a use of a composition comprising obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, wherein obeticholic acid or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof is in the form of particles, and wherein at least 50% of the particles have a diameter of 200 μm or less, in the manufacture of a medicament for treating primary biliary cirrhosis (PBC) in a patient in need thereof.

[0008] The present disclosure also relates to a method of treating primary sclerosing cholangitis (PSC), chronic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), hepatitis C infection, alcoholic liver disease, liver damage due to progressive fibrosis, or liver fibrosis in a patient in need thereof by

administering a composition that includes obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, optionally in a titration period, where the obeticholic acid or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof is in the form of particles. In one example, at least 50% of the particles have a diameter of 200 μm or less.

[0008a] In a further aspect of the present disclosure, there is provided a composition comprising obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, wherein obeticholic acid or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof is in the form of particles, and wherein at least 50% of the particles have a diameter of 200 μm or less, for use in treating primary sclerosing cholangitis (PSC), chronic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), hepatitis C infection, alcoholic liver disease, liver damage due to progressive fibrosis, or liver fibrosis in a patient in need thereof.

[0008b] In another aspect of the present disclosure, there is provided a use of a composition comprising obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, wherein obeticholic acid or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof is in the form of particles, and wherein at least 50% of the particles have a diameter of 200 μm or less, in the manufacture of a medicament for treating primary sclerosing cholangitis (PSC), chronic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), hepatitis C infection, alcoholic liver disease, liver damage due to progressive fibrosis, or liver fibrosis in a patient in need thereof.

[0009] The present disclosure also relates to a method of treating a solid-tumor cancer in a patient in need thereof by administering a composition that includes obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, optionally in a titration period, where the obeticholic acid or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof is in the form of particles. In one example, at least 50% of the particles have a diameter of 200 μm or less.

[0010] The present disclosure also relates to a method of treating an autoimmune disease in a patient in need thereof by administering a composition that obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, optionally in a titration period, where the obeticholic acid or a pharmaceutically acceptable salt, ester, or

amino acid conjugate thereof is in the form of particles. In one example, at least 50% of the particles have a diameter of 200 μm or less.

[0011] The present disclosure also relates to methods of treating a disease or condition described herein by administering a obeticholic acid composition described herein where the obeticholic acid composition is administered as part of a treatment regimen that includes a titration period and a starting dose of the obeticholic acid composition at an amount of about 5 mg or 10 mg. In particular instances, such methods include daily (QD) administration of an obeticholic acid described herein during the titration period. In particular instances, such methods also include administration of an adjusted dose of an obeticholic acid composition described herein after the titration period.

[0012] The present disclosure also relates to a composition comprising obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, wherein obeticholic acid or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof is in the form of particles, and wherein at least 50% of the particles have a diameter of less than 200 μm. The present disclosure also relates to a composition comprising obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof,

and a pharmaceutically acceptable excipient (*e.g.*, sodium starch glycolate) having a low alcohol (*e.g.*, ethanol or methanol) content (*e.g.*, less than 5% (wt/wt)).

[0013] The present disclosure also relates to a pharmaceutical composition, comprising a therapeutically effective amount of obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, in the form of particles, and a pharmaceutically acceptable excipient (*e.g.*, sodium starch glycolate) having a low alcohol (*e.g.*, ethanol or methanol) content (*e.g.*, less than 5% (wt/wt)), wherein at least 50% of the particles have a diameter of less than 200 μm.

[0014] The present disclosure also relates to a pharmaceutical composition, comprising obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, in the form of particles, wherein at least 50% of the particles have a diameter of less than 200 μm, at about 1% to about 6% by weight, sodium starch glycolate at about 2% to about 8 % by weight having a low alcohol (*e.g.*, ethanol or methanol) content (*e.g.*, less than 5% (wt/wt)), a lubricant (*e.g.*, magnesium stearate) at about 0.1% to about 2.0% by weight, and a diluent (*e.g.*, microcrystalline cellulose) at about 85% to about 95 % by weight.

[0015] The present disclosure also relates to a method for preparing a composition comprising obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, in the form of particles, wherein at least 50% of the particles have a diameter of less than 200 μm, comprising forming the particles through jet-milling.

[0015a] In yet another aspect of the present disclosure, there is provided a method for preparing a composition comprising obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, in the form of particles, wherein at least 50% of the particles have a diameter of 200 μm or less, comprising forming the particles through jet-milling.

[0016] The present disclosure also relates to a tablet comprising an intra-granular portion and an extra-granular portion, the intra-granular portion comprising obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, microcrystalline cellulose, and one or more additional pharmaceutical excipients, and the extra-granular portion comprising one or more pharmaceutical excipients.

[0017] The present disclosure also relates to a tablet comprising an intra-granular portion and an extra-granular portion, the intra-granular portion comprising obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, microcrystalline cellulose, and one or more additional pharmaceutical excipients, and the extra-granular portion comprising microcrystalline cellulose and one or more additional pharmaceutical excipients.

[0017a] In yet another aspect of the present disclosure, there is provided a tablet comprising an intra-granular portion and an extra-granular portion, the intra-granular portion comprising obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, microcrystalline cellulose, and one or more additional pharmaceutical excipients, and the extra-granular portion comprising one or more pharmaceutical excipients, optionally wherein the obeticholic acid or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof is jet-milled.

[0018] The present disclosure also relates to methods for treating or preventing an FXR mediated disease or condition or a disease or condition in which elevated concentrations of circulating lipid compounds or glucose in the blood, or decreased insulin level, or increased insulin resistance is involved, or inhibiting or reversing fibrosis, comprising administering a therapeutically effective amount of a composition of the present disclosure to a subject in need thereof.

[0019] The present disclosure also relates to use of a composition of the present disclosure for treating or preventing an FXR mediated disease or condition or a disease or condition in which elevated concentrations of circulating lipid compounds or glucose in the blood, or decreased insulin level, or increased insulin resistance is involved, or for inhibiting or reversing fibrosis.

[0020] The present disclosure also relates to use of a composition of the present disclosure in the manufacture of a medicament for treating or preventing an FXR mediated disease or condition or a disease or condition in which elevated concentrations of circulating lipid compounds or glucose in the blood, or decreased insulin level, or increased insulin resistance is involved, or for inhibiting or reversing fibrosis.

[0021] The compositions and methods of the present disclosure address unmet needs in the treatment or prevention of an FXR mediated disease or a disease or disorder in which elevated concentrations of circulating lipid compounds in the blood such as cholesterol and triglycerides or glucose are involved.

[0022] The compositions and methods of the present disclosure address unmet needs in the treatment of diseases and conditions described herein, including for example, PBC, PSC, NAFLD, NASH, cancer, and autoimmune diseases described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] FIG. 1 is a particle size distribution histogram of obeticholic acid before jet-milling.

[0024] FIG. 2 is a particle size distribution histogram of obeticholic acid after jet-milling.

[0025] FIG. 3 is a graph showing the dissolution profile of 10 mg tablets containing unmilled/non-agglomerated, unmilled/agglomerated, or jet-milled obeticholic acid.

[0026] FIG. 4 is a graph showing the dissolution profile of 5 mg tablets containing unmilled or jet-milled obeticholic acid.

CLAIMS

1. A composition comprising obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, wherein obeticholic acid or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof is in the form of particles, and wherein at least 50% of the particles have a diameter of 200 μm or less.

2. The composition of claim 1, wherein at least 50% of the particles have a diameter of 100 μm or less; 50 μm or less; 10 μm or less; or 5 μm or less,

or wherein at least 90% of the particles have a diameter of 200 μm or less; 100 μm or less; or 25 μm or less.

3. The composition of any one of claims 1-2 further comprising at least one pharmaceutically acceptable excipient having an alcohol content of less than about 6% (wt/wt).

4. The composition of claim 1, wherein the composition is in a unit dosage form.

5. The composition of claim 4, wherein the unit dosage form is a tablet;

optionally wherein the tablet comprises an intra-granular portion and an extra-granular portion;

further optionally wherein the intra-granular portion comprises microcrystalline cellulose and obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof in a ratio between about 20:1 to about 1:5.

6. A tablet comprising an intra-granular portion and an extra-granular portion, the intra-granular portion comprising obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, microcrystalline cellulose, and one or more additional pharmaceutical excipients, and the extra-granular portion comprising one or more pharmaceutical excipients,

optionally wherein the obeticholic acid or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof is jet-milled.

7. The tablet of claim 6, wherein obeticholic acid or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof is in the form of particles, and wherein at least 50% of the particles have a diameter of 200 μm or less.

8. A method for preparing a composition comprising obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, in the form of particles, wherein at least 50% of the particles have a diameter of 200 μm or less, comprising forming the particles through jet-milling.

9. A composition comprising obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, wherein obeticholic acid or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof is in the form of particles, and wherein at least 50% of the particles have a diameter of 200 μm or less, for use in treating primary biliary cirrhosis (PBC) in a patient in need thereof.

10. A composition comprising obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, wherein obeticholic acid or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof is in the form of particles, and wherein at least 50% of the particles have a diameter of 200 μm or less, for use in treating primary sclerosing cholangitis (PSC), chronic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), hepatitis C infection, alcoholic liver disease, liver damage due to progressive fibrosis, or liver fibrosis in a patient in need thereof.

11. The composition for use according to claim 10, wherein said condition is nonalcoholic steatohepatitis (NASH).

12. The composition for use according to any one of claims 9-11, wherein said obeticholic acid composition is to be administered as a starting dose.

13. The composition for use according to claim 12, wherein said starting dose is to be administered in a titration period,

optionally wherein said titration period comprises 1 to 6 months,

further optionally wherein said titration period is 3 or 6 months.

14. The composition for use according to claim 12, wherein said starting dose is to be administered to said patient once daily, once every other day, or once weekly.

15. The composition for use according to claim 9, wherein said composition comprises obeticholic acid in an amount of about 0.05 mg to 50 mg, 0.5 mg to 50 mg, 1 mg to 50 mg; about 1 mg to 25 mg; or about 1 mg to 10 mg, or about 1 mg to 5 mg,

or wherein said composition comprises about 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 10 mg, 25 mg or 50 mg of obeticholic acid.

16. The composition for use according to claim 12, wherein said starting dose is adjusted to about 5 mg or 10 mg after a titration period of about 1 to 6 months.

17. The composition for use according to claim 9, wherein a bile acid binding resin is to be administered at least 4 hours before the composition is to be administered, or at least 4 hours after the composition is to be administered.

18. The composition for use according to claim 9, wherein ursodeoxycholic acid is also to be administered to the patient,

or wherein the patient is not responsive to treatment with ursodeoxycholic acid.

19. Use of a composition comprising obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, wherein obeticholic acid or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof is in the form of particles, and wherein at least 50% of the particles have a diameter of 200 μm or less, in the manufacture of a medicament for treating primary biliary cirrhosis (PBC) in a patient in need thereof.

20. Use of a composition comprising obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, wherein obeticholic acid or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof is in the form of particles, and wherein at least 50% of the particles have a diameter of 200 μm or less, in the manufacture of a medicament for treating primary sclerosing cholangitis (PSC), chronic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), hepatitis C infection, alcoholic liver disease, liver damage due to progressive fibrosis, or liver fibrosis in a patient in need thereof.

21. The use according to claim 20 in the manufacture of a medicament for treating nonalcoholic steatohepatitis (NASH).