Solid-phase synthesis of AVE0010 is described in WO 01/04156 A1. AVE0010 has the sequence: desPro^{36}exendin-4(1-39)-Lys$_6$-NH$_2$. This substance is published as SEQ ID NO:93 in WO 01/04156:

H-G-E-G-T-F-T-S-D-L-S-K-Q-M-E-E-E-A-V-R-L-F-I-E-W-L-K-N-G-G-P-S-S-G-A-P-P-S-K-K-K-K-K-K-NH$_2$ (SEQ ID NO:1)

Exendin-4 (39 AS) has the sequence:

H-G-E-G-T-F-T-S-D-L-S-K-Q-M-E-E-E-A-V-R-L-F-I-E-W-L-K-N-G-G-P-S-S-G-A-P-P-P-S-NH$_2$ (SEQ ID NO:2)

Exendin-3 has the sequence (J. Bio. Chem., 267, 1992, 7402-7405):

H-His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH$_2$ (SEQ ID NO: 3)

GLP-1 has the sequence:

H-A-E-G-T-F-T-S-D-V-S-S-Y-L-E-G-Q-A-A-K-E-F-I-A-W-L-V-K-G-R-NH$_2$ (SEQ ID NO: 4)

It is an object of the present invention to increase the stability of liquid formulations comprising a GLP-1 agonist. More particularly, it is an object of the present invention to improve physical and chemical integrity. We have found that this object is achieved by formulating the GLP-1 agonist with methionine.

Summary

In a first aspect, the present invention refers to a liquid composition comprising a GLP-1 agonist or/and a pharmacologically tolerable salt thereof, wherein the GLP-1 agonist is

desPro^{36}exendin-4(1-39)-Lys$_6$-NH$_2$, and, optionally, at least one pharmaceutically acceptable excipient, wherein the composition comprises methionine, the composition is free of histidine and the GLP-1 agonist is in an amount of 0.01 mg/ml to 1.5 mg/ml.

In a second aspect, the present invention refers to a method for manufacturing a composition of the present invention, comprising formulating a GLP-1 agonist or/and a pharmacologically tolerable salt thereof with methionine and, optionally, at least one pharmaceutically acceptable excipient.

In a third aspect, the present invention refers to a composition of the present invention for use as a pharmaceutical.

In a fourth aspect, the present invention refers to a use of the composition of the present invention in the manufacture of a pharmaceutical for treating diabetes mellitus and/ or obesity, wherein said pharmaceutical is to be administered with metformin, a sulfonylurea, a glitazone, and/or a long-acting insulin/insulin derivate, and/or a combination thereof, and/or a pharmacologically tolerable salt to a patient in need thereof.

It was found that methionine is able to increase the storage stability of a composition comprising a GLP-1 agonist such as AVE0010. Methionine does not affect the physical integrity of these compositions.

Claims:

1. A liquid composition comprising a GLP-1 agonist or/and a pharmacologically tolerable salt thereof, wherein the GLP-1 agonist is desPro^{36}exendin-4(1-39)-Lys_6-NH_2, and, optionally, at least one pharmaceutically acceptable excipient, wherein the composition comprises methionine, the composition is free of histidine and the GLP-1 agonist is in an amount of 0.01 mg/ml to 1.5 mg/ml.

2. The liquid composition as claimed in claim 1, wherein the composition comprises a pharmaceutically acceptable preservative, more particularly m-cresol.

3. The liquid composition as claimed in claim 1 or 2, wherein the composition comprises 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, preferably 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 has the following constituents:
   (a) desPro^{36}exendin-4(1-39)-Lys_6-NH_2,
   (b) sodium acetate,
   (c) m-cresol,
   (d) L-methionine,
   (e) 85% glycerol,
   (f) approximately 0.1 N hydrochloric acid, if adjustment to a pH of approximately 4.5 is required,
   (g) approximately 0.1 N NaOH solution, if adjustment to a pH of approximately 4.5 is required, and
   (h) water.

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

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

9. The use of a composition as claimed in any one of claims 1 to 8 in the manufacture of a pharmaceutical for treating diabetes mellitus, more particularly type II diabetes.

10. A method for manufacturing a composition as claimed in any one of claims 1 to 8, comprising formulating a GLP-1 agonist or/and a pharmacologically tolerable salt thereof with methionine and, optionally, at least one pharmaceutically acceptable excipient.

11. A composition as claimed in any one of claims 1 to 8 for use as a pharmaceutical.

12. Use of the composition as claimed in any one of preceding claims 1 to 7 in the manufacture of a pharmaceutical for treating diabetes mellitus and/ or obesity, wherein said pharmaceutical is to be administered with metformin, a sulfonylurea, a glitazone, and/or a long-acting insulin/insulin derivate, and/or a combination thereof, and/or a pharmacologically tolerable salt to a patient in need thereof.

13. The use as claimed in claim 9 or 12, comprising an add-on therapy in patients where sufficient blood sugar control could not be achieved with metformin, a sulfonylurea, a glitazone, and/or a long-acting insulin/insulin derivate.

14. The use of the composition as claimed in claim 9, or 12 or 13, wherein the treated patients have an HbA1c value in the range from 7% to 10%.

15. The use of the composition as claimed in claim 12 wherein diabetes mellitus is type II diabetes.

16. The use of the composition as claimed in any one of claims 9, and 12 to 15 and wherein said composition is to be administered in patients with type II diabetes as a supplement to a diet in order to improve blood sugar control.

17. The use of the composition as claimed in any one of claims 9 and 12 to 16, wherein said composition is to be administered in patients once a day.

Claims:

1. A liquid composition comprising a GLP-1 agonist 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, more particularly m-cresol.

3. The liquid composition as claimed in claim 1 or 2, wherein the composition comprises 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, preferably 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 composition has the following constituents:

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

(b) sodium acetate,

(c) m-cresol,

(d) L-methionine,

(e) 85% glycerol,

(f) approximately 0.1 N hydrochloric acid, if adjustment to a pH of approximately 4.5 is required,

(g) approximately 0.1 N NaOH solution, if adjustment to a pH of approximately 4.5 is required, and

(h) water.

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

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

12. The use of a composition as claimed in any one of claims 1 to 11 in the manufacture of a pharmaceutical for treating diabetes mellitus, more particularly type II diabetes.

13. A method for manufacturing a composition as claimed in any one of claims 1 to 11, comprising formulating a GLP-1 agonist or/and a pharmacologically tolerable salt thereof with methionine and, optionally, at least one pharmaceutically acceptable excipient.

14. A method for treating a patient with a composition as claimed in any one of claims 1 to 11, comprising administering of the composition to the patient.

15. The use of the composition as claimed in any one of preceding claims 1 to 11 together with administration of metformin, a sulfonylurea, a glitazone, and/or a long-acting insulin/insulin derivate, and/or a combination thereof, and/or a pharmacologically tolerable salt.

16. The use as claimed in claim 15, comprising an add-on therapy in patients where sufficient blood sugar control could not be achieved with metformin, a sulfonylurea, a glitazone, and/or a long-acting insulin/insulin derivate.

17. The use of the composition as claimed in claim 15 or 16, wherein the treated patients have an HbA1c value in the range from 7% to 10%.

18. The use of the composition as claimed in claim 15, 16, or 17 for treating type II diabetes and/or obesity.

19. The use of the composition as claimed in claims 1 to 11 for administration in patients with type II diabetes as a supplement to a diet in order to improve blood sugar control.

20. The use of the composition as claimed in claims 1 to 19 for administration in patients once a day.