Description

Pharmaceutical composition comprising a GLP-1 agonist, an insulin and methionine

The present application relates to a liquid composition comprising a GLP-1 agonist or/and a pharmacologically tolerable salt thereof, an insulin or/and a pharmacologically tolerable salt thereof, and, optionally, at least one pharmaceutically acceptable excipient, wherein the composition comprises methionine.

The present application further relates to the composition according to the present invention for treating diabetes mellitus. The present application further relates to the use of a composition according to the present invention in the manufacture of a pharmaceutical for treating diabetes mellitus. The present application further relates to a method for manufacturing a composition according to the present invention, comprising formulating a GLP-1 agonist or/and a pharmacologically tolerable salt thereof with an insulin or/and a pharmaceutically acceptable salt thereof, methionine, and, optionally, at least one pharmaceutically acceptable excipient. The present application further relates to a method for treating a patient with a composition according to the present invention, comprising administering the composition to the patient.

Customary compositions of insulin and GLP-1 compounds comprise an isotonicity agent, a buffer for adjusting the pH, and a preservative. A further frequently used constituent of insulin compositions is zinc, which forms a complex with insulin. This results in a delayed action of insulin being achieved.

WO 2003/02021 (Eli Lilly) relates to a liquid pre-mixed formulation comprising a GLP-1 compound and a basal insulin. A specific formulation contains Val^{8}-GLP-1 or exendin-4, insulin NPH, glycerol as an isotonicity agent, m-cresol and phenol as preservatives, and a phosphate buffer at a pH of 7.6 or 8. Another formulation comprises exendin-4 or Val^{8}-Glu^{22}GLP-1(7-37)OH, insulin glargine (Lantus), zinc, glycerol and mannitol as isotonicity agents, m-cresol as a preservative, zinc, and sodium acetate, pH 4.

Claims:

1. A liquid composition comprising a GLP-1 agonist or/and a pharmacologically tolerable salt thereof, an insulin or/and a pharmacologically tolerable salt thereof, and, optionally, at least one pharmaceutically acceptable excipient, wherein the composition comprises methionine.

2. The liquid composition as claimed in claim 1, wherein the composition comprises a pharmaceutically acceptable preservative or/and a pharmaceutically acceptable isotonicity agent.

3. The liquid composition as claimed in claim 1 or 2, wherein the composition comprises m-cresol or/and glycerol.

4. The liquid composition as claimed in any one of the preceding claims, wherein the composition has a pH in the range from 3.5 to 5.

5. The liquid composition as claimed in any one of the preceding claims, wherein the composition comprises methionine in an amount ranging from 0.5 mg/mL to 20 mg/mL, more particularly in an amount ranging from 1 mg/mL to 5 mg/mL.

6. The liquid composition as claimed in any one of the preceding claims, wherein the composition exhibits chemical integrity after storage for 6 months at a temperature of +25°C.

7. The liquid composition as claimed in any one of the preceding claims, wherein the composition exhibits physical integrity after storage for 6 months at a temperature of +25°C.

8. The liquid composition as claimed in any one of the preceding claims, wherein the GLP-1 agonist is selected from the group consisting of GLP-1 and analogs and derivates thereof, exendin-3 and analogs and derivates thereof,

exendin-4 and analogs and derivates thereof, wherein the GLP-1 agonist is preferably selected from the group consisting of desPro^{36}exendin-4(1-39)-Lys$_6$-NH_2 and exendin-4.

9. The liquid composition as claimed in any one of the preceding claims, wherein the insulin is selected from the group consisting of human insulins, analogs, derivatives, and metabolites thereof.

10. The liquid composition as claimed in any one of the preceding claims, wherein the insulin is selected from the group consisting of Gly(A21)-Arg(B31)-Arg(B32) human insulin, Lys^{B28}Pro^{B29} human insulin, B28Asp human insulin, and B29Lys(ε-tetradecanoyl),desB30 human insulin.

11. The liquid composition as claimed in any one of the preceding claims, wherein the composition has the following constituents:

(a) desPro^{36}exendin-4(1-39)-Lys$_6$-NH_2,

(b) Gly(A21)-Arg(B31)-Arg(B32) human insulin,

(c) zinc chloride,

(d) m-cresol (optional),

(e) L-methionine,

(f) glycerol,

(g) hydrochloric acid, if adjustment to a pH of approximately 4.5 is required,

(h) NaOH solution, if adjustment to a pH of approximately 4.5 is required, and

(i) water.

12. The composition as claimed in any one of the preceding claims, wherein the composition is an injectable composition.

13. The composition as claimed in any one of the preceding claims for treating diabetes mellitus.

14. A combination comprising a first pharmaceutical composition as claimed in any one of claims 1 to 13 and a second pharmaceutical composition as claimed in any one of claims 1 to 13, and, optionally, at least one further pharmaceutical composition as claimed in any one of claims 1 to 13, each comprising at least one insulin and at least one GLP-1 agonist, and containing the at least one insulin and/or the at least one GLP-1 agonist in different weight fractions relative to the total weight of the composition.

15. The combination as claimed in claim 14, wherein the weight fractions of the at least one insulin and of the at least one GLP-1 agonist may be selected in the first pharmaceutical composition, the second pharmaceutical composition, and, where used, the at least one further pharmaceutical composition in such a way that the pharmaceutical compositions contain different ratios of insulin to GLP-1 agonist, based on the weight fraction.

16. The combination as claimed in claim 14 or 15, wherein the first, second, and, where used, further composition(s) contain the at least one insulin in a substantially identical weight fraction and the at least one GLP-1 agonist in different weight fractions.

17. The combination as claimed in claim 14 or 15, wherein the first, second, and, where used, further composition(s) contain the at least one GLP-1 agonist in a substantially identical weight fraction and the at least one insulin in different weight fractions.

18. A kit comprising a combination as claimed in any one of claims 14 to 17.

19. Use of a composition as claimed in any one of claims 1 to 13, of a combination as claimed in claims 14 to 17, or of a kit as claimed in claim 18 in the manufacture of a medicament for the treatment of diabetes mellitus.

20. A method for manufacturing a composition as claimed in any one of claims 1 to 13, a combination as claimed in claims 14 to 17, or a kit as claimed in claim 18,

comprising formulating a GLP-1 agonist or/and a pharmacologically tolerable salt thereof with an insulin or/and a pharmaceutically acceptable salt thereof, methionine, and, optionally, at least one pharmaceutically acceptable excipient.

21. A composition as claimed in any one of claims 1 to 13, a combination as claimed in claims 14 to 17, or a kit as claimed in claim 18 for use in therapy .

22. The use of the composition as claimed in any one of preceding claims 1 to 18 together with administration of metformin, an insulin, and/or a GLP-1 agonist, and/or a pharmacologically tolerable salt.

23. The use as claimed in claim 22, comprising an add-on therapy, more particularly with an insulin and/or a GLP-1 agonist.

24. Use of the composition as claimed in any one of claims 22 and 23, in the manufacture of a medicament for the treatment of type II diabetes that cannot be sufficiently controlled with an insulin and/or a GLP-1 agonist.

25. Use of the composition as claimed in any one of claims 1 to 18 in the manufacture of a medicament for controlling the blood sugar level in type II diabetes patients when the application of an insulin or a GLP-1 agonist is indicated, wherein the medicament is to be administered as a supplement to a diet.

26. The use of the composition as claimed in either of claims 22 and 23, wherein the treated patients have an HbA1c value in the range from 7% to 10%.

27. The use of the composition as claimed in any one of claims 22, 23, and 24 in the manufacture of a medicament for the treatment of type II diabetes and/or obesity.

Description

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The present application further relates to the composition according to the present invention for treating diabetes mellitus. The present application further relates to the use of a composition according to the present invention in the manufacture of a pharmaceutical for treating diabetes mellitus. The present application further relates to a method for manufacturing a composition according to the present invention, comprising formulating a GLP-1 agonist or/and a pharmacologically tolerable salt thereof with an insulin or/and a pharmaceutically acceptable salt thereof, methionine, and, optionally, at least one pharmaceutically acceptable excipient. The present application further relates to a method for treating a patient with a composition according to the present invention, comprising administering the composition to the patient.

Customary compositions of insulin and GLP-1 compounds comprise an isotonicity agent, a buffer for adjusting the pH, and a preservative. A further frequently used constituent of insulin compositions is zinc, which forms a complex with insulin. This results in a delayed action of insulin being achieved.

Claims

1. A liquid composition comprising a GLP-1 agonist or/and a pharmacologically tolerable salt thereof, insulin or/and a pharmacologically tolerable salt thereof and optionally at least one pharmaceutically acceptable excipient, characterized in that it contains L-methionine and has a pH between 3.5 and 4.5, wherein the GLP-1 agonist is desPro^{36}exendin-4(1-39)-Lys$_6$-NH$_2$ and the insulin is Gly(A21)-Arg(B31)-Arg(B32)-human insulin.

2. The liquid composition according to claim 1, characterized in that it contains m-cresol or/and glycerol.

3. The liquid composition according to any one of the preceding claims, characterized in that it contains L-methionine in an amount of 0.5 mg/mL to 20 mg / ml, in particular in an amount of 1 mg/ml to 5 mg/mL.

4. The liquid composition according to any one of the preceding claims, characterized in that it comprises the following components:
   (a) desPro^{36}Exendin-4 (1 -39) -Lys$_6$-NH$_2$,
   (b) Gly(A21)-Arg(B31)Arg(B32)-human insulin
   (c) zinc chloride,
   (d) m-cresol (optionally),
   (e) L-methionine,
   (f) glycerol,
   (g) hydrochloric acid, if adjustment to a pH of approximately 4.5 is required,
   (h) NaOH solution, if adjustment to a pH of approximately 4.5 is required, and

(i) water.

5. A combination comprising a first pharmaceutical composition according to any one of claims 1 to 4 and a second pharmaceutical composition according to any one of claims 1 to 4 and optionally at least one further pharmaceutical composition according to any one of claims 1 to 4, each comprising at least one insulin and at least one GLP-1 agonist and containing the at least one insulin or/and the at least one GLP-1 agonist in different fractions, relative to the total weight of the composition.

6. The combination according to claim 5, wherein the first, second and, where used, further composition(s) contain the at least one insulin in a substantially identical weight fraction, and the at least one GLP-1 agonist in different weight fractions.

7. The combination according to claim 5, wherein the first, second and, where used, further composition(s) contain the at least one GLP-1 agonist in a substantially identical weight fraction and the at least one insulin in different weight fractions.

8. Use of a composition according to any one of claims 1 to 4 or the combination according to claims 5 to 7 in the manufacture of a medicament for treating diabetes mellitus.

9. The use according to claim 8, characterized in that the use is carried out together with the administration of metformin, an insulin or/and a GLP-1 agonist or/and a pharmacologically tolerable salt thereof.

10. The use according to claim 9, characterized in that the treated patients have a HbA1c value in the range of 7% to 10%.

11. The use according to any one of claims 8 to 10 for

the treatment of type II diabetes.