treating diabetes mellitus including insulin and a GLP-1/glucagon dual agonist.

[11A] In one aspect, the present invention provides a pharmaceutical composition for treating diabetes mellitus comprising a long-acting insulin conjugate and a long-acting glucagon-like peptide-1 (GLP-1)/glucagon dual agonist conjugate, wherein the long-acting insulin conjugate is a conjugate in which insulin is linked to an immunoglobulin Fc region via a non-peptidyl polymer; and wherein the long-acting GLP-1/glucagon dual agonist conjugate is a conjugate in which GLP-1/glucagon dual agonist is linked to an immunoglobulin Fc region via a non-peptidyl polymer.

[12] Another objective of the present disclosure is to provide a method for preventing or treating diabetes, including administering the composition to a subject at high risk of or having diabetes mellitus.

[12A] In another aspect, the present invention provides the use of the composition as disclosed herein, in the manufacture of a medicament for preventing or treating diabetes, wherein the composition disclosed herein is to be administered to a subject at high risk of or having the diabetes mellitus.

[13]

Advantageous Effects of Invention

[14] The long-acting insulin or its analog conjugate and a long-acting GLP-1/glucagon

Claims

1. A pharmaceutical composition for treating diabetes mellitus comprising a long-acting insulin conjugate and a long-acting glucagon-like peptide-1 (GLP-1)/glucagon dual agonist conjugate, wherein the long-acting insulin conjugate is a conjugate in which insulin is linked to an immunoglobulin Fc region via a non-peptidyl polymer; and wherein the long-acting GLP-1/glucagon dual agonist conjugate is a conjugate in which GLP-1/glucagon dual agonist is linked to an immunoglobulin Fc region via a non-peptidyl polymer.

2. The composition according to claim 1, wherein the insulin is native insulin, rapid-acting insulin, basal insulin, an insulin analog which is an insulin variant comprising substitution, addition, deletion, modification, or a combination thereof of the amino acid sequence of the native insulin, or a fragment thereof and has a blood glucose control functionality *in vivo* which is the same as that of insulin, and the GLP-1/glucagon dual agonist simultaneously activates GLP-1 receptor and glucagon receptors.

3. The composition according to claim 1, wherein the long-acting glucagon-like peptide-1 (GLP-1)/glucagon dual agonist has the amino acid sequence of SEQ ID NO.40 and the amino acid at position 16 and 20 form a ring.

4. The composition according to claim 1, wherein the non-peptidyl polymer is selected from the group consisting of polyethylene glycol, 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, and a combination thereof.

5. The composition according to claim 1, wherein the immunoglobulin Fc region is a glycosylated.

6. The composition according to claim 5, wherein the immunoglobulin Fc region comprises one to four region(s) selected from the group consisting of CH1, CH2, CH3 and CH4 domains.

7. The composition according to claim 6, wherein the immunoglobulin Fc region further comprises a hinge region.

8. The composition according to claim 7, wherein the immunoglobulin Fc region is an Fc region derived from IgG, IgA, IgD, IgE, or IgM.

9. The composition according to claim 8, wherein each domain of the immunoglobulin Fc region is a hybrid of domains having a different origin selected from the group consisting of IgG, IgA, IgD, IgE, and IgM.

10. The composition according to claim 9, wherein the immunoglobulin Fc region is a dimer or a multimer consisting of single-chain immunoglobulins consisting of domains having the same origin.

11. The composition according to claim 1, wherein the composition further comprises a pharmaceutically acceptable carrier.

12. The composition according to claim 1, wherein the long-acting insulin is a conjugate in which an insulin analog comprising substitution of the 14th amino acid in the insulin A-chain with a glutamic acid and an immunoglobulin Fc region are linked by a non-peptidyl polymer linker, and the long-acting GLP-1/glucagon dual agonist is a conjugate in which a GLP-1/glucagon dual agonist represented by SEQ ID NO: 40 and an immunoglobulin Fc region are linked by a non-peptidyl polymer linker.

13. The composition according to claim 12, wherein the 16th and 20th amino acid of the long-acting glucagon-like peptide-1 (GLP-1)/glucagon dual agonist represented by SEQ ID NO: 40 form a ring.

14. The composition according to claim 12, wherein the non-peptidyl polymer linker is PEG.

15. Use of the composition of any one of claims 1 to 14, in the manufacture of a medicament for preventing or treating diabetes, wherein the composition of any one of claims 1 to 14 is to be administered to a subject at high risk of or having the diabetes mellitus.

16. The use according to claim 15, wherein the administering step is to be performed by combined administration of the long-acting insulin conjugate and the long-acting GLP-1/glucagon dual agonist conjugate.

17. The use according to claim 16, wherein the combined administration is to be performed by simultaneously, sequentially, or reversely administrating the long-acting insulin conjugate and the long-acting GLP-1/glucagon dual agonist conjugate.