

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, in an amount of 1 mg to 50 mg, 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; and

at least one pharmaceutically acceptable excipient having an alcohol content of less than 6% (w/w).

[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 another aspect of the present disclosure, there is provided a composition disclosed herein for use in treating primary biliary cirrhosis (PBC) in a patient in need thereof.

[0007b] In a further aspect of the present disclosure, there is provided a use of a composition disclosed herein, 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 another aspect of the present disclosure, there is provided a composition disclosed herein 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 disclosed herein, 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

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 disclosed herein, 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.

CLAIMS

1. A composition comprising obeticholic acid, or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof, in an amount of 1 mg to 50 mg, 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; and

at least one pharmaceutically acceptable excipient having an alcohol content of less than 6% (w/w).

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, wherein the at least one pharmaceutically acceptable excipient having an alcohol content of less than 6% (wt/wt) is sodium starch glycolate.

4. The composition of any one of claims 1-3, wherein the composition is in a unit dosage form.

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

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

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 20:1 to 1:5, and wherein the obeticholic acid or a pharmaceutically acceptable salt, ester, or amino acid conjugate thereof is jet-milled.

6. A method for preparing a composition of claim 1, comprising forming the particles through jet-milling.

7. A composition of any one of claims 1-5 for use in treating primary biliary cirrhosis (PBC) in a patient in need thereof.

8. A composition of any one of claims 1-5 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.

9. The composition for use according to claim 8, wherein said condition is nonalcoholic steatohepatitis (NASH).

10. The composition for use according to any one of claims 7-9, wherein said obeticholic acid composition is to be administered as a starting dose.

11. The composition for use according to claim 10, 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.

12. The composition for use according to claim 10, wherein said starting dose is to be administered to said patient once daily, once every other day, or once weekly.

13. The composition for use according to claim 7, wherein said composition comprises obeticholic acid in an amount of 1 mg to 50 mg; 1 mg to 25 mg; or 1 mg to 10 mg, or 1 mg to 5 mg,

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

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

15. The composition for use according to claim 7, 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.

16. The composition for use according to claim 7, wherein ursodeoxycholic acid is also to be administered to the patient,

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

17. Use of the composition of claim 1, in the manufacture of a medicament for treating primary biliary cirrhosis (PBC) in a patient in need thereof.

18. Use of the composition of claim 1, 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.

19. The use according to claim 18 in the manufacture of a medicament for treating nonalcoholic steatohepatitis (NASH).

20. The composition for use according to claim 9, wherein said composition comprises obeticholic acid in an amount of 5 mg, or 10 mg, or 25 mg.