A PEG-asparaginase liquid injection formulation (Oncaspar®) has been previously approved for commercial marketing by the U.S. Food and Drug Administration. Oncaspar® was approved as a first-line treatment of patients with acute lymphoblastic leukemia (ALL) as a component of a multi-agent chemotherapy regimen. In addition, Oncaspar® was approved for the treatment of patients with ALL and hypersensitivity to asparaginase (e.g., native forms ofL-asparaginase).

SUMMARY

In one aspect, the present disclosure refers to a reconstituted lyophilized composition comprising: a polyalkylene oxide-asparaginase at a concentration of 100 to 5,000 IU per ml of said composition; dibasic sodium phosphate at a concentration of 0.1 to 0.8 wt. %; monobasic sodium phosphate at a concentration of 0.01 to 0.5 wt. %; a salt at a concentration of 0.05 to 1 wt. %; and a sugar at a concentration of 0.1 to 25 wt. %, wherein the polyalkylene oxide-asparaginase comprises an asparaginase covalently linked to a polyalkylene oxide group.

In another aspect, the present disclosure refers to a lyophilized storage stable composition comprising: a polyalkylene oxide-asparaginase; a buffer which comprises dibasic sodium phosphate and monobasic sodium phosphate; a salt; and a sugar, wherein the lyophilized storage stable composition is capable of forming the composition disclosed herein by reconstituting the lyophilized storage stable composition with water for injection (WFI).

In yet another aspect, the present disclosure refers to a method of making a lyophilized polyalkylene oxide-asparaginase composition wherein the method comprises lyophilizing an aqueous concentrate composition comprising: (i) a polyalkylene oxide-asparaginase comprising a polyalkylene oxide group covalently linked by a linker to an asparaginase; (ii) a buffer, which comprises dibasic sodium phosphate and monobasic sodium phosphate; (iii) a salt; and (iv) a sugar in a manner sufficient to produce a lyophilized storage stable polyalkylene oxide asparaginase composition disclosed herein, optionally wherein the method further comprises introducing an aqueous concentrate composition into a unit dosage container and lyophilizing the aqueous concentrate composition in the unit dosage container, optionally wherein the unit dosage container is a vial, such as a sealed glass vial.

In yet another aspect, the present disclosure refers to use of a composition as disclosed herein in the manufacture of a medicament for treating a subject for a neoplastic condition.

In yet another aspect, the present disclosure refers to a kit comprising one or more unit dosage containers each containing a lyophilized storage stable composition disclosed herein.

Examples of the disclosure include polyalkylene oxide-asparaginase compositions. In some instances, the compositions include one or more of a buffer and a salt. In other examples, the composition is a lyophilized storage stable composition. In some instances, the lyophilized compositions include one or more of a buffer, a salt, and a sugar. Examples of the disclosure further include methods of making the compositions. The compositions find use in a variety of applications, e.g., in the treatment of a neoplastic condition in a subject.

BRIEF DESCRIPTION OF THE FIGURES

FIG. I shows a process flow diagram for a method of making a lyophilized storage stable composition according to embodiments of the present disclosure.

FIG.2 shows a graph of purity(%) vs. time (weeks) at 40 °C for a lyophilized storage stable composition according to embodiments of the present disclosure.

FIG. 3 shows a graph of potency (IU/mL) vs. time (weeks) at 40 °C for a lyophilized storage stable composition according to embodiments of the present disclosure.

FIG.4 shows a graph of purity(%) vs. time (weeks) at 25 °C for a lyophilized storage stable composition according to embodiments of the present disclosure.

FIG. 5 shows a graph of potency (IU/mL) vs. time (weeks) at 25 °C for a lyophilized storage stable composition according to embodiments of the present disclosure.

FIG. 6 shows a process flow diagram of a method of making a lyophilized storage stable composition, according to embodiments of the present disclosure. The final formulation and filtration steps are shown.

CLAIMS

What is claimed is:

1. A reconstituted lyophilized composition comprising:

   a polyalkylene oxide-asparaginase at a concentration of 100 to 5,000 IU per ml of said composition;

   dibasic sodium phosphate at a concentration of 0.1 to 0.8 wt. %;

   monobasic sodium phosphate at a concentration of 0.01 to 0.5 wt. %;

   a salt at a concentration of 0.05 to 1 wt. %; and

   a sugar at a concentration of 0.1 to 25 wt. %,

   wherein the polyalkylene oxide-asparaginase comprises an asparaginase covalently linked to a polyalkylene oxide group.

2. The composition according to claim 1, wherein:

   a. the concentration of dibasic sodium phosphate is from 0.1 to 0.5 wt. %, or 0.2 to 0.3 wt. %; and

   b. the concentration of monobasic sodium phosphate is from 0.01 to 0.1 wt. % or 0.05-0.07 wt. %.

3. The composition according to any one of the preceding claims, wherein the concentration of sugar is from 0.5 to 20 wt. %, 1 to 10 wt. %, or 4 to 5 wt. %.

4. The composition according to any of the preceding claims, wherein the salt is sodium chloride, potassium chloride, calcium chloride, magnesium chloride, or a combination thereof, optionally wherein the salt is sodium chloride.

5. The composition according to any of the preceding claims, wherein the sugar is a monosaccharide, a disaccharide, or a polysaccharide; optionally wherein the sugar is sucrose, mannitol, maltose, trehalose, 2-hydroxypropyl-beta-cyclodextrin (β-HPCD), lactose, glucose, fructose, galactose, glucosamine, or combinations thereof, further optionally wherein the sugar is sucrose.

6. The composition according to any of the preceding claims, wherein the concentration of the

polyalkylene oxide-asparaginase is:

a. 500 to 1,000 IU per ml of said composition;

b. 700 to 800 IU per ml of said composition; or

c. 750 IU per ml of said composition.

7. The composition according to any of the preceding claims, wherein the polyalkylene oxide group comprises a polyethylene glycol group, optionally wherein

a. the polyethylene glycol group has a molecular weight ranging from 2,000 to 10,000 daltons; or

b. the polyethylene glycol group has a molecular weight is 5,000 daltons.

8. The composition according to any of the preceding claims, wherein the linker is a urethane or succinate linker.

9. The composition according to any of claims 1-8, wherein the composition further comprises sodium hydroxide or hydrochloric acid.

10. A lyophilized storage stable composition comprising:

a polyalkylene oxide-asparaginase;

a buffer which comprises dibasic sodium phosphate and monobasic sodium phosphate;

a salt; and

a sugar,

wherein the lyophilized storage stable composition is capable of forming the composition of any one of claims 1-9 by reconstituting the lyophilized storage stable composition with water for injection (WFI).

11. A method of making a lyophilized polyalkylene oxide-asparaginase composition wherein the method comprises lyophilizing an aqueous concentrate composition comprising:

(i) a polyalkylene oxide-asparaginase comprising a polyalkylene oxide group covalently linked by a linker to an asparaginase;

(ii) a buffer, which comprises dibasic sodium phosphate and monobasic sodium phosphate;

(iii) a salt; and

(iv) a sugar

in a manner sufficient to produce a lyophilized storage stable polyalkylene oxide asparaginase composition of claim 10,

optionally wherein the method further comprises introducing an aqueous concentrate composition into a unit dosage container and lyophilizing the aqueous concentrate composition in the unit dosage container, optionally wherein the unit dosage container is a vial, such as a sealed glass vial.

12. Use of a composition of any one of claims 1-10 in the manufacture of a medicament for treating a subject for a neoplastic condition.

13. The use according to claim 12, wherein the neoplastic condition is a cancer, optionally wherein the cancer is leukemia, optionally wherein the leukemia is:

(i) acute lymphoblastic leukemia (ALL), or

(ii) acute myeloid leukemia (AML).

14. The use according to claim 12 or claim 13, wherein the subject has been prescribed a treatment regimen that includes an induction phase, a consolidation phase and a maintenance phase,

optionally wherein the use comprises a single dosage unit to be administered to the subject in the induction phase and multiple dosage units to be administered during the maintenance phase,

further optionally wherein the multiple dosage units are to be administered to the subject by administering a dosage unit to the subject every 3 weeks or every 2 weeks.

15. The use according to any of claims 12-14, wherein:

a. the subject is a juvenile; or

b. the subject is an adult.

16. A kit comprising one or more unit dosage containers each containing a lyophilized storage stable composition according to claim 10.