Methods of Using and Compositions Containing Dulaglutide

The present invention relates to the field of medicine. More particularly, the present invention relates to methods of using new doses of dulaglutide and compositions containing such higher doses of dulaglutide.

Dulaglutide, the active ingredient in Trulicity®, is a glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1 RA) that is approved for use as an adjunct to diet and exercise to improve glycemic control in patients with Type 2 diabetes (T2D). Two once weekly dulaglutide doses, 0.75 mg and 1.5 mg, were studied in the Phase 3 development program and received regulatory approval in the United States (US), European Union and other jurisdictions in 2014. Since their approval in 2014, these two doses of dulaglutide have been used to treat many patients with T2D, resulting in significant reductions in HbA1c with low risk of hypoglycemia, and reductions in body weight.

While therapy with currently approved doses of dulaglutide enabled the majority of patients included in the Phase 3 program to attain their glycemic targets (with or without use of other concomitant medications for T2D), significant numbers of patients receiving approved therapies today, including dulaglutide, are not reaching glycemic control goals (*see, e.g.*, Stark Casagrande et al. The prevalence of meeting A1c, blood pressure, and LDL goals among people with diabetes, 1988-2010. *Diabetes Care*. 2013;36(8):2271-2279). Therefore, there remains an important medical need to provide enhanced efficacy of pharmaceutical agents while also preserving an overall acceptable benefit/risk profile.

The doses, methods and compositions of the present invention seek to meet that need. The benefits of the present invention include providing additional glycemic control, as evidenced for example by further reductions in HbA1c, and/or weight loss as compared to the currently approved doses of dulaglutide. Moreover, the present invention provides such benefits while maintaining an acceptable profile of safety risks and adverse events.

Summary

In one aspect of the present disclosure, there is provided a use of dulaglutide in the manufacture of a medicament for improving glycemic control in a subject having type 2 diabetes (T2D) and in need of additional glycemic control, wherein:

a) a subject having T2D and in need of further glycemic control is identified;

b) a first dose of dulaglutide is to be administered once weekly to said subject for a minimum of four weeks; and

c) the dose is increased to a second dose which is to be administered once weekly,

wherein the first dose is selected from the group consisting of 1.5 and 3.0 mg, and the second dose is selected from the group consisting of 3.0 and 4.5 mg.

In another aspect of the present disclosure, there is provided a use of dulaglutide in the manufacture of a medicament for improving glycemic control in a subject having type 2 diabetes (T2D) and in need of further glycemic control, wherein:

a) a subject having T2D and in need of further glycemic control is identified;

b) 0.75 mg of dulaglutide is to be administered to said subject once weekly for a minimum of four weeks;

c) 1.5 mg of dulaglutide is to be administered to said subject once weekly for a minimum of four weeks; and

d) 3.0 mg of dulaglutide is to be administered to said subject once weekly.

In a further aspect of the present disclosure, there is provided a use of dulaglutide in the manufacture of a medicament for improving glycemic control in a subject having type 2 diabetes (T2D), wherein after said subject is to be treated with a 1.5 mg dose of dulaglutide once weekly but is in need of further glycemic control, the dose of dulaglutide to be administered is increased to 3.0 mg once weekly.

In another aspect of the present disclosure, there is provided aa use of dulaglutide in the manufacture of a medicament for improving glycemic control in a subject having type 2 diabetes (T2D), wherein after said subject is to be treated with a 3.0 mg dose of dulaglutide once weekly but is in need of further glycemic control, the dose of dulaglutide to be administered is increased to 4.5 mg once weekly.

In a further aspect of the present disclosure, there is provided a use of dulaglutide in the manufacture of a medicament for treating a subject having T2D and in need of further glycemic control, wherein 1.5 mg of dulaglutide is to be administered once weekly for a minimum of four weeks, and then the dose is increased to 3.0 mg once weekly.

In another aspect of the present disclosure, there is provided a use of dulaglutide in the manufacture of a medicament for treating a subject having T2D and in need of further glycemic control, wherein 0.75 mg of dulaglutide is to be administered once weekly for a minimum of four weeks, then the dose is increased to 1.5 mg of dulaglutide once weekly for a minimum of four weeks, and then the dose is increased to 3.0 mg once weekly.

In a further aspect of the present disclosure, there is provided a use of dulaglutide in the manufacture of a medicament for treating a subject having T2D and in need of further glycemic control, wherein:

a) 3.0 mg of dulaglutide is to be administered once weekly for a minimum of four weeks; and

the dose is increased to 4.5 mg once weekly.

In another aspect of the present disclosure, there is provided a use of dulaglutide in the manufacture of a medicament for providing chronic weight management to a subject in need thereof, wherein:

a) 0.75 mg of dulaglutide is to be administered to said subject once weekly for a minimum of four weeks;

b) 1.5 mg of dulaglutide is to be administered to said subject once weekly for a minimum of four weeks; and

c) the dose is increased to 3.0 mg once weekly.

In a further aspect of the present disclosure, there is provided a use of dulaglutide in the manufacture of a medicament for providing chronic weight management to a subject in need thereof, wherein:

a) a subject is identified who has been previously treated with 1.5 mg of dulaglutide once weekly for a minimum of four weeks; and

b) the dose is increased to 3.0 mg once weekly.

In another aspect of the present disclosure, there is provided a use of dulaglutide in the manufacture of a medicament for providing chronic weight management to a subject in need thereof, wherein:

a) a subject is identified who has been previously treated with 3.0 mg of dulaglutide once weekly for a minimum of four weeks; and

b) the dose is increased to 4.5 mg once weekly.

In a further aspect of the present disclosure, there is provided a stable pharmaceutical formulation comprising:

a) dulaglutide, in a concentration selected from the group consisting of 6.0 or 9.0 mg/mL;

b) mannitol, in a concentration of 46.4 mg/mL;

c) trisodium citrate, in a concentration of 2.74 mg/mL; and

d) polysorbate 80, in a concentration between 0.25 and 0.5 mg/mL.

In another aspect of the present disclosure, there is provided a use of the stable pharmaceutical composition disclosed herein in the manufacture of a medicament for improving glycemic control in a subject having type 2 diabetes (T2D), wherein 0.5 mL of the stable pharmaceutical composition is to be administered to said subject.

In a further aspect of the present disclosure, there is provided an autoinjector comprising the stable pharmaceutical composition disclosed herein.

Description

The present invention provides a method of improving glycemic control in a subject having type 2 diabetes (T2D) and in need of additional glycemic control, comprising:

a) identifying a subject having T2D and in need of further glycemic control;

WE CLAIM:

1. Use of dulaglutide in the manufacture of a medicament for improving glycemic control in a subject having type 2 diabetes (T2D) and in need of additional glycemic control, wherein:

a) a subject having T2D and in need of further glycemic control is identified;

b) a first dose of dulaglutide is to be administered once weekly to said subject for a minimum of four weeks; and

c) the dose is increased to a second dose which is to be administered once weekly,

wherein the first dose is selected from the group consisting of 1.5 and 3.0 mg, and the second dose is selected from the group consisting of 3.0 and 4.5 mg.

2. The use of claim 1 wherein the first dose is 1.5 mg and the second dose is 3.0 mg.

3. The use of claim 2, wherein the subject had been treated with a 0.75 mg dose of dulaglutide for a minimum of four weeks before the 1.5 mg dose is to be administered.

4. The use of either of claims 2 or 3, further comprising increasing the 3.0 mg dose to 4.5 mg once weekly after the subject has been treated with the 3.0 mg dose for a minimum of four weeks.

5. The use of claim 1 wherein the first dose is 3.0 mg and the second dose is 4.5 mg.

6. Use of dulaglutide in the manufacture of a medicament for improving glycemic control in a subject having type 2 diabetes (T2D) and in need of further glycemic control, wherein:

a) a subject having T2D and in need of further glycemic control is identified;

b) 0.75 mg of dulaglutide is to be administered to said subject once weekly for a minimum of four weeks;

c) 1.5 mg of dulaglutide is to be administered to said subject once weekly for a minimum of four weeks; and

d) 3.0 mg of dulaglutide is to be administered to said subject once weekly.

7. The use of claim 6, wherein after the 3.0 mg dose is to be administered to the subject once weekly for a minimum of four weeks, the dose is increased to 4.5 mg once weekly.

8. Use of dulaglutide in the manufacture of a medicament for improving glycemic control in a subject having type 2 diabetes (T2D), wherein after said subject is to be treated with a 1.5 mg dose of dulaglutide once weekly but is in need of further glycemic control, the dose of dulaglutide to be administered is increased to 3.0 mg once weekly.

9. The use of claim 8, wherein the dose is increased to 4.5 mg once weekly after the subject is to be treated with 3.0 mg dulaglutide once weekly for a minimum of four weeks.

10. Use of dulaglutide in the manufacture of a medicament for improving glycemic control in a subject having type 2 diabetes (T2D), wherein after said subject is to be treated with a 3.0 mg dose of dulaglutide once weekly but is in need of further glycemic control, the dose of dulaglutide to be administered is increased to 4.5 mg once weekly.

11. Use of dulaglutide in the manufacture of a medicament for treating a subject having T2D and in need of further glycemic control, wherein 1.5 mg of dulaglutide is to be administered once weekly for a minimum of four weeks, and then the dose is increased to 3.0 mg once weekly.

12. Use of dulaglutide in the manufacture of a medicament for treating a subject having T2D and in need of further glycemic control, wherein 0.75 mg of dulaglutide is to be administered once weekly for a minimum of four weeks, then the dose is increased to 1.5 mg of dulaglutide once weekly for a minimum of four weeks, and then the dose is increased to 3.0 mg once weekly.

13. The use of either of claim 11 or 12, wherein the the dose is increased to 4.5 mg once weekly after the subject is to be treated with 3.0 mg dulaglutide once weekly for a minimum of four weeks.

14. Use of dulaglutide in the manufacture of a medicament for treating a subject having T2D and in need of further glycemic control, wherein:

a) 3.0 mg of dulaglutide is to be administered once weekly for a minimum of four weeks; and

b) the dose is increased to 4.5 mg once weekly.

15. Use of dulaglutide in the manufacture of a medicament for providing chronic weight management to a subject in need thereof, wherein:

a) 0.75 mg of dulaglutide is to be administered to said subject once weekly for a minimum of four weeks;

b) 1.5 mg of dulaglutide is to be administered to said subject once weekly for a minimum of four weeks; and

c) the dose is increased to 3.0 mg once weekly.

16. The use of claim 15, wherein the dose is increased to 4.5 mg once weekly after the subject is to be treated with 3.0 mg dulaglutide once weekly for a minimum of four weeks.

17. Use of dulaglutide in the manufacture of a medicament for providing chronic weight management to a subject in need thereof, wherein:

a) a subject is identified who has been previously treated with 1.5 mg of dulaglutide once weekly for a minimum of four weeks; and

b) the dose is increased to 3.0 mg once weekly.

18. The use of claim 17, wherein the dose is increased to 4.5 mg once weekly after the subject is to be treated with 3.0 mg dulaglutide once weekly for a minimum of four weeks.

19. Use of dulaglutide in the manufacture of a medicament for providing chronic weight management to a subject in need thereof, wherein:

a) a subject is identified who has been previously treated with 3.0 mg of dulaglutide once weekly for a minimum of four weeks; and

b) the dose is increased to 4.5 mg once weekly.

20. The use of any of claims 1-19, wherein the dulaglutide is to be administered in a 0.5 mL aqueous composition comprising:

a) dulaglutide in an amount selected from the group consisting of 3.0 mg and 4.5 mg;

b) 0.07 mg citric acid;

c) 23.2 mg mannitol;

d) 1.37 mg trisodium citrate; and

e) polysorbate 80 in an amount between 0.125 mg and 0.25 mg.

21. The use of claim 21 wherein the polysorbate amount is 0.125 mg.

22. The use of any of claims 20-1, wherein the composition remains chemically and physically stable for 24 months at 2-8°C.

23. The use of any of claims 20-22, wherein the composition remains chemically and physically stable for 14 days at 30°C.

24. The use of any of claims 1-23, wherein administration of the increased dose of dulaglutide does not result in unacceptable tolerability.

25. The use of any of claims 1-24, wherein the subject's HbA1c is lowered.

26. The use of any of claims 1-25, wherein the subject's body weight decreases.

27. A stable pharmaceutical formulation comprising:

a) dulaglutide, in a concentration selected from the group consisting of 6.0 or 9.0 mg/mL;

b) mannitol, in a concentration of 46.4 mg/mL;

c) trisodium citrate, in a concentration of 2.74 mg/mL; and

d) polysorbate 80, in a concentration between 0.25 and 0.5 mg/mL.

28. The stable pharmaceutical formulation of claim 27 wherein the polysorbate 80 concentration is 0.25 mg/mL.

29. The stable pharmaceutical composition of either of claims 27-28, wherein the concentration of dulaglutide is 6.0 mg/mL.

30. The stable pharmaceutical composition of either of claims 27-28, wherein the concentration of dulaglutide is 9.0 mg/mL.

31. The stable pharmaceutical formulation of any of claims 27-30, wherein the composition remains chemically and physically stable for 24 months at 2-8°C.

32. The stable pharmaceutical formulation of any of claims 27-31, wherein the composition remains chemically and physically stable for 14 days at 30°C.

33. Use of the stable pharmaceutical composition of any of claims 27-32 in the manufacture of a medicament for improving glycemic control in a subject having type 2 diabetes (T2D), wherein 0.5 mL of the stable pharmaceutical composition is to be administered to said subject.

34. The use of claim 33, wherein the formulation is provided as a 0.5 mL aqueous solution.

35. An autoinjector comprising the stable pharmaceutical composition of any of claims 27-31.