activity of the peptide. Alternatively or additionally, a preservative may be detrimental to the physical stability of a peptide active, enhancing aggregation of the peptide into inactive covalent oligomers and/or causing the peptide to precipitate out of solution. Not only does such loss of physical stability reduce the medical potency of the peptide, but also formation of particulate matter has practical and safety implications if the composition is delivered by injection.

Given the great sequence variety, and thus different chemical structures, of peptides, it is inherently unpredictable whether a given substance will act as an effective preservative for a particular therapeutic peptide composition without negatively affecting the peptide in the ways described above.

The present invention concerns pharmaceutical compositions comprising selected peptides disclosed in WO2018/104561 (e.g. compound 18 of WO2018/104561), which describes the compounds and their uses in detail.

SUMMARY

This application provides compositions comprising one or more GLP-1/GLP-2 dual agonist and one or more preservative in a buffer. In examples aspects, the compositions are isotonic parenteral pharmaceutical compositions suitable for administration to human subjects.

The GLP-1/GLP-2 dual agonist is a peptide. Particular preservatives have been identified that can be used in a composition comprising a specific GLP-1/GLP-2 dual agonist peptide and a particular buffer without substantially impacting the chemical or physical stability of the peptide. It has been surprisingly found that particular preservatives have little to no effect on chemical stability and oligomerisation of the peptide in phosphate buffer.

The compositions of the disclosure therefore benefit from the advantages associated with preservatives, namely that contamination with microorganisms is prevented or reduced.

Of particular advantage, the preservative effect in the composition of the disclosure allows the composition to be provided in a multi-dose administration setup. The composition of the disclosure can be provided in a device that is used to administer sequential therapeutic doses of the composition at intervals over an extended period. The preservative effect prevents growth of microorganisms in the composition over this period, whilst chemical and physical stability of the peptide is maintained. This has the practical benefit of needing to load the device only once, instead of preparing a new dose for each administration.

In one example, the pharmaceutical compositions according to the disclosure are for, or suitable for, administration in a multi-dose device.

In one aspect, the disclosure provides a composition comprising:

(a) one or more GLP-1/GLP-2 dual agonist comprising general formula A:

H[Aib]EG-X5-F-X7-SELATILD-[Ψ]-QAARDFIAWLI-X28-HKITD (A),

wherein X5 is T or S; X7 is T or S; X28 is Q, E, A, H, Y, L, K, R or S and at least one of X5 and X7 is T,

wherein [Ψ] indicates an L or D lysine residue in which an albumin binding moiety is conjugated to the GLP-1/GLP-2 dual agonist, and

wherein said albumin binding moiety is [K([17-carboxy-heptadecanoyl]-isoGlu)];

(b) one or more preservative,

wherein the one or more preservative comprises or is benzoate, benzalkonium chloride and/or benzyl alcohol; and

(c) phosphate buffer.

In some examples, particular and specific compositions, such as isotonic parenteral compositions, are described in detail in the description of the disclosure.

The chemical stability at time point Y of GLP-1/GLP-2 dual agonist in any of the tested compositions disclosed herein can be expressed as the relative purity X^Y of the GLP-1/GLP-2 dual agonist and is determined by measuring the absolute purity X' of the GLP-1/GLP-2 dual agonist and normalising it to the absolute purity X^0 of the GLP-1/GLP-2 dual agonist at day zero (day 0), wherein said absolute purities are determined by HPLC at a given time point Y by identifying the purity of peak corresponding to the GLP-1/GLP-2 dual agonist.

It was surprisingly found that the disclosed GLP-1/GLP-2 dual agonists in compositions comprising phosphate buffer and particular preservatives have chemical stability and degree of oligomerisation which is at least as good as (i.e. comparable to) chemical stability and degree of oligomerisation in compositions that do not comprise any preservative.

The disclosure also provides the composition according to the disclosure for use in:

(i) increasing intestinal mass, improving intestinal function, increasing intestinal blood flow, or repairing intestinal damage or dysfunction, in a subject in need thereof; or

(ii) the prophylaxis or treatment of malabsorption, ulcers, short-bowel syndrome, cul-de-sac syndrome, inflammatory bowel disease, irritable bowel syndrome, pouchitis, celiac sprue,

tropical sprue, hypogammaglobulinemic sprue, mucositis induced by chemotherapy or radiation therapy, diarrhoea induced by chemotherapy or radiation therapy, low grade inflammation, metabolic endotoxemia, necrotising enterocolitis, primary biliary cirrhosis, hepatitis, fatty liver disease, or gastrointestinal side-effects of inflammatory conditions, in a subject in need thereof; or

(iii) reducing or inhibiting weight gain, reducing gastric emptying or intestinal transit, reducing food intake, reducing appetite, or promoting weight loss, in a subject in need thereof; or

(iv) the prophylaxis or treatment of obesity, morbid obesity, obesity-linked gallbladder disease, obesity-induced sleep apnoea, inadequate glucose control, glucose tolerance, dyslipidaemia, diabetes, pre-diabetes, metabolic syndrome or hypertension, in a subject in need thereof.

The disclosure further provides a method for preserving a composition comprising the one or more GLP-1/GLP-2 dual agonist of the disclosure and phosphate buffer, wherein the method comprises adding one or more preservative to the composition, wherein the wherein the one or more preservative comprises or is benzoate, benzalkonium chloride and/or benzyl alcohol.

The disclosure additionally provides use of a preservative for preserving a composition comprising the one or more GLP-1/GLP-2 dual agonist of the disclosure and phosphate buffer, wherein the preservative comprises or is benzoate, benzalkonium chloride and/or benzyl alcohol.

DESCRIPTION OF THE INVENTION

Compounds

The composition of this invention comprises one or more GLP-1/GLP-2 dual agonist comprising general formula A:

H[Aib]EG-X5-F-X7-SELATILD-[Ψ]-QAARDFIAWLI-X28-HKITD (A),

wherein X5 is T or S; X7 is T or S; X28 is Q, E, A, H, Y, L, K, R or S and at least one of X5 and X7 is T, wherein [Ψ] indicates an L or D lysine residue in which an albumin binding moiety is conjugated to the GLP-1/GLP-2 dual agonist, and wherein said albumin binding moiety is [K([17-carboxy-heptadecanoyl]-isoGlu)].

In some aspects, the one or more GLP-1/GLP-2 dual agonist comprising general formula A is of the general formula B:

H[Aib]EG-X5-FT-SELATILD-[Ψ]-QAARDFIAWLI-X28-HKITD (B),