EXHIBIT 4

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Moeller et al.

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(54) **GLP-1 COMPOSITIONS AND USES THEREOF**

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(58) **Field of Classification Search**

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See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to pharmaceutical compositions of the GLP-1 peptide semaglutide comprising no more than 0.01% (w/w) phenol, their preparation, kits comprising such compositions as well as uses thereof.

14 Claims, No Drawings

GLP-1 COMPOSITIONS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of International Application PCT/EP2018/072835 (WO/2019/038412), filed Aug. 24, 2018, which claims priority to European Patent Application 17187676.6, filed Aug. 24, 2017; the contents of which are incorporated herein by reference.

The present invention relates to the field of pharmaceutical compositions comprising the GLP-1 peptide semaglutide.

BACKGROUND

GLP-1 peptides are known to be prone to develop lack of stability in liquid solutions, for example lack of physical stability. Thus, liquid pharmaceutical compositions comprising GLP-1 peptides with even better stability are desired. Such improved stability may be physical stability and/or chemical stability.

SUMMARY

In some embodiments the invention relates to liquid pharmaceutical compositions comprising semaglutide and no more than 0.01% (w/w) phenol. In some embodiments the invention relates to kits comprising the pharmaceutical composition as defined herein. In some embodiments the invention relates to the pharmaceutical composition as defined herein for use in medicine.

DESCRIPTION

The present invention relates to liquid pharmaceutical compositions comprising the GLP-1 peptide semaglutide and no more than 0.01% (w/w) phenol. Surprisingly, the present inventors found that such compositions have improved chemical and/or physical stability. In some embodiments the composition comprises no phenol. In some embodiments the composition comprises 0.01-10 mg/ml semaglutide. In some embodiments the composition has a pH in the range of 6.0-10.0, such as pH 7.0-7.8.

In some embodiments the composition of the invention is a liquid pharmaceutical composition comprising semaglutide and no more than 0.01% (w/w) phenol, wherein said composition

a. is for parenteral administration;
b. is an aqueous solution comprising at least 60% w/w water; or
c. further comprises one or more pharmaceutically acceptable excipients selected from the group consisting of a buffer or an isotonic agent.

In some embodiments the composition of the invention is a liquid pharmaceutical composition comprising semaglutide, no more than 0.01% (w/w) phenol, and optionally one or more pharmaceutically acceptable excipients, wherein the formulation is for parenteral administration, such as subcutaneous administration.

In some embodiments the composition of the invention is a liquid pharmaceutical composition comprising semaglutide, no more than 0.01% (w/w) phenol, at least 60% w/w

In some embodiments the term "stability" as used herein refers to stability of semaglutide in a liquid pharmaceutical composition. In some embodiments stability is chemical stability of the GLP-1 peptide (e.g. determined by HPLC, such as Assay (I) herein), and optionally physical stability of the GLP-1 peptide (e.g. determined by Thioflavine T assay, such as Assay (II) herein).

In some embodiments the term "chemical stability" in relation to semaglutide as used herein refers to the covalent bonds of the semaglutide compound being substantially intact. In some embodiments chemical stability of a GLP-1 peptide is determined by HPLC, such as Assay (I) herein. In some embodiments a composition possess chemical stability if its covalent bonds are intact in at least 80% (w/v) of said GLP-1 peptides after storage for 3 months at 25° C. In some embodiments chemical stability of semaglutide is determined by Assay (IV) herein.

In some embodiments the term "physical stability" in relation to semaglutide as used herein refers to semaglutide forming substantially no aggregates, e.g. in the form of fibril formation. In some embodiments physical stability is determined by Thioflavine T assay, such as Assay (II) herein.

In some embodiments the composition of the present invention is a stable pharmaceutical composition. The term "stable pharmaceutical composition" when used herein refers to a pharmaceutical composition, e.g. a solution or suspension, comprising GLP-1 peptide, and which composition following storage comprises at least 80% (w/v) of said GLP-1 peptide (e.g. after quiescent storage for 3 months at 25° C.). Storage conditions for stability testing may be 2-8° C., such as 5° C., or at least 2.5 years at 5° C. Alternatively, storage conditions for stability testing may be at least 4 weeks, such as 6 weeks or 3 months, optionally at 30° C. The conditions of storage for this stable pharmaceutical composition may be at 5° C. for 1 or 2 years. The conditions of storage for this stable pharmaceutical composition may be at 5° C. for 3 years. Alternatively, the conditions of this storage may be at 25° C. for 24 hours or 1 week. In yet another alternative, the conditions of this storage may be room temperature for two months, such as up to two months.

In some embodiments, chemical stability of the GLP-1 peptide requires at least 80% (w/v), such as at least 90% (w/v) or at least 95% (w/v), of said GLP-1 peptide remaining with its covalent bonds intact at the end of the storage period. In some embodiments chemical stability of the GLP-1 peptide requires at least 95% (w/v), such as at least 97% (w/v) or at least 99% (w/v), of said GLP-1 peptide remaining with its covalent bonds intact at the end of the storage period.

The composition of the invention comprises no more than 0.01% (w/w) phenol. In some embodiments the composition comprises substantially no phenol.

Pharmaceutical Compositions

The terms "pharmaceutical composition" and "composition" are used interchangeably herein and refer to pharmaceutical compositions suitable for administration to a subject in need thereof.

In some embodiments the composition comprises 0.01-100 mg/ml semaglutide. In some embodiments the composition comprises 0.1-50 mg/ml, such as 0.5-25 mg/ml or 1-15 mg/ml, semaglutide. In some embodiments the composition comprises 0.1-10 mg/ml, such as 0.5-5 mg/ml or 1-2 mg/ml, semaglutide. In some embodiments the composition comprises 0.01-10 mg/ml, such as 0.01-5 mg/ml, semaglutide. In some embodiments the composition com-

ments the composition comprises no more than 6 mg/ml, such as no more than 5 mg/ml or no more than 4 mg/ml, semaglutide. In some embodiments the composition comprises no more than 3 mg/ml, such as no more than 2 mg/ml or no more than 1 mg/ml, semaglutide. In some embodiments the composition comprises at least 0.01 mg/ml, such as at least 0.02 mg/ml or at least 0.05 mg/ml, semaglutide. In some embodiments the composition comprises 1.34 mg/ml semaglutide.

In some embodiments the composition of the invention has a pH in the range of 3-10, such as pH 6-10 or 6-9. In some embodiments the composition of the invention has a pH in the range of pH 6.5-8.5, such as pH 7.0-7.8.

In some embodiments the composition of the invention comprises one or more pharmaceutically acceptable excipients.

In some embodiments the composition of the invention comprises an isotonic agent, such as propylene glycol. In some embodiments the isotonic agent is propylene glycol or sodium chloride.

In some embodiments the composition of the invention comprises a buffer, such as phosphate buffer, TRIS, citrate, or no buffer. In some embodiments the phosphate buffer is a sodium phosphate buffer, such as disodium hydrogen phosphate.

In some embodiments the composition of the invention comprises no preservative.

The composition of the invention is in the form of a liquid pharmaceutical composition. In some embodiments the liquid pharmaceutical composition is a solution or a suspension. In some embodiments the composition of the invention is in the form of a solution, such as an aqueous solution. In some embodiments the term "aqueous solution" as used herein refers to a solution comprising at least 60% w/w water. In some embodiments the aqueous solution comprises 60-99% w/w water. In some embodiments the aqueous solution comprises at least 75% w/w water, such as at least 80% w/w water or at least 85% w/w water. In some embodiments the aqueous solution comprises at least 90% w/w water, such as at least 92% w/w water or at least 94% w/w water.

Semaglutide

The GLP-1 peptide semaglutide may be prepared as described in WO2006/097537, Example 4. Semaglutide is also known as $N^{6,26}$-{18-[N-(17-carboxyheptadecanoyl)-L-γ-glutamyl]-10-oxo-3,6,12,15-tetraoxa-9,18-diazaoctadecanoyl}-[8-(2-amino-2-propanoic acid),34-L-arginine]human glucagon-like peptide 1(7-37), see WHO Drug Information Vol. 24, No. 1, 2010. In some embodiments semaglutide may be present in the composition in its fully or partly ionised form; for example one or more carboxylic acid groups (—COOH) may be deprotonated into the carboxylate group ($—COO^-$) and/or one or more amino groups ($—NH_2$) may be protonated into the $—NH_3+$ group. In some embodiments semaglutide is added to the composition in the form of a salt.

Administration and Kits

The composition of the invention is for parenteral administration. In some embodiments the composition is for subcutaneous administration.

In some embodiments the composition of the invention is for administration once weekly. In some embodiments the composition of the invention is for administration once daily, once every second or once every third day.

herein and instructions for use. In some embodiments the instructions for use comprise the package insert of a drug.

In some embodiments the invention relates to a kit comprising the pharmaceutical composition as defined herein and an injection device. In some embodiments the injection device is selected from the group consisting of a durable pen and a prefilled pen. Examples of durable pens are NovoPen® 4 or NovoPen® 5 (both from Novo Nordisk A/S, Denmark). An example of a prefilled pen is FlexPen® (Novo Nordisk A/S, Denmark).

Indications

In some embodiments the compositions of the invention are for use in medicine. In some embodiments the composition of the invention may be used for the following medical treatments:

(i) prevention and/or treatment of all forms of diabetes, such as hyperglycaemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, non-insulin dependent diabetes, MODY (maturity onset diabetes of the young), gestational diabetes, and/or for reduction of HbA1c;

(ii) delaying or preventing diabetic disease progression, such as progression in type 2 diabetes, delaying the progression of impaired glucose tolerance (IGT) to insulin requiring type 2 diabetes, and/or delaying the progression of non-insulin requiring type 2 diabetes to insulin requiring type 2 diabetes;

(iii) prevention and/or treatment of eating disorders, such as obesity, e.g. by decreasing food intake, reducing body weight, suppressing appetite, inducing satiety; treating or preventing binge eating disorder, bulimia nervosa, and/or obesity induced by administration of an antipsychotic or a steroid; reduction of gastric motility; and/or delaying gastric emptying.

In some embodiments the indication is (i). In some embodiments the indication is (ii). In a still further particular aspect the indication is (iii). In some embodiments the indication is type 2 diabetes and/or obesity.

In some embodiments the method or use comprises prevention, treatment, reduction and/or induction in one or more diseases or conditions defined herein. In some embodiments the indication is (i) and (iii). In some embodiments the indication is (ii) and (iii). In some embodiments the invention comprises administration of an effective amount of a GLP-1 peptide. In some embodiments the invention relates to administration of an effective amount of a GLP-1 peptide.

Generally, all subjects suffering from obesity are also considered to be suffering from overweight. In some embodiments the invention relates to a method for treatment or prevention of obesity. In some embodiments the invention relates to use of the composition for treatment or prevention of obesity. In some embodiments the subject suffering from obesity is human, such as an adult human or a paediatric human (including infants, children, and adolescents). Body mass index (BMI) is a measure of body fat based on height and weight. The formula for calculation is BMI=weight in kilograms/height in meters^2. A human subject suffering from obesity may have a BMI of ≥30; this subject may also be referred to as obese. In some embodiments the human subject suffering from obesity may have a BMI of ≥35 or a BMI in the range of ≥30 to <40. In some embodiments the obesity is severe obesity or morbid obesity, wherein the human subject may have a BMI of ≥40.

In some embodiments the invention relates to a method for treatment or prevention of overweight, optionally in the presence of at least one weight-related comorbidity. In some

presence of at least one weight-related comorbidity. In some embodiments the subject suffering from overweight is human, such as an adult human or a paediatric human (including infants, children, and adolescents). In some embodiments a human subject suffering from overweight may have a BMI of ≥25, such as a BMI of ≥27. In some embodiments a human subject suffering from overweight has a BMI in the range of 25 to <30 or in the range of 27 to <30. In some embodiments the weight-related comorbidity is selected from the group consisting of hypertension, diabetes (such as type 2 diabetes), dyslipidaemia, high cholesterol, and obstructive sleep apnoea.

In some embodiments the invention relates to a method for reduction of body weight. In some embodiments the invention relates to use of the composition for reduction of body weight. A human to be subjected to reduction of body weight according to the present invention may have a BMI of ≥25, such as a BMI of ≥27 or a BMI of ≥30. In some embodiments the human to be subjected to reduction of body weight according to the present invention may have a BMI of ≥35 or a BMI of ≥40. The term "reduction of body weight" may include treatment or prevention of obesity and/or overweight.

In some embodiments, as used herein, specific values given in relation to numbers or intervals may be understood as the specific value or as about the specific value (e.g. plus or minus 10 percent of the specific value).

Embodiments of the Invention

The following are non-limiting embodiments of the invention:

1. A liquid pharmaceutical composition comprising semaglutide and no more than 0.01% (w/w) phenol.
2. A liquid pharmaceutical composition comprising semaglutide and substantially no phenol.
3. The composition according to claim **1** or **2**, wherein said composition does not comprise phenol.
4. The composition according to any one of the preceding claims, wherein said composition is an aqueous solution comprising at least 60% w/w water, such as at least 70% w/w water or at least 80% w/w water.
5. The composition according to any one of the preceding claims, wherein the concentration of semaglutide is 0.5-10 mg/ml of said composition.
6. The composition according to any one of the preceding claims, wherein said semaglutide is in the form of a pharmaceutically acceptable salt.
7. The composition according to any one of the preceding claims, wherein said composition comprises one or more pharmaceutically acceptable excipients.
8. The composition according to any one of the preceding claims, wherein said composition comprises one or more agents for adjusting pH, such as HCl, NaOH, or acetate.
9. The composition according to any one of the preceding claims, wherein said composition comprises a buffer and/or an isotonic agent.
10. The composition according to any one of the preceding claims, wherein said buffer is present in a concentration of 0.01-50 mM of said composition.
11. The composition according to any one of the preceding claims, wherein said buffer is a phosphate buffer.
12. The composition according to any one of the preceding claims, wherein said phosphate buffer is selected from the
13. The composition according to any one of the preceding claims, wherein said isotonic agent is present in a concentration from 8 mg/ml to 50 mg/ml, such as 14 mg/ml to 30 mg/ml, of said composition.
14. The composition according to any one of the preceding claims, wherein said isotonic is propylene glycol.
15. The composition according to any one of the preceding claims, wherein said composition comprises no preservative.
16. The composition according to any one of the preceding claims, wherein said composition has a pH in the range of 6.0-10.0.
17. The composition according to any one of the preceding claims, wherein said composition is for parenteral administration.
18. The composition according to any one of the preceding claims, wherein said composition is for subcutaneous administration.
19. A kit comprising the pharmaceutical composition as defined in any one of the preceding claims and instructions for use.
20. A kit comprising the pharmaceutical composition as defined in any one of the preceding claims and an injection device for administration of said composition to a subject, wherein said injection device is selected from the group consisting of a durable pen and a prefilled pen.
21. A pharmaceutical composition as defined in any one of the preceding claims for use in medicine.
22. The pharmaceutical composition for use as defined in any one of the preceding claims for use in the treatment of diabetes or obesity.
23. A method for the prevention or treatment of diabetes or obesity, wherein the pharmaceutical composition as defined in any one of the preceding claims is administered to a subject in need thereof.

EXAMPLES

General Methods and Characterisation

Preparation of Semaglutide Compositions:

Unless otherwise noted, compositions of semaglutide were prepared by dissolving buffer (e.g. disodiumhydrogenphosphate dihydrate), isotonic agent (e.g. propylene glycol) and optionally preservative (phenol) in water. Semaglutide was dissolved therein, pH was adjusted to 7.4 using sodium hydroxide and/or hydrochloric acid, and the composition was finally sterilised by filtration through a 0.22 µm sterile filter.

Preparation of Liraglutide Compositions:

Unless otherwise noted, compositions of liraglutide were prepared from Solution 1 and Solution 2: Solution 1 was prepared by dissolving buffer (disodiumhydrogenphosphate dihydrate), isotonic agent (mannitol), and optionally preservative (phenol) in water. Solution 2 was prepared by dissolving liraglutide while stirring slowly. Solution 1 and Solution 2 were mixed, pH was adjusted to 8.15 using sodium hydroxide and/or hydrochloric acid, and the composition was finally sterilised by filtration through a 0.22 µm sterile filter.

Assay (I): Determination of High Molecular Weight Proteins (HMWP) Content of Semaglutide Compositions

Determination of HMWP content was performed using size exclusion chromatography (SE-HPLC) using a Waters Insulin HMWP column with a mobile phase of sodium chloride, sodium phosphate, phosphoric acid and isopropa-

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