[Technical Solution]

In one aspect, the present invention refers to a pharmaceutical composition for use in therapy for preventing or treating congenital hyperinsulinism, wherein the pharmaceutical composition comprises a peptide comprising the amino acid sequence of the following General Formula 1:

X1-X2-QGTF-X7-SD-X10-S-X12-X13-X14-X15-X16-X17-X18-X19-X20-X21-F-X23-X24-W-L-X27-X28-X29-X30 (General Formula 1, SEQ ID NO: 45)

wherein, in General Formula 1,

X1 is histidine (H), desamino-histidyl, N-dimethyl-histidyl, β-hydroxy imidazopropionyl, 4-imidazoacetyl, β-carboxy imidazopropionyl, tryptophan (W), or tyrosine (Y), or is absent;

X2 is α-methyl-glutamic acid, aminoisobutyric acid (Aib), D-alanine, glycine (G), Sar (N-methylglycine), serine (S), or D-serine;

X7 is threonine (T), valine (V), or cysteine (C);

X10 is tyrosine (Y) or cysteine (C);

X12 is lysine (K) or cysteine (C);

X13 is tyrosine (Y) or cysteine (C);

X14 is leucine (L) or cysteine (C);

X15 is aspartic acid (D), glutamic acid (E), or cysteine (C);

X16 is glutamic acid (E), aspartic acid (D), serine (S), α-methyl-glutamic acid, or cysteine (C), or is absent;

X17 is aspartic acid (D), glutamine (Q), glutamic acid (E), lysine (K), arginine (R), serine (S), cysteine (C), or valine (V), or is absent;

X18 is alanine (A), aspartic acid (D), glutamic acid (E), arginine (R), valine (V), or cysteine (C), or is absent;

X19 is alanine (A), arginine (R), serine (S), valine (V), or cysteine (C), or is absent;

X20 is lysine (K), histidine (H), glutamine (Q), aspartic acid (D), arginine (R), α-methyl-glutamic acid, or cysteine (C), or is absent;

X21 is aspartic acid (D), glutamic acid (E), leucine (L), valine (V), or cysteine (C), or is absent;

X23 is isoleucine (I), valine (V), or arginine (R), or is absent;

X24 is valine (V), arginine (R), alanine (A), cysteine (C), glutamic acid (E), lysine (K), glutamine (Q), α-methyl-glutamic acid, or leucine (L), or is absent;

X27 is isoleucine (I), valine (V), alanine (A), lysine (K), methionine (M), glutamine (Q), or arginine (R), or is absent;

X28 is glutamine (Q), lysine (K), asparagine (N), or arginine (R), or is absent;

X29 is lysine (K), alanine (A), glycine (G), or threonine (T), or is absent; and

X30 is cysteine (C), or is absent;

with the proviso that when the amino acid sequence of General Formula 1 is identical to

SEQ ID NO: 1, it is excluded.

In another aspect, the present invention refers to use of a pharmaceutical composition in the manufacture of a medicament for preventing or treating congenital hyperinsulinism, wherein the pharmaceutical composition comprises a peptide comprising the amino acid sequence of the following General Formula 1:

X1-X2-QGTF-X7-SD-X10-S-X12-X13-X14-X15-X16-X17-X18-X19-X20-X21-F-X23-X24-W-L-X27-X28-X29-X30 (General Formula 1, SEQ ID NO: 45)

wherein, in General Formula 1,

X1 is histidine (H), desamino-histidyl, N-dimethyl-histidyl, β-hydroxy imidazopropionyl, 4-imidazoacetyl, β-carboxy imidazopropionyl, tryptophan (W), or tyrosine (Y), or is absent;

X2 is α-methyl-glutamic acid, aminoisobutyric acid (Aib), D-alanine, glycine (G), Sar (N-methylglycine), serine (S), or D-serine;

X7 is threonine (T), valine (V), or cysteine (C);

X10 is tyrosine (Y) or cysteine (C);

X12 is lysine (K) or cysteine (C);

X13 is tyrosine (Y) or cysteine (C);

X14 is leucine (L) or cysteine (C);

X15 is aspartic acid (D), glutamic acid (E), or cysteine (C);

X16 is glutamic acid (E), aspartic acid (D), serine (S), α-methyl-glutamic acid, or cysteine (C), or is absent;

X17 is aspartic acid (D), glutamine (Q), glutamic acid (E), lysine (K), arginine (R), serine (S), cysteine (C), or valine (V), or is absent;

X18 is alanine (A), aspartic acid (D), glutamic acid (E), arginine (R), valine (V), or cysteine (C), or is absent;

X19 is alanine (A), arginine (R), serine (S), valine (V), or cysteine (C), or is absent;

X20 is lysine (K), histidine (H), glutamine (Q), aspartic acid (D), arginine (R), α-methyl-glutamic acid, or cysteine (C), or is absent;

X21 is aspartic acid (D), glutamic acid (E), leucine (L), valine (V), or cysteine (C), or is absent;

X23 is isoleucine (I), valine (V), or arginine (R), or is absent;

X24 is valine (V), arginine (R), alanine (A), cysteine (C), glutamic acid (E), lysine (K), glutamine (Q), α-methyl-glutamic acid, or leucine (L), or is absent;

X27 is isoleucine (I), valine (V), alanine (A), lysine (K), methionine (M), glutamine (Q), or arginine (R), or is absent;

X28 is glutamine (Q), lysine (K), asparagine (N), or arginine (R), or is absent;

X29 is lysine (K), alanine (A), glycine (G), or threonine (T), or is absent; and

X30 is cysteine (C), or is absent;

with the proviso that when the amino acid sequence of General Formula 1 is identical to

SEQ ID NO: 1, it is excluded.

In yet another aspect, the present invention refers to an isolated peptide comprising the amino acid sequence of the following General Formula 2:

Y-Aib-QGTF-X7-SD-X10-S-X12-Y-L-X15-X16-X17-R-A-X20-X21-F-V-X24-W-L-M-N-T-X30 (General Formula 2, SEQ ID NO: 46)

wherein, in General Formula 2,
X7 is threonine (T), valine (V), or cysteine (C);
X10 is tyrosine (Y) or cysteine (C);
X12 is lysine (K) or cysteine (C);
X15 is aspartic acid (D) or cysteine (C);
X16 is glutamic acid (E) or serine (S);
X17 is lysine (K) or arginine (R);
X20 is glutamine (Q) or lysine (K);
X21 is aspartic acid (D) or glutamic acid (E);
X24 is valine (V) or glutamine (Q); and
X30 is cysteine (C) or is absent,
with the proviso that the peptides corresponding to SEQ ID NOS: 19, 33, 49, and 50 are excluded from the isolated peptides comprising the amino acid sequence of General Formula 2.

In yet another aspect, the present invention refers to a pharmaceutical composition for use in therapy for preventing or treating hypoglycemia, wherein the pharmaceutical composition comprises (i) the isolated peptide as described in the present invention or the isolated conjugate as described in the present invention; and (ii) a pharmaceutically acceptable excipient.

In yet another aspect, the present invention refers to use of a pharmaceutical composition in the manufacture of a medicament for preventing or treating hypoglycemia, wherein the pharmaceutical composition comprises (i) the isolated peptide as described in the present invention or the isolated conjugate as described in the present invention; and (ii) a pharmaceutically acceptable excipient.

In still another aspect, the present invention refers to a pharmaceutical composition for use in therapy for preventing or treating metabolic syndrome, wherein the pharmaceutical composition comprises (i) the isolated peptide as described in the present invention or the isolated conjugate as described in the present invention; and (ii) a pharmaceutically acceptable excipient.

In still another aspect, the present invention refers to use of a pharmaceutical composition in the manufacture of a medicament for preventing or treating metabolic syndrome, wherein the pharmaceutical composition comprises (i) the isolated peptide as described in the

present invention or the isolated conjugate as described in the present invention; and (ii) a pharmaceutically acceptable excipient.

In still another aspect, the present invention refers to use of the isolated peptide as described in the present invention or the isolated conjugate as described in the present invention for use in the manufacture of a medicament for preventing or treating hypoglycemia, wherein the isolated peptide or the isolated conjugate is to be administered to a subject in need thereof.

In still another aspect, the present invention refers to use of the isolated peptide as described in the present invention or the isolated conjugate as described in the present invention for use in the manufacture of a medicament for preventing or treating metabolic syndromes, wherein the isolated peptide or the isolated conjugate is to be administered to a subject in need thereof.

An example of the present disclosure provides a composition containing a glucagon derivative or a conjugate containing the same, and specifically, a pharmaceutical composition for preventing or treating congenital hyperinsulinism, hypoglycemia, or metabolic syndrome containing a glucagon derivative or a conjugate containing the same.

In a specific example, the present disclosure relates to a composition containing a glucagon derivative peptide including the amino acid sequence of the following General Formula 1, and specifically, a pharmaceutical composition for preventing or treating congenital hyperinsulinism, hypoglycemia, or metabolic syndrome containing a glucagon derivative peptide including the amino acid sequence of the following General Formula 1:

X1-X2-QGTF-X7-SD-X10-S-X12-X13-X14-X15-X16-X17-X18-X19-X20-X21-F-X23-X24-W-L-X27-X28-X29-X30 (General Formula 1, SEQ ID NO: 45)

wherein, in General Formula 1,

X1 is histidine (H), desamino-histidyl, N-dimethyl-histidyl, β-hydroxy imidazopropionyl, 4-imidazoacetyl, β-carboxy imidazopropionyl, tryptophan (W), or tyrosine (Y), or is absent;

X2 is α-methyl-glutamic acid, aminoisobutyric acid (Aib), D-alanine, glycine (G), Sar (N-methylglycine), serine (S), or D-serine;

X7 is threonine (T), valine (V), or cysteine (C);

X10 is tyrosine (Y) or cysteine (C);

X12 is lysine (K) or cysteine (C);

X13 is tyrosine (Y) or cysteine (C);

X14 is leucine (L) or cysteine (C);

X15 is aspartic acid (D), glutamic acid (E), or cysteine (C);

X16 is glutamic acid (E), aspartic acid (D), serine (S), α-methyl-glutamic acid, or cysteine (C), or is absent;

X17 is aspartic acid (D), glutamine (Q), glutamic acid (E), lysine (K), arginine (R), serine (S), cysteine (C), or valine (V), or is absent;

X18 is alanine (A), aspartic acid (D), glutamic acid (E), arginine (R), valine (V), or cysteine (C), or is absent;

X19 is alanine (A), arginine (R), serine (S), valine (V), or cysteine (C), or is absent;

X20 is lysine (K), histidine (H), glutamine (Q), aspartic acid (D), arginine (R), α-methyl-glutamic acid, or cysteine (C), or is absent;

X21 is aspartic acid (D), glutamic acid (E), leucine (L), valine (V), or cysteine (C), or is absent;

X23 is isoleucine (I), valine (V), or arginine (R), or is absent;

X24 is valine (V), arginine (R), alanine (A), cysteine (C), glutamic acid (E), lysine (K), glutamine (Q), α-methyl-glutamic acid, or leucine (L), or is absent;

X27 is isoleucine (I), valine (V), alanine (A), lysine (K), methionine (M), glutamine (Q), or arginine (R), or is absent;

X28 is glutamine (Q), lysine (K), asparagine (N), or arginine (R), or is absent;

X29 is lysine (K), alanine (A), glycine (G), or threonine (T), or is absent; and

X30 is cysteine (C), or is absent;

with the proviso that when the amino acid sequence of General Formula 1 is identical to SEQ ID NO: 1, it is excluded.

The following are additional specific examples of the present disclosure.

Specifically, as a pharmaceutical composition according to the previous specific example:

in General Formula 1,

X1 is histidine (H), tryptophan (W), or tyrosine (Y), or is absent;

X2 is serine (S) or aminoisobutyric acid (Aib);

X7 is threonine (T), valine (V), or cysteine (C);

X10 is tyrosine (Y) or cysteine (C);

X12 is lysine (K) or cysteine (C);

X13 is tyrosine (Y) or cysteine (C);

X14 is leucine (L) or cysteine (C);

X15 is aspartic acid (D) or cysteine (C);

X16 is glutamic acid (E), serine (S), or cysteine (C);

X17 is aspartic acid (D), glutamic acid (E), lysine (K), arginine (R), serine (S), cysteine (C), or valine (V);

X18 is aspartic acid (D), glutamic acid (E), arginine (R), or cysteine (C);

X19 is alanine (A) or cysteine (C);

X20 is glutamine (Q), aspartic acid (D), lysine (K), or cysteine (C);

X21 is aspartic acid (D), glutamic acid (E), leucine (L), valine (V), or cysteine (C);

X23 is isoleucine (I), valine (V), or arginine (R);

X24 is valine (V), arginine (R), alanine (A), glutamic acid (E), lysine (K), glutamine (Q), or leucine (L);

X27 is isoleucine (I), valine (V), alanine (A), methionine (M), glutamine (Q), or arginine (R);

X28 is glutamine (Q), lysine (K), asparagine (N), or arginine (R);

X29 is threonine (T); and

X30 is cysteine (C) or is absent.

As the pharmaceutical composition according to any one of the previous specific examples:

in General Formula 1,

X1 is histidine (H), tryptophan (W), or tyrosine (Y);

X2 is serine (S) or aminoisobutyric acid (Aib);

X7 is cysteine (C), threonine (T), or valine (V);

X10 is tyrosine (Y) or cysteine (C);

X12 is lysine (K) or cysteine (C);

X13 is tyrosine (Y) or cysteine (C);

X14 is leucine (L) or cysteine (C);

X15 is aspartic acid (D) or cysteine (C);

X16 is glutamic acid (E), serine (S), or cysteine (C);

X17 is glutamic acid (E), lysine (K), arginine (R), cysteine (C), or valine (V);

X18 is arginine (R) or cysteine (C);

X19 is alanine (A) or cysteine (C);

X20 is glutamine (Q) or lysine (K);

X21 is aspartic acid (D), glutamic acid (E), valine (V), or cysteine (C);

X23 is valine (V);

X24 is valine (V) or glutamine (Q);

X27 is methionine (M);

X28 is asparagine (N) or arginine (R);

X29 is threonine (T); and

X30 is cysteine (C) or is absent.

As the pharmaceutical composition according to any one of the previous specific examples:

in General Formula 1,

X1 is tyrosine (Y);

X2 is aminoisobutyric acid (Aib);

X7 is cysteine (C), threonine (T), or valine (V);

X10 is tyrosine (Y) or cysteine (C);

X12 is lysine (K);

X13 is tyrosine (Y) or cysteine (C);

X14 is leucine (L) or cysteine (C);

X15 is aspartic acid (D) or cysteine (C);

X16 is glutamic acid (E), serine (S), or cysteine (C);

X17 is lysine (K), arginine (R), cysteine (C), or valine (V);

X18 is arginine (R) or cysteine (C);

X19 is alanine (A) or cysteine (C);

X20 is glutamine (Q) or lysine (K);

X21 is aspartic acid (D), glutamic acid (E), or cysteine (C);

X23 is valine (V);

X24 is glutamine (Q);

X27 is methionine (M);

X28 is asparagine (N) or arginine (R);

X29 is threonine (T); and

X30 is cysteine (C) or is absent.

As the pharmaceutical composition according to any one of the previous specific

examples:

in General Formula 1,

X1 is histidine (H), tryptophan (W), or tyrosine (Y), or is absent;

X2 is serine (S) or aminoisobutyric acid (Aib);

X7 is threonine (T), valine (V), or cysteine (C);

X10 is tyrosine (Y) or cysteine (C);

X12 is lysine (K) or cysteine (C);

X13 is tyrosine (Y) or cysteine (C);

X14 is leucine (L) or cysteine (C);

X15 is aspartic acid (D) or cysteine (C);

X16 is glutamic acid (E), serine (S), or cysteine (C);

X17 is aspartic acid (D), glutamic acid (E), lysine (K), arginine (R), serine (S), cysteine (C), or valine (V);

X18 is aspartic acid (D), glutamic acid (E), arginine (R), or cysteine (C);

X19 is alanine (A) or cysteine (C);

X20 is glutamine (Q), aspartic acid (D), or lysine (K);

X21 is aspartic acid (D) or glutamic acid (E);

X23 is valine (V);

X24 is valine (V) or glutamine (Q);

X27 is isoleucine (I) or methionine (M);

X28 is asparagine (N) or arginine (R);

X29 is threonine (T); and

X30 is cysteine (C) or is absent.

As the pharmaceutical composition according to any one of the previous specific examples:

in General Formula 1,

X1 is tyrosine (Y);

X2 is aminoisobutyric acid (Aib);

X7 is threonine (T);

X10 is tyrosine (Y);

X12 is lysine (K);

X13 is tyrosine (Y);

X14 is leucine (L);

X15 is aspartic acid (D) or cysteine (C);

X16 is glutamic acid (E), serine (S), or cysteine (C);

X17 is lysine (K) or arginine (R);

X18 is arginine (R);

X19 is alanine (A);

X20 is glutamine (Q), cysteine (C), or lysine (K);

X21 is aspartic acid (D), cysteine (C), valine (V), or glutamic acid (E);

X23 is valine (V) or arginine (R);

X24 is glutamine (Q) or leucine (L);

X27 is methionine (M);

X28 is asparagine (N) or arginine (R);

X29 is threonine (T); and

X30 is absent.

As the pharmaceutical composition according to any one of the previous specific examples, the peptide contains the amino acid sequence of the following General Formula 2:

Y-Aib-QGTF-X7-SD-X10-S-X12-Y-L-X15-X16-X17-R-A-X20-X21-F-V-X24-W-L-M-N-T-X30 (General Formula 2, SEQ ID NO: 46)

wherein, in General Formula 2,

X7 is threonine (T), valine (V), or cysteine (C);

X10 is tyrosine (Y) or cysteine (C);

X12 is lysine (K) or cysteine (C);

X15 is aspartic acid (D) or cysteine (C);

X16 is glutamic acid (E) or serine (S);

X17 is lysine (K) or arginine (R);

X20 is glutamine (Q) or lysine (K);

X21 is aspartic acid (D) or glutamic acid (E);

X24 is valine (V) or glutamine (Q); and

X30 is cysteine (C) or is absent.

As the pharmaceutical composition according to any one of the previous specific examples, the peptide has an isoelectric point (pI) value different from that of native glucagon (6.8), *e.g.*, a pI of 6.5 or less, or a pI of 7.0 or higher.

As the pharmaceutical composition according to any one of the previous specific examples, in a specific example of the present disclosure, each amino acid in at least one amino acid pair among the amino acid pairs of X10 and X14, X12 and X16, X16 and X20, X17 and X21, X20 and X24, and X24 and X28 in General Formula 1 or 2 is substituted with glutamic acid or lysine, which is capable of forming a ring, respectively.

As the pharmaceutical composition according to any one of the previous specific examples, in a specific example of the present disclosure, each amino acid in the amino acid pair of X12 and X16 or each amino acid in the amino acid pair of X16 and X20 or each amino acid in the amino acid pair of X17 and X21 in General Formula 1 or 2 is respectively substituted with glutamic acid or lysine, which is capable of forming a ring.

As the pharmaceutical composition according to any one of the previous specific examples, in a specific example of the present disclosure, in General Formula 1 or 2, a ring (*e.g.*, a lactam ring) is formed between each amino acid in at least one amino acid pair among the amino acid pairs of X10 and X14, X12 and X16, X16 and X20, X17 and X21, X20 and X24, and X24 and X28.

As the pharmaceutical composition according to any one of the previous specific examples, in a specific example of the present disclosure, in General Formula 1 or 2, X16 is glutamic acid, X20 is lysine, and the side chains of X16 and X20 form a lactam ring.

As the pharmaceutical composition according to any one of the previous specific

examples, the C-terminus of the peptide is amidated or unmodified.

As the pharmaceutical composition according to any one of the previous specific examples, the peptide is a native glucagon derivative capable of activating a glucagon receptor.

As the pharmaceutical composition according to any one of the previous specific examples, the peptide includes an amino acid sequence selected from the group consisting of SEQ ID NOS: 2 to 44.

As the pharmaceutical composition according to any one of the previous specific examples, the peptide includes an amino acid sequence selected from the group consisting of SEQ ID NOS: 12, 13, 15, and 36 to 44.

As the pharmaceutical composition according to any one of the previous specific examples, the peptide includes the amino acid sequence of SEQ ID NO: 37.

As the pharmaceutical composition according to any one of the previous specific examples, the peptide is in the form of a long-acting conjugate, in which a biocompatible material moiety is linked to the peptide moiety, and specifically to the peptide moiety including the amino acid sequence of General Formula 1 or 2.

As the pharmaceutical composition according to any one of the previous specific examples, the biocompatible material moiety is selected from the group consisting of a polymer, fatty acid, cholesterol, albumin and a fragment thereof, an albumin-binding material, a polymer of repeating units of a particular amino acid sequence, an antibody, an antibody fragment, an FcRn-binding material, *in vivo* connective tissue or a derivative thereof, a nucleotide, fibronectin, transferrin, a saccharide, heparin, and elastin.

As the pharmaceutical composition according to any one of the previous specific examples, the polymer is selected from the group consisting of a polyethylene glycol, a polypropylene glycol, an ethylene glycol-propylene glycol copolymer, polyoxyethylated polyol,

polyvinyl alcohol, a polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer, a lipid polymer, chitin, hyaluronic acid, an oligonucleotide, and a combination thereof.

As the pharmaceutical composition according to any one of the previous specific examples, the FcRn-binding material is a polypeptide containing an immunoglobulin Fc region.

As the pharmaceutical composition according to any one of the previous specific examples, the peptide moiety and the biocompatible material moiety are linked through a linker.

As the pharmaceutical composition according to any one of the previous specific examples, the linker is selected from the group consisting of a peptide, fatty acid, a saccharide, a polymer, a low molecular weight compound, a nucleotide, and a combination thereof.

As the pharmaceutical composition according to any one of the previous specific examples, the polymer is selected from the group consisting of a polyethylene glycol, a polypropylene glycol, an ethylene glycol-propylene glycol copolymer, polyoxyethylated polyol, polyvinyl alcohol, a polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer, a lipid polymer, chitin, hyaluronic acid, an oligonucleotide, and a combination thereof.

As the pharmaceutical composition according to any one of the previous specific examples, the linker is a polyethylene glycol.

As the pharmaceutical composition according to any one of the previous specific examples, the immunoglobulin Fc region is aglycosylated.

As the pharmaceutical composition according to any one of the previous specific examples, the immunoglobulin Fc region is selected from the group consisting of:

(a) a CH1 domain, a CH2 domain, a CH3 domain, and a CH4 domain;

(b) a CH1 domain and a CH2 domain;

(c) a CH1 domain and a CH3 domain;

(d) a CH2 domain and a CH3 domain;

(e) a combination between one or at least two domains among a CH1 domain, a CH2 domain, a CH3 domain, and a CH4 domain, and an immunoglobulin hinge region or a part of the hinge region; and

(f) a dimer between each domain of the heavy chain constant region and the light chain constant region.

As the pharmaceutical composition according to any one of the previous specific examples, the polypeptide containing an immunoglobulin Fc region is in the form of a dimer.

As the pharmaceutical composition according to any one of the previous specific examples, the immunoglobulin Fc region is a native Fc derivative in which the region capable of forming a disulfide bond is deleted, a native Fc derivative in which a part of the amino acid(s) in the N-terminus is removed, a native Fc derivative in which a methionine residue is added to the N-terminus, a native Fc derivative in which a complement-binding site is deleted, or a native Fc derivative in which an antibody dependent cell mediated cytotoxicity (ADCC) site is deleted.

As the pharmaceutical composition according to any one of the previous specific examples, the immunoglobulin Fc region is derived from an immunoglobulin selected from the group consisting of IgG, IgA, IgD, IgE, and IgM.

As the pharmaceutical composition according to any one of the previous specific examples, the immunoglobulin Fc region is an IgG4 Fc region.

As the pharmaceutical composition according to any one of the previous specific examples, the immunoglobulin Fc region is an aglycosylated Fc region derived from human IgG4.

As the pharmaceutical composition according to any one of the previous specific examples, the linker is linked to a cysteine residue of a peptide including the amino acid sequence of General Formula 1 or 2.

As the pharmaceutical composition according to any one of the previous specific examples, in a specific example of the present disclosure, the linker of the conjugate is respectively linked to the peptide moiety and the biocompatible material moiety through covalent bonds, which were respectively formed when one end of the linker reacted with an amine group or thiol group of the biocompatible material moiety while the other end of the linker reacted with an amine group or thiol group of the peptide moiety including the amino acid sequence of General Formula 1 or 2, respectively.

Another example of the present disclosure provides a glucagon derivative.

In a specific example, the present disclosure relates to an isolated peptide including the amino acid sequence of General Formula 1 represented by SEQ ID NO: 45.

In another specific example, the present disclosure relates to an isolated peptide including the amino acid sequence of the following General Formula 2:

Y-Aib-QGTF-X7-SD-X10-S-X12-Y-L-X15-X16-X17-R-A-X20-X21-F-V-X24-W-L-M-N-T-X30 (General Formula 2, SEQ ID NO: 46)

wherein, in General Formula 2,

X7 is threonine (T), valine (V), or cysteine (C);

X10 is tyrosine (Y) or cysteine (C);

X12 is lysine (K) or cysteine (C);

X15 is aspartic acid (D) or cysteine (C);

X16 is glutamic acid (E) or serine (S);

X17 is lysine (K) or arginine (R);

X20 is glutamine (Q) or lysine (K);

X21 is aspartic acid (D) or glutamic acid (E);

X24 is valine (V) or glutamine (Q); and

X30 is cysteine (C) or is absent.

In the isolated peptide according to the previous specific example, the peptides corresponding to SEQ ID NOS: 19, 33, 49, and 50 may be excluded from the isolated peptides

including the amino acid sequence of General Formula 2.

In the isolated peptide according to any one of the previous specific examples, in General Formula 2, X16 is glutamic acid, X20 is lysine, and the side chains of X16 and X20 form a lactam ring.

In the isolated peptide according to any one of the previous specific examples, the C-terminus of the peptide comprising the amino acid sequence of General Formula 2 is amidated or unmodified.

In the isolated peptide according to any one of the previous specific examples, the peptide is a glucagon derivative capable of activating a glucagon receptor.

In the isolated peptide according to any one of the previous specific examples, the peptide includes an amino acid sequence selected from the group consisting of SEQ ID NOS: 12, 13, 15, and 36 to 44.

Still another example of the present disclosure provides an isolated polynucleotide encoding the isolated peptide (specifically, the isolated peptide which includes the amino acid sequence of General Formula 1 or 2), a vector including the isolated polynucleotide, and an isolated cell including the polynucleotide or vector.

Still another example of the present disclosure provides an isolated conjugate including a peptide moiety and a biocompatible material moiety covalently linked to the peptide moiety, in which the peptide moiety has the same amino acid sequence of General Formula 1 or 2 or includes the same.

In a specific example, the present disclosure relates to an isolated conjugate including a peptide moiety and a biocompatible material moiety covalently linked to the peptide moiety, in which the peptide moiety has the same amino acid sequence of General Formula 1 or includes the same.

In a specific example, the present disclosure relates to an isolated conjugate including a peptide moiety and a biocompatible material moiety covalently linked to the peptide moiety, in which the peptide moiety has the same amino acid sequence of General Formula 2 or includes the same.

In the conjugate according to the previous specific example, the biocompatible material moiety is selected from the group consisting of a polymer, fatty acid, cholesterol, albumin and a fragment thereof, an albumin-binding material, a polymer of repeating units of a particular amino acid sequence, an antibody, an antibody fragment, an FcRn-binding material, *in vivo* connective tissue or a derivative thereof, a nucleotide, fibronectin, transferrin, a saccharide, heparin, and elastin.

In the conjugate according to any one of the previous specific examples, the polymer is selected from the group consisting of a polyethylene glycol, a polypropylene glycol, an ethylene glycol-propylene glycol copolymer, polyoxyethylated polyol, polyvinyl alcohol, a polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer, a lipid polymer, chitin, hyaluronic acid, an oligonucleotide, and a combination thereof.

In the conjugate according to any one of the previous specific examples, the FcRn-binding material is a polypeptide comprising an immunoglobulin Fc region.

In the conjugate according to any one of the previous specific examples, the peptide region and the biocompatible material moiety are linked through a linker.

As the conjugate according to any one of the previous specific examples, the linker is selected from the group consisting of a peptide, fatty acid, a saccharide, a polymer, a low molecular weight compound, a nucleotide, and a combination thereof.

In the conjugate according to any one of the previous specific examples, the linker is a polymer selected from the group consisting of a polyethylene glycol, a polypropylene glycol, an

ethylene glycol-propylene glycol copolymer, polyoxyethylated polyol, polyvinyl alcohol, a polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer, a lipid polymer, chitin, hyaluronic acid, an oligonucleotide, and a combination thereof.

In the conjugate according to any one of the previous specific examples, the biocompatible material moiety is an FcRn-binding material, and the biocompatible material moiety is linked to the peptide moiety through a linker selected from the group consisting of a peptide, fatty acid, a saccharide, a polymer, a low molecular weight compound, a nucleotide, and a combination thereof.

In the conjugate according to any one of the previous specific examples, the linker is a polyethylene glycol.

In the conjugate according to any one of the previous specific examples, the immunoglobulin Fc region is aglycosylated.

In the conjugate according to any one of the previous specific examples, the immunoglobulin Fc region is selected from the group consisting of: (a) a CH1 domain, a CH2 domain, a CH3 domain, and a CH4 domain; (b) a CH1 domain and a CH2 domain; (c) a CH1 domain and a CH3 domain; (d) a CH2 domain and a CH3 domain; (e) a combination between one or at least two domains among a CH1 domain, a CH2 domain, a CH3 domain, and a CH4 domain, and an immunoglobulin hinge region or a part of the hinge region; and (f) a dimer between each domain of the heavy chain constant region and the light chain constant region.

In the conjugate according to any one of the previous specific examples, the polypeptide including an immunoglobulin Fc region is in the form of a dimer.

In the conjugate according to any one of the previous specific examples, the immunoglobulin Fc region is a native Fc derivative in which the region capable of forming a disulfide bond is deleted, a native Fc derivative in which a part of the amino acid(s) in the N-terminus is removed, a native Fc derivative in which a methionine residue is added to the

N-terminus, a native Fc derivative in which a complement-binding site is deleted, or a native Fc derivative in which an antibody dependent cell mediated cytotoxicity (ADCC) site is deleted.

In the conjugate according to any one of the previous specific examples, the immunoglobulin Fc region is derived from an immunoglobulin selected from the group consisting of IgG, IgA, IgD, IgE, and IgM.

In the conjugate according to any one of the previous specific examples, the immunoglobulin Fc region is an IgG4 Fc region.

In the conjugate according to any one of the previous specific examples, the immunoglobulin Fc region is an aglycosylated Fc region derived from human IgG4.

In the conjugate according to any one of the previous specific examples, the linker is linked to a cysteine residue of the peptide.

In the conjugate according to any one of the previous specific examples, in a specific example of the present disclosure, the linker of the conjugate is respectively linked to the peptide moiety and the biocompatible material moiety through covalent bonds, which were respectively formed when one end of the linker reacted with an amine group or thiol group of the biocompatible material moiety while the other end of the linker reacted with an amine group or thiol group of the peptide moiety including the amino acid sequence of General Formula 1 or 2, respectively.

Still another example of the present disclosure provides a pharmaceutical composition for preventing or treating hypoglycemia containing a glucagon derivative or a conjugate containing the same and a pharmaceutically acceptable excipient.

In a specific example, the present disclosure relates to a pharmaceutical composition for preventing or treating hypoglycemia, which contains the isolated peptide or the isolated conjugate, which includes a peptide moiety, that has the same sequence as that of the isolated

peptide or includes a sequence including the same, and a biocompatible material moiety covalently linked to the peptide moiety.

Still another example of the present disclosure provides a pharmaceutical composition for preventing or treating metabolic syndrome containing a glucagon derivative or a conjugate containing the same and a pharmaceutically acceptable excipient.

In a specific example, the present disclosure relates to a pharmaceutical composition for preventing or treating metabolic syndrome, which contains the isolated peptide; or the isolated conjugate, which includes a peptide moiety, that has the same sequence as that of the isolated peptide or includes a sequence including the same, and a biocompatible material moiety covalently linked to the peptide moiety.

In the pharmaceutical composition according to any one of the previous specific examples, the pharmaceutical composition further contains at least one compound or material having the therapeutic activity for metabolic syndrome.

In the pharmaceutical composition according to any one of the previous specific examples, the compound or material having the therapeutic activity for metabolic syndrome is selected from the group consisting of an insulinotropic peptide, a glucagon like peptide-1 (GLP-1) receptor agonist, a leptin receptor agonist, a dipeptidyl peptidase-IV (DPP-IV) inhibitor, a Y5 receptor antagonist, a melanin-concentrating hormone (MCH) receptor antagonist, a Y2/4 receptor agonist, a melanocortin 3/4 (MC 3/4) receptor agonist, a gastric/pancreatic lipase inhibitor, an agonist of 5-hydroxytryptamine receptor 2C ($5HT2_C$, G-protein coupled), a β3A receptor agonist, an amylin receptor agonist, a ghrelin antagonist, a ghrelin receptor antagonist, a peroxisome proliferator-activated receptor alpha (PPARα) agonist, a peroxisome proliferator-activated receptor delta (PPARδ) agonist, a Farnesoid X receptor (FXR) agonist, an acetyl-CoA carboxylase inhibitor, a peptide YY, cholecystokinin (CCK), xenin, glicentin, obestatin, secretin, nesfatin, insulin, and a glucose-dependent insulinotropic peptide (GIP).

In the pharmaceutical composition according to any one of the previous specific

examples, the insulinotropic peptide is selected from the group consisting of GLP-1, exendin-3, exendin-4, an agonist thereof, a derivative thereof, a fragment thereof, a variant thereof, and a combination thereof.

In the pharmaceutical composition according to any one of the previous specific examples, the insulinotropic peptide is an insulinotropic peptide derivative in which the N-terminal histidine of the insulinotropic peptide is substituted with one selected from the group consisting of desamino-histidyl, N-dimethyl-histidyl, β-hydroxy imidazopropionyl, 4-imidazoacetyl, and β-carboxy imidazopropionyl.

In the pharmaceutical composition according to any one of the previous specific examples, the insulinotropic peptide is selected from the group consisting of a native exendin-4; an exendin-4 derivative in which the N-terminal amine group of exendin-4 is deleted; an exendin-4 derivative in which the N-terminal amine group of exendin-4 is substituted with a hydroxyl group; an exendin-4 derivative in which the N-terminal amine group of exendin-4 is modified with a dimethyl group; an exendin-4 derivative in which the α-carbon of the 1st amino acid of exendin-4, histidine, is deleted; an exendin-4 derivative in which the 12th amino acid of exendin-4, lysine, is substituted with serine, and an exendin-4 derivative in which the 12th amino acid of exendin-4, lysine, is substituted with arginine.

In the pharmaceutical composition according to any one of the previous specific examples, the insulinotropic peptide is in the form of a long-acting conjugate, which includes a peptide moiety, that includes the same amino acid sequence as that of the insulinotropic peptide, and a biocompatible material moiety covalently linked to the peptide moiety.

In the pharmaceutical composition according to any one of the previous specific examples, the biocompatible material moiety is selected from the group consisting of a polymer, fatty acid, cholesterol, albumin and a fragment thereof, an albumin-binding material, a polymer of repeating units of a particular amino acid sequence, an antibody, an antibody fragment, an FcRn-binding material, *in vivo* connective tissue or a derivative thereof, a nucleotide, fibronectin, transferrin, a saccharide, heparin, and elastin.

In the pharmaceutical composition according to any one of the previous specific examples, the polymer is selected from the group consisting of a polyethylene glycol, a polypropylene glycol, an ethylene glycol-propylene glycol copolymer, polyoxyethylated polyol, polyvinyl alcohol, a polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer, a lipid polymer, chitin, hyaluronic acid, an oligonucleotide, and a combination thereof.

In the pharmaceutical composition according to any one of the previous specific exampless, the FcRn-binding material is a polypeptide including an immunoglobulin Fc region.

In the pharmaceutical composition according to any one of the previous specific exampless, the peptide moiety including the amino acid sequence of the insulinotropic peptide is linked to the biocompatible material moiety through a linker.

In the pharmaceutical composition according to any one of the previous specific examples, the linker is selected from the group consisting of a peptide, fatty acid, a saccharide, a polymer, a low molecular weight compound, a nucleotide, and a combination thereof.

In the pharmaceutical composition according to any one of the previous specific examples, the linker is a polymer selected from the group consisting of a polyethylene glycol, a polypropylene glycol, an ethylene glycol-propylene glycol copolymer, polyoxyethylated polyol, polyvinyl alcohol, a polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer, a lipid polymer, chitin, hyaluronic acid, an oligonucleotide, and a combination thereof.

In the pharmaceutical composition according to any one of the previous specific examples, the metabolic syndrome is selected from the group consisting of impaired glucose tolerance, hypercholesterolemia, dyslipidemia, obesity, diabetes, hypertension, nonalcoholic steatohepatitis (NASH), atherosclerosis caused by dyslipidemia, atherosclerosis, arteriosclerosis, coronary heart disease, stroke, *etc.*

In the pharmaceutical composition according to any one of the previous specific

examples, the insulinotropic peptide is linked to a biocompatible material moiety through a linker selected from the group consisting of a polyethylene glycol, a polypropylene glycol, an ethylene glycol-propylene glycol copolymer, polyoxyethylated polyol, polyvinyl alcohol, a polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer such as polylactic acid (PLA) and polylactic-glycolic acid (PLGA), a lipid polymer, chitins, hyaluronic acid, fatty acid, a polymer, a low molecular weight compound, a nucleotide, and a combination thereof.

In the pharmaceutical composition according to any one of the previous specific examples, the biocompatible material moiety is an FcRn-binding material, and the peptide moiety including the amino acid sequence of the insulinotropic peptide is linked to a biocompatible material moiety through a peptide linker; or a non-peptide linker selected from the group consisting of a polyethylene glycol, a polypropylene glycol, an ethylene glycol-propylene glycol copolymer, polyoxyethylated polyol, polyvinyl alcohol, a polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer such as polylactic acid (PLA) and polylactic-glycolic acid (PLGA), a lipid polymer, chitins, hyaluronic acid, and a combination thereof.

In the pharmaceutical composition according to any one of the previous specific examples, the composition may include both (i) a conjugate, which includes the peptide moiety including the amino acid sequence of SEQ ID NO: 37, and a biocompatible material moiety covalently linked to the peptide moiety; and (ii) a conjugate, which includes an imidazo-acetyl exendin-4 moiety where the α-carbon of the 1st amino acid of exendin-4 (*i.e.*, histidine) is deleted and a biocompatible material moiety covalently linked to the imidazo-acetyl exendin-4 moiety.

In the pharmaceutical composition according to any one of the previous specific examples, the peptide moiety including the amino acid sequence of SEQ ID NO: 37 and the imidazo-acetyl exendin-4 moiety are linked to their respective biocompatible material moietys through a linker.

In the pharmaceutical composition according to any one of the previous specific examples, the FcRn-binding material is a polypeptide including an immunoglobulin Fc region.

Still another example of the present disclosure provides a method for preventing or treating congenital hyperinsulinism including administering the glucagon derivative or a conjugate containing the same or a composition containing the same to a subject in need thereof.

Still another example of the present disclosure provides use of the glucagon derivative or the conjugate containing the same or the composition containing the same in the preparation of a medicament for preventing or treating congenital hyperinsulinism.

Still another example of the present disclosure provides a method for preventing or treating hypoglycemia including administering the glucagon derivative or a conjugate containing the same or a composition containing the same to a subject in need thereof.

Still another example of the present disclosure provides use of the glucagon derivative or the conjugate containing the same or the composition containing the same in the preparation of a medicament for preventing or treating hypoglycemia.

Still another example of the present disclosure provides a method for preventing or treating metabolic syndrome including administering the glucagon derivative or a conjugate containing the same or a composition containing the same to a subject in need thereof.

In a specific example, the method further includes administering at least one compound or material having a therapeutic activity for metabolic syndrome.

In the method according to any one of the previous specific examples, the glucagon derivative or a conjugate containing the same and the compound or material having a therapeutic activity for metabolic syndrome is administered simultaneously, individually, or sequentially.

Still another example of the present disclosure provides use of the glucagon derivative or the conjugate containing the same or the composition containing the same in the preparation of a medicament (or pharmaceutical compositon) for preventing or treating metabolic syndrome.

[Claims]

[Claim 1] A pharmaceutical composition for use in therapy for preventing or treating congenital hyperinsulinism, wherein the pharmaceutical composition comprises a peptide comprising the amino acid sequence of the following General Formula 1:

X1-X2-QGTF-X7-SD-X10-S-X12-X13-X14-X15-X16-X17-X18-X19-X20-X21-F-X23-X24-W-L-X27-X28-X29-X30 (General Formula 1, SEQ ID NO: 45)

wherein, in General Formula 1,

X1 is histidine (H), desamino-histidyl, N-dimethyl-histidyl, β-hydroxy imidazopropionyl, 4-imidazoacetyl, β-carboxy imidazopropionyl, tryptophan (W), or tyrosine (Y), or is absent;

X2 is α-methyl-glutamic acid, aminoisobutyric acid (Aib), D-alanine, glycine (G), Sar (N-methylglycine), serine (S), or D-serine;

X7 is threonine (T), valine (V), or cysteine (C);

X10 is tyrosine (Y) or cysteine (C);

X12 is lysine (K) or cysteine (C);

X13 is tyrosine (Y) or cysteine (C);

X14 is leucine (L) or cysteine (C);

X15 is aspartic acid (D), glutamic acid (E), or cysteine (C);

X16 is glutamic acid (E), aspartic acid (D), serine (S), α-methyl-glutamic acid, or cysteine (C), or is absent;

X17 is aspartic acid (D), glutamine (Q), glutamic acid (E), lysine (K), arginine (R), serine (S), cysteine (C), or valine (V), or is absent;

X18 is alanine (A), aspartic acid (D), glutamic acid (E), arginine (R), valine (V), or cysteine (C), or is absent;

X19 is alanine (A), arginine (R), serine (S), valine (V), or cysteine (C), or is absent;

X20 is lysine (K), histidine (H), glutamine (Q), aspartic acid (D), arginine (R), α-methyl-glutamic acid, or cysteine (C), or is absent;

X21 is aspartic acid (D), glutamic acid (E), leucine (L), valine (V), or cysteine (C), or is absent;

X23 is isoleucine (I), valine (V), or arginine (R), or is absent;

X24 is valine (V), arginine (R), alanine (A), cysteine (C), glutamic acid (E), lysine (K), glutamine (Q), α-methyl-glutamic acid, or leucine (L), or is absent;

X27 is isoleucine (I), valine (V), alanine (A), lysine (K), methionine (M), glutamine (Q), or arginine (R), or is absent;

X28 is glutamine (Q), lysine (K), asparagine (N), or arginine (R), or is absent;

X29 is lysine (K), alanine (A), glycine (G), or threonine (T), or is absent; and

X30 is cysteine (C), or is absent;

with the proviso that when the amino acid sequence of General Formula 1 is

identical to SEQ ID NO: 1, it is excluded.

[Claim 2] Use of a pharmaceutical composition in the manufacture of a medicament for preventing or treating congenital hyperinsulinism, wherein the pharmaceutical composition comprises a peptide comprising the amino acid sequence of the following General Formula 1:

X1-X2-QGTF-X7-SD-X10-S-X12-X13-X14-X15-X16-X17-X18-X19-X20-X21-F-X23-X24-W-L-X27-X28-X29-X30 (General Formula 1, SEQ ID NO: 45)

wherein, in General Formula 1,

X1 is histidine (H), desamino-histidyl, N-dimethyl-histidyl, β-hydroxy imidazopropionyl, 4-imidazoacetyl, β-carboxy imidazopropionyl, tryptophan (W), or tyrosine (Y), or is absent;

X2 is α-methyl-glutamic acid, aminoisobutyric acid (Aib), D-alanine, glycine (G), Sar (N-methylglycine), serine (S), or D-serine;

X7 is threonine (T), valine (V), or cysteine (C);

X10 is tyrosine (Y) or cysteine (C);

X12 is lysine (K) or cysteine (C);

X13 is tyrosine (Y) or cysteine (C);

X14 is leucine (L) or cysteine (C);

X15 is aspartic acid (D), glutamic acid (E), or cysteine (C);

X16 is glutamic acid (E), aspartic acid (D), serine (S), α-methyl-glutamic acid, or cysteine (C), or is absent;

X17 is aspartic acid (D), glutamine (Q), glutamic acid (E), lysine (K), arginine (R), serine (S), cysteine (C), or valine (V), or is absent;

X18 is alanine (A), aspartic acid (D), glutamic acid (E), arginine (R), valine (V), or cysteine (C), or is absent;

X19 is alanine (A), arginine (R), serine (S), valine (V), or cysteine (C), or is absent;

X20 is lysine (K), histidine (H), glutamine (Q), aspartic acid (D), arginine (R), α-methyl-glutamic acid, or cysteine (C), or is absent;

X21 is aspartic acid (D), glutamic acid (E), leucine (L), valine (V), or cysteine (C), or is absent;

X23 is isoleucine (I), valine (V), or arginine (R), or is absent;

X24 is valine (V), arginine (R), alanine (A), cysteine (C), glutamic acid (E), lysine (K), glutamine (Q), α-methyl-glutamic acid, or leucine (L), or is absent;

X27 is isoleucine (I), valine (V), alanine (A), lysine (K), methionine (M), glutamine (Q), or arginine (R), or is absent;

X28 is glutamine (Q), lysine (K), asparagine (N), or arginine (R), or is absent;

X29 is lysine (K), alanine (A), glycine (G), or threonine (T), or is absent; and

X30 is cysteine (C), or is absent;

with the proviso that when the amino acid sequence of General Formula 1 is

identical to SEQ ID NO: 1, it is excluded.

[Claim 3]

The pharmaceutical composition of claim 1 or the use of claim 2, wherein, in General Formula 1,

X1 is histidine (H), tryptophan (W), or tyrosine (Y), or is absent;

X2 is serine (S) or aminoisobutyric acid (Aib);

X7 is threonine (T), valine (V), or cysteine (C);

X10 is tyrosine (Y) or cysteine (C);

X12 is lysine (K) or cysteine (C);

X13 is tyrosine (Y) or cysteine (C);

X14 is leucine (L) or cysteine (C);

X15 is aspartic acid (D) or cysteine (C);

X16 is glutamic acid (E), serine (S), or cysteine (C);

X17 is aspartic acid (D), glutamic acid (E), lysine (K), arginine (R), serine (S), cysteine (C), or valine (V);

X18 is aspartic acid (D), glutamic acid (E), arginine (R), or cysteine (C);

X19 is alanine (A) or cysteine (C);

X20 is glutamine (Q), aspartic acid (D), lysine (K), or cysteine (C);

X21 is aspartic acid (D), glutamic acid (E), leucine (L), valine (V), or cysteine (C);

X23 is isoleucine (I), valine (V), or arginine (R);

X24 is valine (V), arginine (R), alanine (A), glutamic acid (E), lysine (K), glutamine (Q), or leucine (L);

X27 is isoleucine (I), valine (V), alanine (A), methionine (M), glutamine (Q), or arginine (R);

X28 is glutamine (Q), lysine (K), asparagine (N), or arginine (R);

X29 is threonine (T); and

X30 is cysteine (C) or is absent.

[Claim 4]

The pharmaceutical composition of claim 1 or the use of claim 2, wherein, in General Formula 1,

X1 is histidine (H), tryptophan (W), or tyrosine (Y);

X2 is serine (S) or aminoisobutyric acid (Aib);

X7 is cysteine (C), threonine (T), or valine (V);

X10 is tyrosine (Y) or cysteine (C);

X12 is lysine (K) or cysteine (C);

X13 is tyrosine (Y) or cysteine (C);

X14 is leucine (L) or cysteine (C);

X15 is aspartic acid (D) or cysteine (C);

X16 is glutamic acid (E), serine (S), or cysteine (C);

X17 is glutamic acid (E), lysine (K), arginine (R), cysteine (C), or valine (V);

X18 is arginine (R) or cysteine (C);
X19 is alanine (A) or cysteine (C);
X20 is glutamine (Q) or lysine (K);
X21 is aspartic acid (D), glutamic acid (E), valine (V), or cysteine (C);
X23 is valine (V);
X24 is valine (V) or glutamine (Q);
X27 is methionine (M);
X28 is asparagine (N) or arginine (R);
X29 is threonine (T); and
X30 is cysteine (C) or is absent.

[Claim 5]

The pharmaceutical composition of claim 1 or the use of claim 2, wherein, in General Formula 1,
X1 is tyrosine (Y);
X2 is aminoisobutyric acid (Aib);
X7 is cysteine (C), threonine (T), or valine (V);
X10 is tyrosine (Y) or cysteine (C);
X12 is lysine (K);
X13 is tyrosine (Y) or cysteine (C);
X14 is leucine (L) or cysteine (C);
X15 is aspartic acid (D) or cysteine (C);
X16 is glutamic acid (E), serine (S), or cysteine (C);
X17 is lysine (K), arginine (R), cysteine (C), or valine (V);
X18 is arginine (R) or cysteine (C);
X19 is alanine (A) or cysteine (C);
X20 is glutamine (Q) or lysine (K);
X21 is aspartic acid (D), glutamic acid (E), or cysteine (C);
X23 is valine (V);
X24 is glutamine (Q);
X27 is methionine (M);
X28 is asparagine (N) or arginine (R);
X29 is threonine (T); and
X30 is cysteine (C) or is absent.

[Claim 6]

The pharmaceutical composition of claim 1 or the use of claim 2, wherein, in General Formula 1,
X1 is histidine (H), tryptophan (W), or tyrosine (Y), or is absent;
X2 is serine (S) or aminoisobutyric acid (Aib);
X7 is threonine (T), valine (V), or cysteine (C);
X10 is tyrosine (Y) or cysteine (C);
X12 is lysine (K) or cysteine (C);

X13 is tyrosine (Y) or cysteine (C);
X14 is leucine (L) or cysteine (C);
X15 is aspartic acid (D) or cysteine (C);
X16 is glutamic acid (E), serine (S), or cysteine (C);
X17 is aspartic acid (D), glutamic acid (E), lysine (K), arginine (R), serine (S), cysteine (C), or valine (V);
X18 is aspartic acid (D), glutamic acid (E), arginine (R), or cysteine (C);
X19 is alanine (A) or cysteine (C);
X20 is glutamine (Q), aspartic acid (D), or lysine (K);
X21 is aspartic acid (D) or glutamic acid (E);
X23 is valine (V);
X24 is valine (V) or glutamine (Q);
X27 is isoleucine (I) or methionine (M);
X28 is asparagine (N) or arginine (R);
X29 is threonine (T); and
X30 is cysteine (C) or is absent.

[Claim 7]
The pharmaceutical composition of claim 1 or the use of claim 2,
wherein, in General Formula 1,
X1 is tyrosine (Y);
X2 is aminoisobutyric acid (Aib);
X7 is threonine (T);
X10 is tyrosine (Y);
X12 is lysine (K);
X13 is tyrosine (Y);
X14 is leucine (L);
X15 is aspartic acid (D) or cysteine (C);
X16 is glutamic acid (E), serine (S), or cysteine (C);
X17 is lysine (K) or arginine (R);
X18 is arginine (R);
X19 is alanine (A);
X20 is glutamine (Q), cysteine (C), or lysine (K);
X21 is aspartic acid (D), cysteine (C), valine (V), or glutamic acid (E);
X23 is valine (V) or arginine (R);
X24 is glutamine (Q) or leucine (L);
X27 is methionine (M);
X28 is asparagine (N) or arginine (R);
X29 is threonine (T); and
X30 is absent.

[Claim 8]
The pharmaceutical composition of claim 1 or the use of claim 2, wherein the

peptide comprises the amino acid sequence of the following General Formula 2:

Y-Aib-QGTF-X7-SD-X10-S-X12-Y-L-X15-X16-X17-R-A-X20-X21-F-V-X24-W-L-M-N-T-X30 (General Formula 2, SEQ ID NO: 46)

wherein, in General Formula 2,
X7 is threonine (T), valine (V), or cysteine (C);
X10 is tyrosine (Y) or cysteine (C);
X12 is lysine (K) or cysteine (C);
X15 is aspartic acid (D) or cysteine (C);
X16 is glutamic acid (E) or serine (S);
X17 is lysine (K) or arginine (R);
X20 is glutamine (Q) or lysine (K);
X21 is aspartic acid (D) or glutamic acid (E);
X24 is valine (V) or glutamine (Q); and
X30 is cysteine (C) or is absent.

[Claim 9]
The pharmaceutical composition of claim 1 or the use of claim 2, wherein the peptide has an isoelectric point (pI) value different from that of native glucagon (6.8).

[Claim 10]
The pharmaceutical composition of claim 1 or the use of claim 2, wherein each amino acid in at least one amino acid pair among the amino acid pairs of X10 and X14, X12 and X16, X16 and X20, X17 and X21, X20 and X24, and X24 and X28 in General Formula 1 is substituted with glutamic acid or lysine, which is capable of forming a ring, respectively.

[Claim 11]
The pharmaceutical composition of claim 10 or the use of claim 10, wherein each amino acid in the amino acid pair of X12 and X16 or each amino acid in the amino acid pair of X16 and X20 or each amino acid in the amino acid pair of X17 and X21 is respectively substituted with glutamic acid or lysine, which is capable of forming a ring.

[Claim 12]
The pharmaceutical composition of claim 1 or the use of claim 2, wherein, in General Formula 1, a ring is formed between each amino acid in at least one amino acid pair among the amino acid pairs of X10 and X14, X12 and X16, X16 and X20, X17 and X21, X20 and X24, and X24 and X28.

[Claim 13]
The pharmaceutical composition of claim 1 or the use of claim 2, wherein the

C-terminus of the peptide is amidated.

[Claim 14]
The pharmaceutical composition of claim 1 or the use of claim 2, wherein the C-terminus of the peptide is unmodified.

[Claim 15]
The pharmaceutical composition of claim 1 or the use of claim 2, wherein the peptide is a native glucagon derivative capable of activating a glucagon receptor.

[Claim 16]
The pharmaceutical composition of claim 1 or the use of claim 2, wherein the peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 2 to 44.

[Claim 17]
The pharmaceutical composition of claim 8 or the use of claim 8, wherein the peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 12, 13, 15, and 36 to 44.

[Claim 18]
The pharmaceutical composition of claim 1 or the use of claim 2, wherein the peptide comprises the amino acid sequence of SEQ ID NO: 37.

[Claim 19]
The pharmaceutical composition according to claim 1, the pharmaceutical composition according to any one of claims 3 to 18 or the use according to any one of claims 2 to 18, wherein the peptide is in the form of a long-acting conjugate, in which a biocompatible material moiety is linked to a peptide moiety comprising the amino acid sequence of General Formula 1.

[Claim 20]
The pharmaceutical composition of claim 19 or the use of claim 19, wherein the biocompatible material moiety is selected from the group consisting of a polymer, fatty acid, cholesterol, albumin and a fragment thereof, an albumin-binding material, a polymer of repeating units of a particular amino acid sequence, an antibody, an antibody fragment, an FcRn-binding material, *in vivo* connective tissue or a derivative thereof, a nucleotide, fibronectin, transferrin, a saccharide, heparin, and elastin.

[Claim 21]
The pharmaceutical composition of claim 20 or the use of claim 20, wherein the polymer is selected from the group consisting of a polyethylene glycol, a

polypropylene glycol, an ethylene glycol-propylene glycol copolymer, polyoxyethylated polyol, polyvinyl alcohol, a polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer, a lipid polymer, chitin, hyaluronic acid, an oligonucleotide, and a combination thereof.

[Claim 22]

The pharmaceutical composition of claim 20 or the use of claim 20, wherein the FcRn-binding material is a polypeptide comprising an immunoglobulin Fc region.

[Claim 23]

The pharmaceutical composition of claim 19 or the use of claim 19, wherein the peptide moiety and the biocompatible material moiety are linked with each other through a linker.

[Claim 24]

The pharmaceutical composition of claim 23 or the use of claim 23, wherein the linker is selected from the group consisting of a peptide, fatty acid, a saccharide, a polymer, a low molecular weight compound, a nucleotide, and a combination thereof.

[Claim 25]

The pharmaceutical composition of claim 24 or the use of claim 24, wherein the polymer is selected from the group consisting of a polyethylene glycol, a polypropylene glycol, an ethylene glycol-propylene glycol copolymer, polyoxyethylated polyol, polyvinyl alcohol, a polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer, a lipid polymer, chitin, hyaluronic acid, an oligonucleotide, and a combination thereof.

[Claim 26]

The pharmaceutical composition of claim 23 or the use of claim 23, wherein the linker is a polyethylene glycol.

[Claim 27]

The pharmaceutical composition of claim 22 or the use of claim 22, wherein the immunoglobulin Fc region is aglycosylated.

[Claim 28]

The pharmaceutical composition of claim 22 or the use of claim 22, wherein the immunoglobulin Fc region is selected from the group consisting of:

(a) a CH1 domain, a CH2 domain, a CH3 domain, and a CH4 domain;

(b) a CH1 domain and a CH2 domain;

(c) a CH1 domain and a CH3 domain;

(d) a CH2 domain and a CH3 domain;

(e) a combination between one or at least two domains among a CH1 domain, a CH2 domain, a CH3 domain, and a CH4 domain, and an immunoglobulin hinge region or a part of the hinge region; and

(f) a dimer between each domain of the heavy chain constant region and the light chain constant region.

[Claim 29]

The pharmaceutical composition of claim 22 or the use of claim 22, wherein the polypeptide comprising an immunoglobulin Fc region is in the form of a dimer.

[Claim 30]

The pharmaceutical composition of claim 22 or the use of claim 22, wherein the immunoglobulin Fc region is a native Fc derivative in which the region capable of forming a disulfide bond is deleted, a native Fc derivative in which a part of the amino acid(s) in the N-terminus is removed, a native Fc derivative in which a methionine residue is added to the N-terminus, a native Fc derivative in which a complement-binding site is deleted, or a native Fc derivative in which an antibody dependent cell mediated cytotoxicity (ADCC) site is deleted.

[Claim 31]

The pharmaceutical composition of claim 22 or the use of claim 22, wherein the immunoglobulin Fc region is derived from an immunoglobulin selected from the group consisting of IgG, IgA, IgD, IgE, and IgM.

[Claim 32]

The pharmaceutical composition of claim 31 or the use of claim 31, wherein the immunoglobulin Fc region is an IgG4 Fc region.

[Claim 33]

The pharmaceutical composition of claim 22 or the use of claim 22, wherein the immunoglobulin Fc region is an aglycosylated Fc region derived from human IgG4.

[Claim 34]

The pharmaceutical composition of claim 23 or the use of claim 23, wherein the linker is linked to a cysteine residue of a peptide comprising the amino acid sequence of General Formula 1.

[Claim 35]

The pharmaceutical composition of claim 23 or the use of claim 23, wherein the linker is respectively linked to the peptide moiety and the biocompatible material moiety through covalent bonds, which are respectively formed by reacting one end of the linker with an amine group or thiol group of the biocompatible material moiety

and reacting the other end of the linker with an amine group or thiol group of the peptide moiety including the amino acid sequence of General Formula 1.

[Claim 36]

An isolated peptide comprising the amino acid sequence of the following General Formula 2:

Y-Aib-QGTF-X7-SD-X10-S-X12-Y-L-X15-X16-X17-R-A-X20-X21-F-V-X24-W-L-M-N-T-X30 (General Formula 2, SEQ ID NO: 46)

wherein, in General Formula 2,
X7 is threonine (T), valine (V), or cysteine (C);
X10 is tyrosine (Y) or cysteine (C);
X12 is lysine (K) or cysteine (C);
X15 is aspartic acid (D) or cysteine (C);
X16 is glutamic acid (E) or serine (S);
X17 is lysine (K) or arginine (R);
X20 is glutamine (Q) or lysine (K);
X21 is aspartic acid (D) or glutamic acid (E);
X24 is valine (V) or glutamine (Q); and
X30 is cysteine (C) or is absent,
with the proviso that the peptides corresponding to SEQ ID NOS: 19, 33, 49, and 50 are excluded from the isolated peptides comprising the amino acid sequence of General Formula 2.

[Claim 37]

The peptide of claim 36, wherein, in General Formula 2, X16 is glutamic acid, X20 is lysine, and the side chains of X16 and X20 form a lactam ring.

[Claim 38]

The peptide of claim 36, wherein the C-terminus of the peptide comprising the amino acid sequence of General Formula 2 is amidated.

[Claim 39]

The peptide of claim 36, wherein the C-terminus of the peptide comprising the amino acid sequence of General Formula 2 is unmodified.

[Claim 40]

The peptide of claim 36, wherein the peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 12, 13, 15, and 36 to 44.

[Claim 41]

An isolated conjugate comprising a peptide moiety and a biocompatible material moiety which is linked to the peptide moiety, wherein the peptide moiety is the same sequence as that of amino acid sequence of the following General Formula 2 or a sequence including the same:

Y-Aib-QGTF-X7-SD-X10-S-X12-Y-L-X15-X16-X17-R-A-X20-X21-F-V-X24-W-L-M-N-T-X30 (General Formula 2, SEQ ID NO: 46)

wherein, in General Formula 2,
X7 is threonine (T), valine (V), or cysteine (C);
X10 is tyrosine (Y) or cysteine (C);
X12 is lysine (K) or cysteine (C);
X15 is aspartic acid (D) or cysteine (C);
X16 is glutamic acid (E) or serine (S);
X17 is lysine (K) or arginine (R);
X20 is glutamine (Q) or lysine (K);
X21 is aspartic acid (D) or glutamic acid (E);
X24 is valine (V) or glutamine (Q); and
X30 is cysteine (C) or is absent.

[Claim 42]

The isolated conjugate of claim 41, wherein the biocompatible material moiety is selected from the group consisting of a polymer, fatty acid, cholesterol, albumin and a fragment thereof, an albumin-binding material, a polymer of repeating units of a particular amino acid sequence, an antibody, an antibody fragment, an FcRn-binding material, *in vivo* connective tissue or a derivative thereof, a nucleotide, fibronectin, transferrin, a saccharide, heparin, and elastin.

[Claim 43]

The isolated conjugate of claim 42, wherein the polymer is selected from the group consisting of a polyethylene glycol, a polypropylene glycol, an ethylene glycol-propylene glycol copolymer, polyoxyethylated polyol, polyvinyl alcohol, a polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer, a lipid polymer, chitin, hyaluronic acid, an oligonucleotide, and a combination thereof.

[Claim 44]

The isolated conjugate of claim 42, wherein the FcRn-binding material is a polypeptide comprising an immunoglobulin Fc region.

[Claim 45]

The isolated conjugate of claim 41, wherein the peptide moiety and the biocompatible material moiety are covalently linked with each other through a linker.

[Claim 46]

The isolated conjugate of claim 45, wherein the linker is selected from the group consisting of a peptide, fatty acid, a saccharide, a polymer, a low molecular weight compound, a nucleotide, and a combination thereof.

[Claim 47]

The isolated conjugate of claim 46, wherein the polymer is selected from the group consisting of a polyethylene glycol, a polypropylene glycol, an ethylene glycol-propylene glycol copolymer, polyoxyethylated polyol, polyvinyl alcohol, a polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer, a lipid polymer, chitin, hyaluronic acid, an oligonucleotide, and a combination thereof.

[Claim 48]

A pharmaceutical composition for use in therapy for preventing or treating hypoglycemia, wherein the pharmaceutical composition comprises

(i) the isolated peptide according to any one of claims 36 to 40 or the isolated conjugate according to any one of claims 41 to 47; and (ii) a pharmaceutically acceptable excipient.

[Claim 49]

Use of a pharmaceutical composition in the manufacture of a medicament for preventing or treating hypoglycemia, wherein the pharmaceutical composition comprises

(i) the isolated peptide according to any one of claims 36 to 40 or the isolated conjugate according to any one of claims 41 to 47; and

(ii) a pharmaceutically acceptable excipient.

[Claim 50]

A pharmaceutical composition for use in therapy for preventing or treating metabolic syndrome, wherein the pharmaceutical composition comprises

(i) the isolated peptide according to any one of claims 36 to 40 or the isolated conjugate according to any one of claims 41 to 47; and (ii) a pharmaceutically acceptable excipient.

[Claim 51]

Use of a pharmaceutical composition in the manufacture of a medicament for preventing or treating metabolic syndrome, wherein the pharmaceutical composition comprises:

(i) the isolated peptide according to any one of claims 36 to 40 or the isolated conjugate according to any one of claims 41 to 47; and

(ii) a pharmaceutically acceptable excipient.

[Claim 52]

The pharmaceutical composition according to claim 50 or the use according to claim 51, further comprising at least one compound or material having a therapeutic activity for metabolic syndrome.

[Claim 53]

The pharmaceutical composition according to claim 50 or the use according to claim 51, wherein the pharmaceutical composition is to be administered in combination with at least one compound or material having a therapeutic activity for metabolic syndrome.

[Claim 54]

The pharmaceutical composition according to claim 52 or 53 or the use according to claim 52 or 53, wherein the compound or material having a therapeutic activity for metabolic syndrome is selected from the group consisting of an insulinotropic peptide, a glucagon like peptide-1 (GLP-1) receptor agonist, a leptin receptor agonist, a dipeptidyl peptidase-IV (DPP-IV) inhibitor, a Y5 receptor antagonist, a melanin-concentrating hormone (MCH) receptor antagonist, a Y2/4 receptor agonist, a melanocortin 3/4 (MC 3/4) receptor agonist, a gastric/pancreatic lipase inhibitor, an agonist of 5-hydroxytryptamine receptor 2C (5HT2C, G-protein coupled), a β3A receptor agonist, an amylin receptor agonist, a ghrelin antagonist, a ghrelin receptor antagonist, a peroxisome proliferator-activated receptor alpha (PPARα) agonist, a peroxisome proliferator-activated receptor delta (PPARδ) agonist, a Farnesoid X receptor (FXR) agonist, an acetyl-CoA carboxylase inhibitor, a peptide YY, cholecystokinin (CCK), xenin, glicentin, obestatin, secretin, nesfatin, insulin, and a glucose-dependent insulinotropic peptide (GIP).

[Claim 55]

The pharmaceutical composition according to claim 50 or the use according to claim 51, wherein the metabolic syndrome is selected from the group consisting of impaired glucose tolerance, hypercholesterolemia, dyslipidemia, obesity, diabetes, hypertension, nonalcoholic steatohepatitis (NASH), atherosclerosis caused by dyslipidemia, atherosclerosis, arteriosclerosis, coronary heart disease, and stroke.

[Claim 56]

The pharmaceutical composition according according to claim 50 or the use to claim 51, comprising:

(i) a conjugate, which comprises the peptide moiety comprising the amino acid sequence of SEQ ID NO: 37, and a biocompatible material moiety covalently linked to the peptide moiety; and

(ii) a conjugate, which comprises an imidazo-acetyl exendin-4 moiety where the α-carbon of the 1st amino acid of exendin-4 (which is histidine) is deleted and a

biocompatible material moiety covalently linked to the imidazo-acetyl exendin-4 moiety.

[Claim 57]

The pharmaceutical composition according to claim 56 or the use according to claim 56, wherein the peptide moiety comprising the amino acid sequence of SEQ ID NO: 37 and the imidazo-acetyl exendin-4 moiety are respectively linked to their respective biocompatible material moietys through a linker.

[Claim 58]

The pharmaceutical composition according to claim 1, the pharmaceutical composition according to any one of claims 3 to 34 or the use according to any one of claims 2 to 35, wherein the pharmaceutical composition is to be administered to a subject in need thereof for preventing or treating congenital hyperinsulinism.

[Claim 59]

Use of the isolated peptide according to any one of claims 36 to 40 or the isolated conjugate according to any one of claims 41 to 47 for use in the manufacture of a medicament for preventing or treating hypoglycemia, wherein the isolated peptide or the isolated conjugate is to be administered to a subject in need thereof.

[Claim 60]

Use of the isolated peptide according to any one of claims 36 to 40 or the isolated conjugate according to any one of claims 41 to 47 for use in the manufacture of a medicament for preventing or treating metabolic syndromes, wherein the isolated peptide or the isolated conjugate is to be administered to a subject in need thereof.

[Claim 61]

The use according to claim 60, wherein at least one compound or material having a therapeutic activity for metabolic syndrome is to be administered.

[Claim 62]

The use according to claim 61, wherein the isolated peptide or the isolated conjugate and at least one compound or material having a therapeutic activity for metabolic syndrome is to be simultaneously, individually or sequentically administered