with longer duration of action; thus, requiring fewer injections than currently available insulin products, including as infrequently as once-weekly.

One category of such insulin products comprises moieties that activate the insulin receptor attached to Fc regions of an antibody, referred to herein as insulin-Fc fusions. Examples of such products are described in U.S. Patent Number 9,855,318, which describes compounds and formulations thereof, including formulations comprising the phenolic preservative m-cresol, which is commonly used in insulin products, including the once-daily basal insulins described above.

It has been found, however, that formulations of insulin-Fc fusions with the concentrations of preservatives described in U.S. Patent Number 9,855,318 and/or in currently available insulin products may lead to unacceptable stability liabilities. Thus, there is a need for new formulations with preservatives that provide sufficient antimicrobial effectiveness but that do not result in unacceptable stability liabilities.

The present invention seeks to meet those needs.

Summary

In a first aspect of the present disclosure, there is provided an aqueous, sterile pharmaceutical composition comprising:

a) an insulin-Fc fusion;
b) phenol;
c) one or more additional preservatives selected from the group consisting of phenoxyethanol and benzyl alcohol;
d) a tonicity agent;
e) a surfactant; and
f) a buffer;

and having a pH between 6 to 7.5; and

wherein the phenol and one or more additional preservatives are present in concentrations that allow for an in-use period of at least 12 weeks without unacceptable loss of stability.

In another aspect of the present disclosure, there is provided an aqueous, sterile pharmaceutical composition comprising:

a) insulin efsitora alfa in a concentration of 5 to 30 mg/mL;
b) phenol in a concentration of 1.5 to 4 mg/mL;
c) benzyl alcohol in a concentration of 4 to 14 mg/mL;

d) glycerin in a concentration of 15 to 35 mg/mL;

e) poloxamer 188 in a concentration of 0.01 to 0.5 mg/mL; and

f) phosphate in a concentration of 5 to 10 mM;

wherein the composition has a pH of 6.3 to 6.8.

In yet 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 treating diabetes.

In a further aspect of the present disclosure, there is provided an article of manufacture comprising any one of the pharmaceutical compositions as disclosed herein.

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

Description

Accordingly, in one aspect the present invention provides an aqueous, sterile pharmaceutical composition comprising:

a) an insulin-Fc fusion;

b) phenol;

c) one or more additional preservatives selected from the group consisting of phenoxyethanol and benzyl alcohol;

d) a tonicity agent;

e) a surfactant;

f) a buffer; and

having a pH between 6 to 7.5; and

wherein the phenol and one or more additional preservatives are present in concentrations that allow for an in-use period of at least 12 weeks without unacceptable loss of stability.

In another aspect, the present invention provides an aqueous, sterile pharmaceutical composition comprising:

a) basal BIF in a concentration between 5-30 mg/mL;

b) phenol in a concentration of 1.5 to 4 mg/mL;

c) benzyl alcohol in a concentration between 4 to 14 mg/mL;

d) glycerin in a concentration of 15 to 35 mg/mL;

e) poloxamer 188 in a concentration of 0.01 to 0.5 mg/mL; and

WE CLAIM:

1. An aqueous, sterile pharmaceutical composition comprising:

a) an insulin-Fc fusion;

b) phenol;

c) one or more additional preservatives selected from the group consisting of phenoxyethanol and benzyl alcohol;

d) a tonicity agent;

e) a surfactant; and

f) a buffer;

and having a pH between 6 to 7.5; and

wherein the phenol and one or more additional preservatives are present in concentrations that allow for an in-use period of at least 12 weeks without unacceptable loss of stability.

2. The composition of claim 1 wherein the concentration of phenol is from 1.5 to 4 mg/mL.

3. The composition of either of claims 1 or 2 wherein the concentration of phenol is about 1.8 mg/mL.

4. The composition of any of claims 1-3 wherein the additional preservative is phenoxyethanol.

5. The composition of claim 4 wherein the concentration of phenoxyethanol is between 4 and 14 mg/mL.

6. The composition of claim 4 wherein the concentration of phenoxyethanol is about 4 mg/mL.

7. The composition of claim 4 wherein the concentration of phenoxyethanol is about 8 mg/mL

8. The composition of any of claims 1-3 wherein the additional preservative is benzyl alcohol.

9. The composition of claim 8 wherein the concentration of benzyl alcohol is between 5 to 10 mg/mL.

10. The composition of claim 9 wherein the concentration of benzyl alcohol is about 9 mg/mL.

11. The composition of any of claims 1-10 wherein the insulin-Fc fusion is insulin efsitora alfa.

12. The composition of claim 11 wherein the concentration of insulin efsitora alfa is between 5 to 30 mg/mL.

13. The composition of claim 12 wherein the concentration of insulin efsitora alfa is selected from the group consisting of about 7.15, 14.3, and 28.6 mg/mL.

14. The composition of any of claims 1-13 wherein the pH of the composition is between 6.3 to 6.8.

15. The composition of any of claims 1-14 wherein the pH of the composition is about 6.5.

16. The composition of any of claims 1-15 wherein the tonicity agent is selected from the group consisting of sodium chloride, mannitol, and glycerin.

17. The composition of any of claims 1-16 wherein the tonicity agent is glycerin.

18. The composition of claim 17 wherein the concentration of glycerin is between 15 to 35 mg/mL.

19. The composition of claim 18 wherein the concentration of glycerin is about 17 mg/mL.

20. The composition of any of claims 1-19 wherein the surfactant is selected from the group consisting of poloxamer 188, polysorbate 20, and polysorbate 80.

21. The composition of any of claims 19-20 wherein the surfactant is poloxamer 188.

22. The composition of claim 21 wherein the concentration of poloxamer 188 is between 0.01 to 0.5 mg/mL.

23. The composition of claim 22 wherein the concentration of poloxamer 188 is about 0.4 mg/mL.

24. The composition of any of claims 1-23 wherein the buffer is selected from the group consisting of phosphate, citrate, and TRIS.

25. The composition of claim 24 wherein the buffer is phosphate.

26. The composition of claim 25 wherein the concentration of phosphate is between 5 to 10 mM.

27. An aqueous, sterile pharmaceutical composition comprising:

a) insulin efsitora alfa in a concentration of 5 to 30 mg/mL;

b) phenol in a concentration of 1.5 to 4 mg/mL;

c) benzyl alcohol in a concentration of 4 to 14 mg/mL;

d) glycerin in a concentration of 15 to 35 mg/mL;

e) poloxamer 188 in a concentration of 0.01 to 0.5 mg/mL; and

f) phosphate in a concentration of 5 to 10 mM;

wherein the composition has a pH of 6.3 to 6.8.

28. The composition of claim 27 wherein:

a) insulin efsitora alfa is in a concentration selected from the group consisting of about 7.15, about 14.3, and about 28.6 mg/mL;

b) phenol is in a concentration of about 1.8 mg/mL;

c) benzyl alcohol is in a concentration of about 9 mg/mL;

d) glycerin is in a concentration of about 17 mg/mL;

e) poloxamer 188 is in a concentration of about 0.4 mg/mL; and

f) phosphate is in a concentration selected from the group consisting of about 5 and about 10 mM;

wherein the composition has a pH of about 6.5.

29. The composition of claim 28, wherein the concentration of insulin efsitora alfa is about 14.3 mg/mL and the concentration of phosphate is about 5 mM.

30. The composition of claim 28, wherein the concentration of insulin efsitora alfa is about 28.6 mg/mL and the concentration of phosphate is about 10 mM.

31. The composition of claim 28, wherein the concentration of insulin efsitora alfa is about 7.15 mg/mL.

32. Use of a pharmaceutical composition of any of claims 1-31 in the manufacture of a medicament for treating diabetes.

33. An article of manufacture comprising any one of the pharmaceutical compositions of claims 1-31.

34. The article of manufacture of claim 33 which is a multi-use vial.

35. The article of manufacture of claim 33 which is a multi-use pen injector.

36. The article of manufacture of claim 33 which is a pump device for continuous subcutaneous insulin infusion therapy.

37. A pharmaceutical composition of any of claims 1-31 for use in therapy.