is proposed in WO2016/001185. US2016/0324932 describes fusion proteins having prolonged duration of action at the insulin receptor sufficient for dosing as infrequently as once-weekly, including BIF. A specific dosing regimen is not described.

Despite these disclosures, there remains a need for insulin therapies requiring fewer injections than currently available insulin products and that can be administered with simple and convenient dosing regimens while still providing sufficient glycemic control. There also remains a need for presentations of such therapies that provide for a simpler, more convenient and/or less painful patient experience. There also remains a need for methods of treatment using such insulin therapies either without increasing or with reducing the risk of hypoglycemia compared to currently available insulin products.

SUMMARY

In an aspect of the present disclosure, there is provided a use of insulin efsitora alfa in the manufacture of a medicament for providing glycemic control in a patient in need thereof with type 2 diabetes (T2D), wherein a fixed dose of insulin efsitora alfa selected from the group consisting of 100, 150, 250 and 400 U is to be administered once-weekly to said patient.

In another aspect of the present disclosure, there is provided a use of insulin efsitora alfa in the manufacture of a medicament for improving glycemic control in a patient in need thereof with type 2 diabetes (T2D), wherein:

a) 100 U of insulin efsitora alfa is to be administered to said patient once-weekly;

b) the dose of insulin efsitora alfa is increased to 150 U once-weekly after at least 4 weeks on the 100 U dose;

c) the dose of insulin efsitora alfa is increased to 250 U once-weekly after at least 4 weeks on the 150 U dose; and

d) the dose of insulin efsitora alfa is increased to 400 U once-weekly after at least 4 weeks on the 250 U dose.

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

a) a fixed dose of insulin efsitora alfa in an amount selected from the group consisting of 100, 150, 250 and 400 U;

b) phosphate in a concentration between about 5 and 10 mM; and

c) glycerol in a concentration between about 15 and 35 mM;

and having a pH between about 5.5 and 7.5.

In another aspect of the present disclosure, there is provided a use of the composition as disclosed herein in the manufacture of a medicament for providing glycemic control in a patient with T2D.

In a further aspect of the present disclosure, there is provided a single-use autoinjector for use in the use as disclosed herein.

In another aspect of the present disclosure, there is provided a single-use autoinjector comprising the aqueous pharmaceutical composition as disclosed herein.

Accordingly, the present disclosure provides a method of providing glycemic control in a patient in need thereof with type 2 diabetes (T2D) comprising: administering to said patient once-weekly a fixed dose of BIF selected from the group consisting of 100, 150, 250 and 400 U.

The present disclosure also provides a method of providing glycemic control in a in a patient with type 2 diabetes (T2D) comprising:

a) administering to said patient an initial dose of 100 U of basal insulin-Fc (BIF) once weekly;
b) increasing the dose to 150 U of BIF once-weekly after at least 4 weeks on the 100 U dose;
c) increasing the dose to 250 U of BIF once-weekly after at least 4 weeks on the 150 U dose; and
d) increasing the dose to 400 U of BIF once-weekly after at least 4 weeks on the 250 U dose.

In certain examples, steps b) through d) are performed when the patient's fasting glucose (FG) is > 130 mg/dL.

The present disclosure also provides an aqueous pharmaceutical composition comprising:

a) a fixed dose of BIF in an amount selected from the group consisting of 100, 150, 250 and 400 U;
b) phosphate in a concentration between about 5 and 10 mM; and

c) glycerol in a concentration between about 15 and 35 mM;

and having a pH between about 5.5 and 7.5.

The present disclosure also provides a single-use autoinjector for use in improving glycemic control in a patient with T2D comprising a fixed dose of BIF selected from the group consisting of 100, 150, 250 and 400 U.

DETAILED DESCRIPTION OF THE INVENTION

The present application provides multiple aspects of dosing regimens, uses and methods of treatment for a long-acting insulin receptor agonists suitable for once-weekly dosing, such as those described in U.S. Patent Application Publication No. 2016/0324932, including BIF. In certain aspects, the regimens and methods described herein include administration of a fixed dose of BIF. In other aspects, the regimens and methods described herein include determination of whether the fixed dose of BIF being used to treat a T2D patient should be changed. In other aspects, the regimens and methods described herein include identification of a simple and convenient device for administering a fixed dose of BIF. In other aspects, the regimens and methods herein describe a non-preserved formulation for use in providing a fixed dose of BIF.

BIF, also known as insulin efsitora alfa, comprises a dimer of an insulin receptor agonist fused to a human IgG Fc region, wherein the insulin receptor agonist comprises an insulin B-chain analog fused to an insulin A-chain analog through the use of a first peptide linker and wherein the C-terminal residue of the insulin A-chain analog is directly fused to the N-terminal residue of a second peptide linker, and the C-terminal residue of the second peptide linker is directly fused to the N-terminal residue of the human IgG Fc region. BIF is identified by CAS registry number 2131038-11-2, which provides the following chemical names: (1) Insulin [16-glutamic acid, 25-histidine, 27-glycine, 28-glycine, 29-glycine, 30-glycine] (human B-chain) fusion protein with peptide (synthetic 7-amino acid linker) fusion protein with insulin [47-threonine, 51-aspartic acid, 58-glycine] (human A-chain) fusion protein with peptide (synthetic 20-amino acid linker) fusion protein with immunoglobulin G2 (human Fc fragment), dimer; and (2) *Homo sapiens* Insulin B-chain [Y16>Y(16), F25>H(25), TPKT27-30>GGGG(27-30)] (1-30) fusion protein with diglycylseryltetraglycyl (31-37) Insulin A-chain [I10>T(47), Y14>D(51), N21>G(58)] (38-58) fusion protein with tris(tetraglycylglutaminyl)pentaglycyl (59-78) *Homo sapiens* Immunoglobulin heavy

WE CLAIM:

1. Use of insulin efsitora alfa in the manufacture of a medicament for providing glycemic control in a patient in need thereof with type 2 diabetes (T2D), wherein a fixed dose of insulin efsitora alfa selected from the group consisting of 100, 150, 250 and 400 U is to be administered once-weekly to said patient.
2. The use of claim 1, wherein the first dose of insulin efsitora alfa to be administered to the patient is 100 U.
3. The use of either of claims 1 or 2, wherein the patient is to be administered the same dose for at least 4 weeks, and wherein the dose is increased when the patient needs additional glycemic control.
4. The use of any of claims 1-3, wherein the patient's dose is increased if the patient's fasting glucose (FG) is > 130 mg/dL after treatment with a first fixed dose for at least 4 weeks.
5. The use of either of claims 3 or 4, wherein the patient's dose is only increased if the patient had 0 episodes of blood glucose < 70 mg/dL.
6. The use of any of claims 1-5, wherein the patient's dose is decreased if the patient's FG is < 80 mg/dL.
7. Use of insulin efsitora alfa in the manufacture of a medicament for improving glycemic control in a patient in need thereof with type 2 diabetes (T2D), wherein:
    a) 100 U of insulin efsitora alfa is to be administered to said patient once-weekly;
    b) the dose of insulin efsitora alfa is increased to 150 U once-weekly after at least 4 weeks on the 100 U dose;
    c) the dose of insulin efsitora alfa is increased to 250 U once-weekly after at least 4 weeks on the 150 U dose; and
    d) the dose of insulin efsitora alfa is increased to 400 U once-weekly after at least 4 weeks on the 250 U dose.
8. The use of claim 7, wherein steps b) through d) are performed to reduce the patient's FG.
9. The use of claim 7, wherein steps b) through d) are performed when the patient's FG is > 130 mg/dL.
10. The use of any of claims 7-9, wherein steps b) through d) are only performed when the patient had 0 episodes of blood glucose < 70 mg/dL.

11. The use of any of claims 7-10, wherein the patient's dose is decreased to the previous lower dose if the patient's FG is < 80 mg/dL.
12. The use of any of claims 1-11, wherein the patient discontinues treatment if the patient experiences one or more episodes of nocturnal hypoglycemia or 2 or more episodes of hypoglycemia.
13. The use of any of claims 1-12, wherein the patient is insulin-naïve.
14. The use of any of claims 1-13, wherein patient has uncontrolled hyperglycemia.
15. The use of any of claims 1-14, wherein the patient has HbA1c between 7 and 10%.
16. The use of any of claims 1-15, wherein the patient is to receive 2 or more oral antihyperglycemic medications.
17. The use of any of claims 1-16, wherein the patient is to receive a GLP-1 receptor agonist.
18. The use of any of claims 1-17, wherein insulin efsitora alfa is to be administered in an aqueous composition comprising: phosphate in a concentration between about 5 and 10 mM; and glycerol in a concentration between about 15 and 35 mM; and having a pH between about 5.5 and 7.5.
19. The use of claim 18, wherein the composition further comprises poloxamer 188 in a concentration between about 0.1 to about 0.5 mg/mL.
20. The use of claim 19, wherein the phosphate is in a concentration of about 10 mM; glycerol is in a concentration of about 25 mM; and poloxamer 188 is in a concentration of about 0.4 mg/mL; and wherein the pH of the composition is about 6.5.
21. An aqueous pharmaceutical composition comprising:
    a) a fixed dose of insulin efsitora alfa in an amount selected from the group consisting of 100, 150, 250 and 400 U;
    b) phosphate in a concentration between about 5 and 10 mM; and
    c) glycerol in a concentration between about 15 and 35 mM;

    and having a pH between about 5.5 and 7.5.
22. The aqueous pharmaceutical composition of claim 21, further comprising poloxamer 188 in a concentration between about 0.1 to about 0.5 mg/mL.

23. The aqueous pharmaceutical composition of claim 22, wherein the phosphate is in a concentration of about 10 mM; glycerol is in a concentration of about 25 mM; and poloxamer 188 is in a concentration of about 0.4 mg/mL; and wherein the pH of the composition is about 6.5.
24. Use of the composition of any of claims 21-23 in the manufacture of a medicament for providing glycemic control in a patient with T2D.
25. The use of any of claims 1-20, wherein the fixed dose of insulin efsitora alfa is provided in a single-use autoinjector.
26. A single-use autoinjector for use in the use of any of claims 1-25.
27. A single-use autoinjector comprising the composition of any of claims 21-23.
28. The use of any of claims 1-20 or 24-25, wherein the use comprises improving glycemic control in the patient.