CLAIMS

1. A peptide conjugate having the formula I

H-HGEGTFTSDLSKQMEEEAVRLFIEWLKN-Peg3-Peg3-YGWLDF-NH_2;

H-HGEGTFTSDLSKQMEEEAVRLFIEWLKN-Peg3-Peg3-GWLDF-NH_2;

H-HGEGTFTSDLSKQMEEEAVRLFIEWLKN-Peg3-Peg3-AGWLDF-NH_2; or

H-HGEGTFTSDLSKQMEEEAVRLFIEWLKNYGWTDF-NH_2;

or a pharmaceutically acceptable salt or solvate thereof.

2. A peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to claim 1 for use as a medicament.

3. Use of a peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to claim 1, in the manufacture of a medicament for the treatment, in a subject in need thereof, of a disease or disorder selected from the group consisting of:

type 1 diabetes, type 2 diabetes, pre-diabetes, Insulin resistance syndrome, impaired glucose tolerance (IGT), disease states associated with elevated blood glucose levels, hyperglycemia, hypertension, atherogenic dyslipidemia, arteriosclerosis (e.g. atherosclerosis), coronary heart disease, peripheral artery disease, stroke, microvascular disease, gastric disease, metabolic syndrome, cancer (e.g. colon cancer), inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS).

4. Use of a peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to claim 1, in the manufacture of a medicament for inducing, in a subject in need thereof, pancreatic islet neogenesis.

5. Use of a peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to claim 1, in the manufacture of a medicament for preventing, in a subject in need thereof, β-cell apoptosis in the pancreatic islets.

6. The use according to any one of claims 3-5, wherein said subject is a human.

7. A pharmaceutical composition comprising a peptide conjugate, or pharmaceutically acceptable salt or solvate thereof, according to claim 1, together with a pharmaceutically acceptable carrier, excipient or vehicle.

8. Use of a peptide conjugate, or pharmaceutically acceptable salt or solvate thereof, according to claim 1, or a pharmaceutical composition according to claim 7, in the manufacture of a medicament for preventing weight gain or promoting weight loss.

9. Use of a peptide conjugate, or pharmaceutically acceptable salt or solvate thereof, according to claim 1, in the manufacture of a medicament for improving circulating glucose levels, glucose tolerance and/or circulating cholesterol levels, lowering circulating LDL levels, and/or increasing HDL/LDL ratio.

10. Use of a peptide conjugate, or pharmaceutically acceptable salt or solvate thereof, according to claim 1 in the manufacture of a medicament for the treatment of a condition caused or characterized by excess body weight, e.g. the treatment and/or prevention of obesity, morbid obesity, obesity linked inflammation, obesity linked gallbladder disease, obesity induced sleep apnea, metabolic syndrome, or pre-diabetes.

11. The use according to any one of claims 3 to 6 or 8 to 10 wherein the compound is to be administered as part of a combination therapy with an agent for treatment of diabetes, obesity, dyslipidaemia, or hypertension.

12. The use according to claim 11 wherein the agent for treatment of diabetes is metformin, a sulfonylurea, a glinide, a DPP-IV inhibitor, a glitazone, insulin or an insulin analogue.

13. The use according to claim 11 wherein the agent for treatment of obesity is a glucagon-like peptide receptor 1 agonist, peptide YY or analogue thereof, cannabinoid receptor 1 antagonist, lipase inhibitor, melanocortin receptor 4 agonist, or melanin concentrating hormone receptor 1 antagonist.

14. The use according to claim 11 wherein the agent for treatment of hypertension is an angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, diuretic, beta-blocker, or calcium channel blocker.

15. The use according to claim 11 wherein the agent for treatment of dyslipidaemia is a statin, a fibrate, a niacin and/or a cholesterol absorbtion inhibitor.

16 A method of manufacturing a peptide conjugate according to claim 1 synthetically.

17. A method of manufacturing a peptide conjugate according to claim 1 recombinantly.

18. Use of a peptide conjugate, or pharmaceutically acceptable salt or solvate thereof according to claim 1 in the manufacture of a medicament for improving circulating glucose levels, glucose tolerance and/or circulating cholesterol levels, lowering circulating LDL levels, and/or increasing HDL/LDL ratio in an individual in need thereof wherein a Drug holiday dosage regimen is used.

19. A process for manufacturing a peptide conjugate, or pharmaceutically acceptable salt or solvate thereof according to claim 1.

20. A device comprising at least one peptide conjugate, or pharmaceutically acceptable salt or solvate thereof, according to claim 1, for delivery of the peptide conjugate to a subject.

21 . A kit comprising at least one peptide conjugate, or pharmaceutically acceptable salt or solvate thereof, according to claim 1, and further comprising packaging or instructions for use.

CLAIMS

1. A peptide conjugate having the formula I

R^1-Z-L-Y-R^2 (I)

wherein

R^1 is H, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;

R^2 is OH or NH_2;

Z comprises the sequence of Exendin-4(1-39)having the sequence

His - Gly - Glu - 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

or an analogue thereof Z_a;

L is an optional linker moiety; and

Y comprises the sequence of Gastrin17 having the sequence

Gln-Gly-Pro-Trp-Leu-Glu-Glu-Glu-Glu-Glu-Ala-Tyr-Gly-Trp-Y15-Asp-Phe

wherein Y15 is selected from Leu, Nle, Phe and Thr

or an analogue thereof Y_a

or a pharmaceutically acceptable salt or solvate thereof.

2. A peptide conjugate or a pharmaceutically acceptable salt or solvate thereof according to claim 1, wherein:

(i) Z_a has substitutions in up to 10 positions, and/or comprises a C-terminal truncation of 1 to 12 amino acids, with respect to the sequence of Exendin-4; and/or

(ii) Y_a has substitutions in up to 5 positions with respect to the sequence of Gastrin17, and/or comprises an N-terminal truncation of 1 to 13 amino acids, with respect to the sequence of Gastrin17.

3. A peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to claim 1 or 2, wherein

Z_a is a peptide sequence having the formula IIa

His - Z2 – Z3 - Gly - Thr - Phe - Thr - Ser - Z9 – Z10 – Z11 – Z12 – Z13 – Z14 – Glu – Z16 – Z17 – Z18 – Z19 – Z20 – Z21 - Z22 – Z23 – Z24 – Z25 – Z26 – Z27 – Z28 – Z29 – Z30 – Z31 – Z32 – Z33 – Z34 – Z35 – Z36 – Z37 – Z38 – Z39 (IIa)

wherein

Z2 is selected from Gly, Ala, Ser, Aib, Thr, Leu and Ile;

Z3 is selected from Glu and Asp;

Z9 is selected from Asp and Glu;

Z10 is selected from Leu, Val, Ile and Ala;

Z11 is selected from Ser and Aib;

Z12 is selected from Ser, Gln, Arg, Cys, Lys, Glu and Orn;

Z13 is selected from Arg, Ser, Gln, Tyr and Glu;

Z14 is selected from Gly, Cys, Phe, Tyr, Trp, Lys, Met, Leu, Nle and Ile;

Z16 is selected from Asp, Gly, Aib, Glu, Lys and Cys;

Z17 is selected from Glu, Cys, Lys, Ser and Gln;

Z18 is selected from Ala and Aib;

Z19 is selected from Val, Leu, Ile and Ala;

Z20 is selected from Arg, Lys, Cys, Orn and Glu;

Z21 is selected from Leu and Glu;

Z22 is selected from Phe and Ala;

Z23 is selected from Ile and Leu;

Z24 is selected from Glu, Cys, Lys, Ala and Arg;

Z25 is selected from Trp, Cys, Lys and Phe;

Z26 is selected from Leu and Ile;

Z27 is selected from Ile, Val, Gln, Lys, Cys, Arg and Orn;

Z28 is selected from Asn, Ser, Asp, Aib, Gln, Lys, Cys, Arg, Tyr, bAla, Glu, Orn and Leu or is absent;

Z29 is selected from Gly, Aib and bAla or is absent;

Z30 is selected from Gly, Cys, Lys and Arg or is absent;

Z31 is selected from Pro, Ser and Asp or is absent;

Z32 is selected from Ser and Lys or is absent;

Z33 is Ser or is absent;

Z34 is selected from Gly and Lys or is absent;

Z35 is Ala or is absent;

Z36 is Pro or is absent;

Z37 is Pro or is absent;

Z38 is Pro or is absent;

Z39 is Ser or is absent;

L is a peptide sequence having the formula IIb

L1-L2-L3-L4 (IIb)

wherein

L1 is selected from Ser, Ala, Lys, Orn, bAla, 8Aoc, DBF, Peg3, Cys and Gln or is absent;

L2 is selected from Ser, Ala, Lys, Orn, bAla, 8Aoc, DBF, Peg3, Cys and Gln or is absent;

L3 is selected from Ser, Ala, Lys, Orn, bAla, 8Aoc, DBF, Peg3, Cys and Gln or is absent;

L4 is selected from Ser, Ala, Lys, Orn, bAla, 8Aoc, DBF, Peg3, Cys and Gln or is absent;

Y_a is a peptide sequence having the formula IIc

Y1-Y2-Y3-Y4-Y5-Y6-Y7-Y8-Y9-Y10-Y11-Y12-Y13-Y14-Y15-Asp-Y17 (IIc)

wherein

Y1 is Gln or is absent;

Y2 is Gly or is absent;

Y3 is Pro or is absent;

Y4 is Trp or is absent;

~~Y5 is Leu or is absent;~~

Y6 is Glu or is absent;

Y7 is Glu or is absent;

Y8 is Glu or is absent;

Y9 is Glu or is absent;

Y10 is Glu or is absent;

Y11 is Ala or is absent;

Y12 is selected from Ala and Tyr or is absent;

Y13 is selected from Gly and Ala or is absent;

Y14 is selected from Trp, Phe, 1Nal and Met;

Y15 is selected from Leu, Nle, Phe and Thr; and

Y17 is selected from Phe and 3-(3-Pyridyl)-alanine.

4. A peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to any one of claims 1-3

wherein

Z_a is a peptide sequence having the formula IIIa

His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Z9-Leu-Ser-Z12-Z13-Z14-Glu-Z16-Glu-Ala-Val-Z20-Leu-Phe-Ile-Z24-Z25-Leu-Z27-Z28 (IIIa)

wherein

Z9 is selected from Asp and Glu;

Z12 is selected from Lys, Arg and Orn;

Z13 is selected from Gln and Tyr;

Z14 is selected from Met and Leu;

Z16 is selected from Glu, Cys and Lys;

Z20 is selected from Arg, Lys and Orn;

Z24 is selected from Lys and Glu;

Z25 is selected from Trp, Lys, Cys and Phe;

Z27 is selected from Lys, Arg and Orn;

Z28 is selected from Asn and Asp or is absent;

L is a peptide sequence having the formula IIIb

L1-L2-L3-L4 (IIIb)

wherein

L1 is selected from Peg3, Gln, Cys, Lys and Orn or is absent;

L2 is selected from Peg3, Gln, Cys, Lys and Orn or is absent;

L3 is selected from Peg3, Gln, Cys, Lys and Orn or is absent;

L4 is selected from Peg3, Gln, Cys, Lys and Orn or is absent;

Y_a is a peptide sequence having the formula IIIc

Y12-Y13-Y14-Y15-Asp-Y17 (IIIc)

wherein

Y12 is selected from Tyr and Ala or is absent;

Y13 is selected from Gly and Ala or is absent;

Y14 is selected from Trp, 1Nal and Phe;

Y15 is selected from Leu, Nle, Thr and Phe.; and

Y17 is selected from Phe and 3-(3-Pyridyl)-alanine.

5. A peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to any one of the claims 1-4 wherein

Z_a is a peptide sequence having the formula IVa

His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Z9-Leu-Ser-Z12-Gln-Met-Glu-Z16-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Z27-Z28 (IVa)

wherein

Z9 is selected from Glu and Asp;

Z12 is selected from Lys and Orn;

Z16 is selected from Glu and Lys;

Z27 is selected from Lys and Orn;

Z28 is selected from Asn and Asp or is absent;

L is a peptide sequence having the formula IVb

L1-L2-L3-L4 (IVb)

wherein

L1 is selected from Peg3, Gln, Cys, Lys and Orn or is absent;

L2 is selected from Peg3, Gln, Cys, Lys and Orn or is absent;

L3 is selected from Peg3, Gln, Cys, Lys and Orn or is absent;

L4 is selected from Peg3, Gln, Cys, Lys and Orn or is absent;

Y_a is a peptide sequence having the formula IVc

Y12-Y13-Trp-Leu-Asp-Phe (IVc)

wherein

Y12 is Tyr or is absent; and

Y13 is Gly or is absent.

6. A peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to any one of the claims 1-5 wherein

Z_a is a peptide sequence having the formula Va

His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Z9-Leu-Ser-Z12-Tyr-Leu-Glu-Z16-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Phe-Leu-Z27-Z28 (Va)

wherein

Z9 is selected from Glu and Asp;

Z12 is selected from Lys and Orn;

~~Z16 is selected from Glu and Lys;~~

Z27 is selected from Lys and Orn;

Z28 is selected from Asn and Asp or is absent;

L is a peptide sequence having the formula Vb

L1-L2-L3-L4 (Vb)

wherein

L1 is selected from Peg3, Gln, Cys, Lys and Orn or is absent;

L2 is selected from Peg3, Gln, Cys, Lys and Orn or is absent;

L3 is selected from Peg3, Gln, Cys, Lys and Orn or is absent;

L4 is selected from Peg3, Gln, Cys, Lys and Orn or is absent;

Y_a is a peptide sequence having the formula Vc

Y12-Y13-Trp-Leu-Asp-Phe (Vc)

wherein

Y12 is Tyr or is absent; and

Y13 is Gly or is absent.

7. A peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to any one of the preceding claims wherein the peptide sequence of formula I comprises one or more intramolecular bridges.

8. A peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to claim 7 wherein said intramolecular bridge is formed between the side chains of two amino acid residues which are separated by three amino acids in the linear amino acid sequence of formula I.

9. A peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to claim 8 wherein the intramolecular bridge is formed between the side chains of residue pairs x and x+3, x+4 or x+5.

10. A peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to any one of claims 7 to 9 wherein the intramolecular bridge is a lactam ring.

11. A peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to any one of claims 7 to 10 wherein the intramolecular bridge involves a pair of residues wherein:

Z12 is Lys and Z16 is Glu; Z12 is Glu and Z16 is Lys;

Z16 is Glu and Z20 is Lys; Z16 is Lys and Z20 is Glu;

Z20 is Glu and Z24 is Lys; Z20 is Lys and Z24 is Glu.

12. A peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to any one of claims 1-11 wherein Z_a has at least 75% identity to native exendin-4, e.g. at least 80, 85, 90 or 95%.

13. A peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to any one of claims 1-11 wherein Y_a has at least 70% identity to native gastrin, e.g. at least 75, 80, 85, 90 or 95%.

14. A peptide conjugate according to any one of the preceding claims wherein the peptide of formula I has the sequence:

Exendin-4(1-39)-Peg3-Peg3-[Gln1,Leu15]Gastrin17,

Exendin-4(1-39)-[Gln1,Leu15]Gastrin17,

Exendin-4(1-39)-K-[Gln1,Leu15]Gastrin17,

Exendin-4(1-39)-AAA-[Gln1,Leu15]Gastrin17,

Exendin-4(1-39)-SKK-[Gln1,Leu15]Gastrin17,

Exendin-4(1-39)-Peg3-SKK-[Gln1,Leu15]Gastrin17,

Exendin-4(1-39)-8Aoc-SKK-[Gln1,Leu15]Gastrin17,

Exendin-4(1-39)-DBF-SKK-[Gln1,Leu15]Gastrin17,

Exendin-4(1-39)-8Aoc-8Aoc-[Gln1,Leu15]Gastrin17,

Exendin-4(1-39)-[Leu4]Gastrin6,

Exendin-4(1-39)-K-[Leu4]Gastrin6,

Exendin-4(1-39)-AAA-[Leu4]Gastrin6,

Exendin-4(1-39)-SKK-[Leu4]Gastrin6,

Exendin-4(1-39)-Peg3-SKK-[Leu4]Gastrin6,

Exendin-4(1-39)-Peg3-Peg3-[Leu4]Gastrin6,

Exendin-4(1-39)-8Aoc-SKK-[Leu4]Gastrin6,

Exendin-4(1-39)-DBF-SKK-[Leu4]Gastrin6,

Exendin-4(1-39)-8Aoc-8Aoc-[Leu4]Gastrin6,

Exendin-4(1-28)-[Gln1,Leu15]Gastrin17,

Exendin-4(1-28)-K-[Gln1,Leu15]Gastrin17,

Exendin-4(1-28)-AAA-[Gln1,Leu15]Gastrin17,

Exendin-4(1-28)-SKK-[Gln1,Leu15]Gastrin17,

Exendin-4(1-28)-Peg3-SKK-[Gln1,Leu15]Gastrin17,

Exendin-4(1-28)-Peg3-Peg3-[Gln1,Leu15]Gastrin17,

Exendin-4(1-28)-8Aoc-SKK-[Gln1,Leu15]Gastrin17,

Exendin-4(1-28)-DBF-SKK-[Gln1,Leu15]Gastrin17,

Exendin-4(1-28)-8Aoc-8Aoc-[Gln1,Leu15]Gastrin17,

Exendin-4(1-28)-[Leu4]Gastrin6,

Exendin-4(1-28)-K-[Leu4]Gastrin6,

Exendin-4(1-28)-AAA-[Leu4]Gastrin6,

Exendin-4(1-28)-SKK-[Leu4]Gastrin6,

Exendin-4(1-28)-Peg3-SKK-[Leu4]Gastrin6,

Exendin-4(1-28)-Peg3-Peg3-[Leu4]Gastrin6,

Exendin-4(1-28)-8Aoc-SKK-[Leu4]Gastrin6,

Exendin-4(1-28)-DBF-SKK-[Leu4]Gastrin6,

Exendin-4(1-28)-8Aoc-8Aoc-[Leu4]Gastrin6.

15. A peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to claims 1 to 11 wherein the peptide of formula I has the sequence:

Exendin-4(1-28)-Peg3-Peg3-[Leu3]Gastrin5

Exendin-4(1-28)-Peg3-Peg3-[Ala1,Leu4]Gastrin6

Exendin-4(1-28)-Peg3-Peg3-[Ala2,Leu4]Gastrin6

Exendin-4(1-27)-Peg3-Peg3-[Leu4]Gastrin6

Exendin-4(1-28)-Peg3-Peg3-[Leu2]Gastrin4

[Leu14]Exendin-4(1-28)-Peg3-Peg3-[Leu4]Gastrin6

[Orn12]Exendin-4(1-28)-Peg3-Peg3-[Leu4]Gastrin6

[Orn27]Exendin-4(1-28)-Peg3-Peg3-[Leu4]Gastrin6

[Phe25]Exendin-4(1-28)-Peg3-Peg3-[Leu4]Gastrin6

[Asp28]Exendin-4(1-28)-Peg3-Peg3-[Leu4]Gastrin6

[Tyr13]Exendin-4(1-28)-Peg3-Peg3-[Leu4]Gastrin6

[Orn20]Exendin-4(1-28)-Peg3-Peg3-[Leu4]Gastrin6

Exendin-4(1-28)-Peg3-[Leu4]Gastrin6

Exendin-4(1-28)-[Leu4]Gastrin6

Exendin-4(1-27)-[Leu4]Gastrin11

Exendin-4(1-27)-Peg3-[Leu4]Gastrin6

Exendin-4(1-27)-Peg3-[Leu3]Gastrin5

Exendin-4(1-26)-Peg3-[Leu3]Gastrin5

Exendin-4(1-27)-Peg3-[Leu2]Gastrin4

[Tyr13,Leu14]Exendin-4(1-27)-Peg3-Peg3-[Leu4]Gastrin6

[Tyr13,Phe25]Exendin-4(1-27)-Peg3-Peg3-[Leu4]Gastrin6

[Leu14,Phe25]Exendin-4(1-27)-Peg3-Peg3-[Leu4]Gastrin6

[Tyr13,Leu14,Phe25]Exendin-4(1-27)-Peg3-Peg3-[Leu4]Gastrin6

Side chain-cyclo([Lys12,Glu16]Exendin-4(1-28)-Peg3-Peg3-[Leu4]Gastrin6

Side chain-cyclo([Glu16,Lys20]Exendin-4(1-28)-Peg3-Peg3-[Leu4]Gastrin6

Side chain-cyclo([Lys20,Glu24]Exendin-4(1-28)-Peg3-Peg3-[Leu4]Gastrin6

~~[Lys16]Exendin-4(1-28)-Peg3-Peg3-[Leu4]Gastrin6~~

Exendin-4(1-28)-Peg3-K-Peg3-[Leu4]Gastrin6

Exendin-4(1-28)-[Thr4]Gastrin6

Exendin-4(1-28)-[Phe4]Gastrin6

[Leu14]Exendin-4(1-28)-[1Nal3,Leu4]Gastrin6

[Leu14]Exendin-4(1-28)-[Nle4]Gastrin6

[Leu14]Exendin-4(1-28)-[Leu4,[3-(3-Pyridyl)-Ala]6]Gastrin6

[Glu9,Leu14,Phe25,Tyr13]Exendin-4(1-27)-Peg3-Peg3-[Leu4]Gastrin6

[Leu14,Phe25,Tyr13]Exendin-4(1-27)-Peg3-Peg3-[Leu4,Phe3]Gastrin6

[Glu9,Leu14,Phe25,Tyr13]Exendin-4(1-27)-Peg3-Peg3-[Leu4,Phe3]Gastrin6

[Arg27,Leu14,Phe25,Tyr13]Exendin-4(1-27)-Peg3-[Leu4]Gastrin6

[Arg12,27,Leu14,Lys16,Phe25,Tyr13]Exendin-4(1-27)-Peg3-[Leu4]Gastrin6

[Arg12,27,Leu14,Lys20,Phe25,Tyr13]Exendin-4(1-27)-Peg3-[Leu4]Gastrin6

[Arg12,27,Leu14,Lys24,Phe25,Tyr13]Exendin-4(1-27)-Peg3-[Leu4]Gastrin6

[Arg12,Leu14,Phe25,Tyr13]Exendin-4(1-27)-Peg3-[Leu4]Gastrin6

[Glu9,Leu14,Phe25,Tyr13]Exendin-4(1-27)-[Leu2]Gastrin4

[Glu9,Leu14,Phe25,Tyr13]Exendin-4(1-27)-Peg3-[Leu2]Gastrin4

[Glu9,Leu14,Phe25,Tyr13]Exendin-4(1-27)-Orn-Peg3-[Leu2]Gastrin4

[Glu9,Leu14,Phe25,Tyr13]Exendin-4(1-27)-Peg3-Orn-[Leu2]Gastrin4

[Glu9,Leu14,Phe25,Tyr13]Exendin-4(1-27)-Orn-Orn-[Leu2]Gastrin4

[Glu9,Leu14,Phe25,Tyr13]Exendin-4(1-27)-[Leu4]Gastrin6

[Glu9,Leu14,Phe25,Tyr13]Exendin-4(1-27)-Peg3-[Leu4]Gastrin6

[Glu9,Leu14,Phe25,Tyr13]Exendin-4(1-27)-Orn-Peg3-[Leu4]Gastrin6

[Glu9,Leu14,Phe25,Tyr13]Exendin-4(1-27)-Peg3-Orn-[Leu4]Gastrin6

[Glu9,Leu14,Phe25,Tyr13]Exendin-4(1-27)-Orn-Orn-[Leu4]Gastrin6.

~~16. A peptide conjugate having the formula VI:~~

R^1-X-L-Y-R^2 (VI)

wherein

R^1 is H, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;

R^2 is OH or NH_2;

X comprises the sequence of GLP-1 (7-36) having the sequence

His – Ala - Glu - Gly - Thr - Phe - Thr - Ser - Asp - Val - Ser - Ser - Tyr –Leu - Glu - Gly - Gln - Ala - Ala – Lys - Glu –Phe - Ile - Ala - Trp - Leu - Val – Lys - Gly – Arg

or an analogue thereof X_a;

L is a linker containing up to 4 naturally or non-naturally amino acids or combinations thereof or is absent;

Y comprises the sequence of Gastrin-17 having the sequence

Gln-Gly-Pro-Trp-Leu-Glu-Glu-Glu-Glu-Glu-Ala-Tyr-Gly-Trp-Y15-Asp-Phe

wherein Y15 is selected from Leu, Nle, Phe and Thr

or an analogue thereof Y_a;

or a pharmaceutically acceptable salt or solvate thereof.

17. A peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to claim 16, wherein:

(i) X_a has substitutions in up to 5 positions and/or comprises a C-terminally truncation of 1-2 amino acids, with respect to the sequence of GLP-1; and/or

(ii) Y_a has substitutions in up to 5 positions with respect to the sequence of Gastrin17, and/or comprises an N-terminal truncation of 1 to 13 amino acids, with respect to the sequence of Gastrin17.

18. A peptide conjugate <u>or pharmaceutically acceptable salt or solvate thereof</u> according to any one of claims 16-17 wherein

X_a is a peptide sequence having the formula VIIa

His – X8 - Glu - Gly - Thr - Phe - Thr - Ser - Asp - Val - Ser - Ser - Tyr –Leu - Glu - Gly - Gln - Ala - Ala – X26 - Glu –Phe - Ile - Ala - Trp - Leu - Val – X34 - Gly – X36 (VIIa)

wherein

X8 is selected from Ala, Aib and Gly;

X26 is selected from Arg and Lys;

X34 is selected from Arg and Lys;

X36 is selected from Arg and Lys;

L is a peptide sequence having the formula VIIb

L1-L2-L3-L4 (VIIb)

wherein

L1 is selected from Ser, Ala, Lys, Orn, bAla, 8Aoc, DBF, Peg3, Cys, Gln or is absent;

L2 is selected from Ser, Ala, Lys, Orn, bAla, 8Aoc, DBF, Peg3, Cys, Gln or is absent;

L3 is selected from Ser, Ala, Lys, Orn, bAla, 8Aoc, DBF, Peg3, Cys, Gln or is absent;

L4 is selected from Ser, Ala, Lys, Orn, bAla, 8Aoc, DBF, Peg3, Cys, Gln or is absent;

Y_a is a peptide sequence having the formula VIIc

Y1-Y2-Y3-Y4-Y5-Y6-Y7-Y8-Y9-Y10-Y11-Y12-Y13-Y14-Y15-Asp-Y17 (VIIc)

wherein

Y1 is Gln or is absent;

Y2 is Gly or is absent;

Y3 is Pro or is absent;

Y4 is Trp or is absent;

Y5 is Leu or is absent;

Y6 is Glu or is absent;

Y7 is Glu or is absent;

Y8 is Glu or is absent;

Y9 is Glu or is absent;

Y10 is Glu or is absent;

Y11 is Ala or is absent;

Y12 is selected from Ala, Tyr or is absent;

Y13 is selected from Gly, Ala or is absent;

Y14 is selected from Trp, Phe, 1Nal and Met;

Y15 is selected from Leu, Nle, Phe and Thr: and

Y17 is selected from Phe and 3-(3-Pyridyl)-alanine.

19. A peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to any one of claims 16-18

wherein

X_a is a peptide sequence having the formula VIIIa

His – X8 - Glu - Gly - Thr - Phe - Thr - Ser - Asp - Val - Ser - Ser - Tyr –Leu - Glu - Gly - Gln - Ala - Ala – X26 - Glu –Phe - Ile - Ala - Trp - Leu - Val – X34 - Gly – X36 (VIIIa)

wherein

X8 is selected from Ala, Aib and Gly;

X26 is selected from Arg and Lys;

X34 is selected from Arg and Lys;

X36 is selected from Arg and Lys;

L is a peptide sequence having the formula VIIIb

L1-L2-L3-L4 (VIIIb)

wherein

L1 is selected from Peg3, Orn, Cys, Lys, Gln or is absent;

L2 is selected from Ser, Ala, Orn, Cys, Lys, Gln or is absent;

L3 is selected from Lys, Ala, Cys, Orn, Gln or is absent;

L4 is selected from Lys, Orn, Ala, Peg3, Cys, Lys, Gln or is absent;

Y_a is a peptide sequence having the formula VIIIc

Y12-Y13-Y14-Y15-Asp-Phe (VIIIc)

wherein

Y12 is selected from Tyr, Ala or is absent;

Y13 is selected from Gly, Ala or is absent;

Y14 is selected from Trp and Phe; and

Y15 is selected from Leu, Thr and Phe.

20. A peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to any one of claims 16-19 wherein

X_a is a peptide sequence having the formula IXa

His – X8 - Glu - Gly - Thr - Phe - Thr - Ser - Asp - Val - Ser - Ser - Tyr –Leu - Glu - Gly - Gln - Ala - Ala – X26 - Glu –Phe - Ile - Ala - Trp - Leu - Val – X34 - Gly – X36 (IXa)

wherein

X8 is selected from Ala, Aib and Gly;

X26 is selected from Arg and Lys;

X34 is selected from Arg and Lys;

X36 is selected from Arg and Lys;

L is a peptide sequence having the formula IXb

L1-L2-L3 (IXb)

wherein

L1 is selected from Peg3, Gln, Cys, Lys and Orn or is absent;

L2 is selected from Peg3, Gln, Cys, Lys and Orn or is absent;

L3 is selected from Peg3, Gln, Cys, Lys and Orn or is absent;

L4 is selected from Peg3, Gln, Cys, Lys and Orn or is absent;

Y_a is a peptide sequence having the formula IXc

Y12-Y13-Trp-Leu-Asp-Phe (IXc)

wherein

Y12 is Tyr or is absent; and

Y13 is Gly or is absent.

21. A peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to any one of claims 16-20 wherein X_a has at least 85% identity to native exendin-4, e.g. at least 90, 95, 97, 98, 99 or 99.5%.

22. A peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to any one of claims 16-21, wherein at least one Lys or Cys is further conjugated to a lipophilic substituent.

23. A peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to any one of claims 16-21 wherein the peptide of formula VI has the sequence:

GLP-1(7-36)-[Gln1,Leu15]Gastrin17,

GLP-1(7-36)-K-[Gln1,Leu15]Gastrin17,

GLP-1(7-36)-AAA-[Gln1,Leu15]Gastrin17,

GLP-1(7-36)-SKK-[Gln1,Leu15]Gastrin17,

GLP-1(7-36)-Peg3-SKK-[Gln1,Leu15]Gastrin17,

GLP-1(7-36)-Peg3-Peg3-[Gln1,Leu15]Gastrin17,

GLP-1(7-36)-8Aoc-SKK-[Gln1,Leu15]Gastrin17,

GLP-1(7-36)-DBF-SKK-[Gln1,Leu15]Gastrin17,

GLP-1(7-36)-8Aoc-8Aoc-[Gln1,Leu15]Gastrin17,

GLP-1(7-36)-[Leu4]Gastrin6,

GLP-1(7-36)-K-[Leu4]Gastrin6,

GLP-1(7-36)-AAA-[Leu4]Gastrin6,

GLP-1(7-36)-SKK-[Leu4]Gastrin6,

GLP-1(7-36)-Peg3-SKK-[Leu4]Gastrin6,

GLP-1(7-36)-Peg3-Peg3-[Leu4]Gastrin6,

GLP-1(7-36)-8Aoc-SKK-[Leu4]Gastrin6,

~~GLP-1(7-36)-DBF-SKK-[Leu4]Gastrin6~~

GLP-1(7-36)-8Aoc-8Aoc-[Leu4]Gastrin6,

[Aib8,Arg34]GLP-1(7-37)-Peg3-Peg3-[Leu4]Gastrin6

[Arg34]GLP-1(7-37)-Peg3-Peg3-[Leu4]Gastrin6.

24. A peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to any one of the claims 16 to 22 wherein the peptide of formula VI has the sequence:

[Lys(Hexadecanoyl-isoGlu)34]GLP-1(7-37)-Peg3-Peg3-[Leu4]Gastrin6,

[Arg34,Lys(Hexadecanoyl-isoGlu)26]GLP-1(7-37)-Peg3-Peg3-[Leu4]Gastrin6

[Arg26,34,Lys(Hexadecanoyl-isoGlu)36]GLP-1(7-37)-Peg3-Peg3-[Leu4]Gastrin6

[Lys(Hexadecanoyl-isoGlu)26]GLP-1(7-37)-Peg3-Peg3-[Leu4]Gastrin6

[Arg26,34,Gly8,Lys(Hexadecanoyl-isoGlu)36]GLP-1(7-37)-Peg3-Peg3-[Leu4]Gastrin6

[Aib8,Arg34,Lys(Hexadecanoyl-isoGlu)26]GLP-1(7-37)-Peg3-Peg3-[Leu4]Gastrin6.

25. A peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to any one of claims 1 to 24 for use as a medicament.

26. Use of a peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to claim 24, in the manufacture of a medicament for the treatment, in a subject in need thereof, of a disease or disorder selected from the group consisting of:

type 1 diabetes, type 2 diabetes, pre-diabetes, Insulin resistance syndrome, impaired glucose tolerance (IGT), disease states associated with elevated blood glucose levels, hyperglycemia, hypertension, atherogenic dyslipidemia, arteriosclerosis (e.g. atherosclerosis), coronary heart disease, peripheral artery disease, stroke, microvascular disease, gastric disease, metabolic syndrome, cancer (e.g. colon cancer), inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS).

27. Use of a peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to claim 24, in the manufacture of a medicament for inducing, in a subject in need thereof, pancreatic islet neogenesis.

28. Use of a peptide conjugate or pharmaceutically acceptable salt or solvate thereof according to claim 24, in the manufacture of a medicament for preventing, in a subject in need thereof, β-cell apoptosis in the pancreatic islets.

29. The use according to any one of claims 26-28, wherein said subject is a human.

30. A pharmaceutical composition comprising a peptide conjugate, or pharmaceutically acceptable salt or solvate thereof, according to any one of claims 1 to 24, together with a pharmaceutically acceptable carrier, excipient or vehicle.

31. Use of a peptide conjugate, or pharmaceutically acceptable salt or solvate thereof, according to any one of claims 1 to 24, or a pharmaceutical composition according to claim 32, in the manufacture of a medicament for preventing weight gain or promoting weight loss.

32. Use of a peptide conjugate, or pharmaceutically acceptable salt or solvate thereof, according to any one of claims 1 to 24 in the manufacture of a medicament for improving circulating glucose levels, glucose tolerance and/or circulating cholesterol levels, lowering circulating LDL levels, and/or increasing HDL/LDL ratio.

33. Use of a peptide conjugate, or pharmaceutically acceptable salt or solvate thereof, according to any one of claims 1 to 24 in the manufacture of a medicament for the treatment of a condition caused or characterized by excess body weight, e.g. the treatment and/or prevention of obesity, morbid obesity, obesity linked inflammation, obesity linked gallbladder disease, obesity induced sleep apnea, metabolic syndrome, or pre-diabetes.

34. Use of a compound according to any one of claims 1 to 24 for preventing weight gain or promoting weight loss in an individual in need thereof.

35. The use according to any one of claims 26 to 29 or 31 to 33 wherein the compound is to be administered as part of a combination therapy with an agent for treatment of diabetes, obesity, dyslipidaemia, or hypertension.

36. The use according to claim 35 wherein the agent for treatment of diabetes is metformin, a sulfonylurea, a glinide, a DPP-IV inhibitor, a glitazone, insulin or an insulin analogue.

37. The use according to claim 35 wherein the agent for treatment of obesity is a glucagon-like peptide receptor 1 agonist, peptide YY or analogue thereof, cannabinoid receptor 1 antagonist, lipase inhibitor, melanocortin receptor 4 agonist, or melanin concentrating hormone receptor 1 antagonist.

38. The use according to claim 35 wherein the agent for treatment of hypertension is an angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, diuretic, beta-blocker, or calcium channel blocker.

39. The use according to claim 35 wherein the agent for treatment of dyslipidaemia is a statin, a fibrate, a niacin and/or a cholesterol absorbtion inhibitor.

40. A method of manufacturing a peptide conjugate according to any one of claims 1 to 24 synthetically.

41. A method of manufacturing a peptide conjugate according to any one of claims 1 to 24 recombinantly.

42. Use of a peptide conjugate, or pharmaceutically acceptable salt or solvate thereof according to any one of claims 1 to 24 in the manufacture of a medicament for improving circulating glucose levels, glucose tolerance and/or circulating cholesterol levels, lowering circulating LDL levels, and/or increasing HDL/LDL ratio in an individual in need thereof wherein a Drug holiday dosage regimen is used.

43 . A process for manufacturing a peptide conjugate, or pharmaceutically acceptable salt or solvate thereof according to any one of claims 1 to 24.

44. A device comprising at least one peptide conjugate, or pharmaceutically acceptable salt or solvate thereof, according to any one of claims 1 to 24, for delivery of the peptide conjugate to a subject.

45. A kit comprising at least one peptide conjugate, or pharmaceutically acceptable salt or solvate thereof, according to any one of claims 1 to 24, and further comprising packaging or instructions for use.