CLAIMS

1. An insulin derivative, comprising an insulin parent, an albumin binding residue and a linker Lin, wherein the insulin parent is a natural insulin or insulin analogue, and the albumin binding residue is linked to the insulin parent via the linker Lin, wherein,

the linker Lin is a hydrophilic linker containing at least 10, preferably at least 15, preferably at least 25, preferably at least 30, preferably at least 36, preferably 15–100, preferably 25-90, preferably 30-80, preferably 30–59, preferably 30-54 carbon atoms; or, the linker Lin comprises at least 5 neutral and alkylene glycol-containing amino acid residues; preferably, the linker Lin comprises at least 6 neutral and alkylene glycol-containing amino acid residues; preferably, the linker Lin comprises 5–9 neutral and alkylene glycol-containing amino acid residues; or, the linker Lin comprises alkylene glycol containing at least 15, preferably at least 20, preferably at least 24, preferably 15–50, preferably 20–39 carbon atoms; and

the albumin binding residue contains 20–40 carbon atoms; preferably, the albumin binding residue is a linear or branched lipophilic group containing 20–40 carbon atoms; preferably, the albumin binding residue is a fatty acid or a fatty diacid containing 20–26 carbon atoms (more preferably a fatty acid or a fatty diacid containing 20–24 carbon atoms), wherein formally, a hydroxyl group has been removed from the carboxyl group in the fatty acid ~~and~~or one of the carboxyl groups in the fatty diacid.

2. The insulin derivative according to claim 1, wherein the insulin parent comprises at least one lysine residue, and the albumin binding residue is linked to an amino group of the lysine residue or an N-terminal amino acid residue of the insulin parent via the linker Lin.

3. The insulin derivative according to claim 1 or 2, wherein the insulin derivative further comprises one or more linkers II, wherein the linker II is an acidic amino acid residue, and the linker II is linked between the albumin binding residue and the linker Lin and/or between the linker Lin and the insulin parent, and is preferably linked between the albumin binding residue and the linker Lin.

4. An insulin derivative, being an acylated insulin, wherein an insulin parent of the

acylated insulin is a natural insulin or an insulin analogue and comprises at least one lysine residue, and an acyl moiety of the acylated insulin is linked to an amino group of the lysine residue or an N-terminal amino acid residue of the insulin parent, wherein the acyl moiety is shown as formula (A):

$III\text{-}(II)_m\text{-}(I)_n\text{-}$ (A),

wherein,

m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, and n is 5, 6, 7, 8 or 9;

I is a neutral and alkylene glycol-containing amino acid residue;

II is an acidic amino acid residue;

III is a fatty acid or a fatty diacid containing 20–26 (preferably 20–24) carbon atoms, wherein formally, a hydroxyl group has been removed from the carboxyl group in the fatty acid ~~and~~or one of the carboxyl groups in the fatty diacid;

III, II and I are linked by amide bonds; and

the order of II and I presented in the formula (A) can be interchanged independently; or

the acyl moiety is shown as formula (A'):

$III\text{-}(II)_m\text{-}(I')_{n'}\text{-}$ (A'),

wherein,

m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, and n' is an integer;

I' is a neutral and alkylene glycol-containing amino acid residue;

II is an acidic amino acid residue;

III is a fatty acid or a fatty diacid containing 20–26 (preferably 20–24) carbon atoms, wherein formally, a hydroxyl group has been removed from the carboxyl group in the fatty acid ~~and~~or one of the carboxyl groups in the fatty diacid;

III, II and I' are linked by amide bonds;

the order of II and I' presented in the formula (A') can be interchanged independently; and

the total number of carbon atoms in $(I')_{n'}$ is 15–100, preferably 20–100, preferably 25–90, preferably 30–80, preferably 30–59, preferably 30-54.

~~5. An insulin derivative, being an acylated insulin, wherein an insulin parent of the acylated insulin is a natural insulin or an insulin analogue and comprises at least one lysine residue, and an acyl moiety of the acylated insulin is linked to an amino group~~

~~of the lysine residue or an N-terminal amino acid residue of the insulin parent, wherein the acyl moiety is shown as formula (A):~~

~~III-(II)$_m$-(I)$_n$-----(A),~~

~~wherein,~~

~~m is 0, or an integer from 1 to 10, and n is 5, 6, 7, 8 or 9;~~

~~I is a neutral and alkylene glycol-containing amino acid residue;~~

~~II is an acidic amino acid residue;~~

~~III is a fatty diacid containing 20–26 (preferably 20–24) carbon atoms, wherein formally, a hydroxyl group has been removed from one of the carboxyl groups in the fatty diacid;~~

~~III, II and I are linked by amide bonds;~~

~~the order of II and I presented in the formula (A) can be interchanged independently; or~~

~~the acyl moiety is shown as formula (A'):~~

~~III-(II)$_m$-(I')$_{n'}$-----(A'),~~

~~wherein,~~

~~m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, and n' is an integer;~~

~~I' is a neutral and alkylene glycol-containing amino acid residue;~~

~~II is an acidic amino acid residue;~~

~~III is a fatty diacid containing 20–26 (preferably 20–24) carbon atoms, wherein formally, a hydroxyl group has been removed from one of the carboxyl groups in the fatty diacid;~~

~~III, II and I' are linked by amide bonds;~~

~~the order of II and I' presented in the formula (A') can be interchanged independently; and~~

~~the total number of carbon atoms in (I')$_{n'}$ is 25-90, preferably 30-80, preferably 30-59, preferably 30-54.~~

~~6~~5. The insulin derivative according to claim 4 ~~or 5~~, wherein,

~~n is preferably,~~ n is 5, 6, 7 or 8; and/or

m is an integer from 1 to 6; preferably, m is 1, 2, 3 or 4; preferably, m is 1 or 2; preferably, m is 1; and/or

III is a fatty diacid containing 20–26 (preferably 20–23) carbon atoms, and

preferably III is a fatty diacid containing 20, 21 or 22 carbon atoms, wherein formally, a hydroxyl group has been removed from one of the carboxyl groups in the fatty diacid; and/or

the insulin parent comprises one lysine residue.

~~7~~6. The insulin derivative according to any one of claims 4–5, wherein,

I is: -HN-$(CH_2)_2$-O-$(CH_2)_2$-O-CH_2-CO-, -HN-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-CO-, -HN-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-CO-, -HN-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-CO-, -HN-$(CH_2)_3$-O-$(CH_2)_4$-O-$(CH_2)_3$-NH-CO-, -HN-$(CH_2)_3$-O-$(CH_2)_4$-O-$(CH_2)_3$-NH-CO-CH_2-O-CH_2-CO-, -HN-$(CH_2)_3$-O-$(CH_2)_4$-O-$(CH_2)_3$-NH-CO-$(CH_2)_2$-CO-, -HN-$(CH_2)_2$-O-$(CH_2)_2$-O-CH_2-CO-CH_2-O-CH_2-CO-, -HN-$(CH_2)_3$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_3$-NH-CO-$(CH_2)_2$-CO-, -HN-$(CH_2)_3$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_3$-NH-CO-CH_2-O-CH_2-CO-, -HN-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-NH-CO-$(CH_2)_2$-CO-, -HN-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-NH-CO-CH_2-O-CH_2-CO-, -HN-$(CH_2)_3$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_3$-NH-CO-CH_2-O-CH_2-CO-, -HN-$(CH_2)_3$-O-$(CH_2)_3$-O-CH_2-CO-, or -HN-$(CH_2)_4$-O-$(CH_2)_4$-O-CH_2-CO-; preferably, I is -HN-$(CH_2)_2$-O-$(CH_2)_2$-O-CH_2-CO-; or I' is HN-$(CH_2$-CH_2-O$)_{10}$-CH_2-CO-, -HN-$(CH_2$-CH_2-O$)_{11}$-CH_2-CO-, -HN-$(CH_2$-CH_2-O$)_{12}$-CH_2-CO-, or -HN-$(CH_2$-CH_2-CH_2-O$)_8$-CH_2-CO-; and/or

II is an amino acid residue selected from the group consisting of γGlu, αGlu, βAsp, αAsp, γ-D-Glu, α-D-Glu, β-D-Asp and α-D-Asp; preferably, II is selected from γGlu and βAsp; and/or

III is HOOC-$(CH_2)_{18}$-CO-, HOOC-$(CH_2)_{19}$-CO-, HOOC-$(CH_2)_{20}$-CO-, HOOC-$(CH_2)_{21}$-CO-, HOOC-$(CH_2)_{22}$-CO-, or HOOC-$(CH_2)_{24}$-CO-; preferably, III is HOOC-$(CH_2)_{18}$-CO-, HOOC-$(CH_2)_{19}$-CO-, HOOC-$(CH_2)_{20}$-CO-, HOOC-$(CH_2)_{21}$-CO- or HOOC-$(CH_2)_{22}$-CO-; preferably, III is HOOC-$(CH_2)_{18}$-CO-, HOOC-$(CH_2)_{20}$-CO- or HOOC-$(CH_2)_{22}$-CO-.

~~8~~7. The insulin derivative according to any one of claims 4~~–7~~6, wherein the formula (A) is linked to the amino group of the lysine residue or the N-terminal amino acid residue of the insulin parent via the C-terminal of I, or the formula (A') is linked to the amino group of the lysine residue or the N-terminal amino acid residue of the insulin parent via the C-terminal of I'.

~~9~~8. The insulin derivative according to any one of claims 4~~–8~~7, wherein the acyl moiety is linked to an ε amino group of the lysine residue of the insulin parent.

~~10~~9. The insulin derivative according to any one of claims 1~~–9~~8, wherein the lysine residue of the insulin parent is at position B29.

~~11~~10. The insulin derivative according to any one of claims 1~~–10~~9, wherein the insulin parent is selected from the group consisting of desB30 human insulin; A14E, B16H, B25H, desB30 human insulin; A14E, B16E, B25H, desB30 human insulin; human insulin; A21G human insulin; A21G, desB30 human insulin; and B28D human insulin; preferably, the insulin parent is desB30 human insulin; A14E, B16H, B25H, desB30 human insulin; or A14E, B16E, B25H, desB30 human insulin.

~~12~~11. The insulin derivative according to claim 4 or 5, wherein the acylated insulin is selected from the group consisting of B29K(N(ε)-eicosanedioyl-γGlu-5xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-γGlu-6xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-γGlu-γGlu-5xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-γGlu-γGlu-6xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-5xOEG-γGlu), desB30 human insulin; B29K(N(ε)-eicosanedioyl-6xOEG-γGlu), desB30 human insulin; B29K(N(ε)-eicosanedioyl-6xOEG-γGlu-γGlu), desB30 human insulin; B29K(N(ε)-eicosanedioyl-5xOEG-γGlu-γGlu), desB30 human insulin; B29K(N(ε)-eicosanedioyl-βAsp-5xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-βAsp-6xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-αGlu-5xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-αGlu-6xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-αGlu-αGlu-5xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-αGlu-αGlu-6xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-αAsp-5xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-αAsp-6xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-γGlu-7xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-γGlu-8xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-γGlu-γGlu-7xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-γGlu-γGlu-8xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-7xOEG-γGlu), desB30 human insulin; B29K(N(ε)-eicosanedioyl-8xOEG-γGlu), desB30 human insulin; B29K(N(ε)-eicosanedioyl-8xOEG-γGlu-γGlu), desB30 human insulin; B29K(N(ε)-eicosanedioyl-7xOEG-

γGlu-γGlu), desB30 human insulin; B29K(N(ε)-eicosanedioyl-βAsp-7xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-βAsp-8xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-αGlu-7xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-αGlu-8xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-αGlu-αGlu-7xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-αGlu-αGlu-8xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-αAsp-7xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-αAsp-8xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-γGlu-5xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-γGlu-6xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-γGlu-γGlu-5xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-γGlu-γGlu-6xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-5xOEG-γGlu), desB30 human insulin; B29K(N(ε)-docosanedioyl-6xOEG-γGlu), desB30 human insulin; B29K(N(ε)-docosanedioyl-6xOEG-γGlu-γGlu), desB30 human insulin; B29K(N(ε)-docosanedioyl-5xOEG-γGlu-γGlu), desB30 human insulin; B29K(N(ε)-docosanedioyl-βAsp-5xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-βAsp-6xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-αGlu-5xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-αGlu-6xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-αGlu-αGlu-5xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-αGlu-αGlu-6xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-αAsp-5xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-αAsp-6xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-γGlu-7xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-γGlu-8xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-γGlu-γGlu-7xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-γGlu-γGlu-8xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-7xOEG-γGlu), desB30 human insulin; B29K(N(ε)-docosanedioyl-8xOEG-γGlu), desB30 human insulin; B29K(N(ε)-docosanedioyl-8xOEG-γGlu-γGlu), desB30 human insulin; B29K(N(ε)-docosanedioyl-7xOEG-γGlu-γGlu), desB30 human insulin; B29K(N(ε)-docosanedioyl-βAsp-7xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-βAsp-8xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-αGlu-7xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-αGlu-8xOEG), desB30 human insulin; B29K(N(ε)-

docosanedioyl-αGlu-αGlu-7xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-αGlu-αGlu-8xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-αAsp-7xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-αAsp-8xOEG), desB30 human insulin; B29K(N(ε)-heneicosanoyl-γGlu-5xOEG), desB30 human insulin; B29K(N(ε)-heneicosanoyl-γGlu-6xOEG), desB30 human insulin; B29K(N(ε)-heneicosanoyl-γGlu-7xOEG), desB30 human insulin; B29K(N(ε)-heneicosanoyl-γGlu-8xOEG), desB30 human insulin; B29K(N(ε)-tricosanesanoyl-γGlu-5xOEG), desB30 human insulin; B29K(N(ε)-tricosanesanoyl-γGlu-6xOEG), desB30 human insulin; B29K(N(ε)-tricosanesanoyl-γGlu-7xOEG), desB30 human insulin; B29K(N(ε)-tricosanesanoyl-γGlu-8xOEG), desB30 human insulin; B29K(N(ε)-tetracosanedioyl-γGlu-5xOEG), desB30 human insulin; B29K(N(ε)-tetracosanedioyl-γGlu-6xOEG), desB30 human insulin; B29K(N(ε)-tetracosanedioyl-γGlu-7xOEG), desB30 human insulin; B29K(N(ε)-tetracosanedioyl-γGlu-8xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-γGlu-9xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-γGlu-9xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-γGlu-5xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-γGlu-6xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-γGlu-γGlu-5xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-γGlu-γGlu-6xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-5xOEG-γGlu), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-6xOEG-γGlu), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-6xOEG-γGlu-γGlu), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-5xOEG-γGlu-γGlu), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-βAsp-5xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-βAsp-6xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-αGlu-5xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-αGlu-6xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-αGlu-αGlu-5xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-αGlu-αGlu-

6xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-αAsp-5xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-αAsp-6xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-γGlu-7xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-γGlu-8xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-γGlu-γGlu-7xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-γGlu-γGlu-8xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-7xOEG-γGlu), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-8xOEG-γGlu), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-8xOEG-γGlu-γGlu), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-7xOEG-γGlu-γGlu), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-βAsp-7xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-βAsp-8xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-αGlu-7xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-αGlu-8xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-αGlu-αGlu-7xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-αGlu-αGlu-8xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-αAsp-7xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-αAsp-8xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-γGlu-5xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-γGlu-6xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-γGlu-γGlu-5xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-γGlu-γGlu-6xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-5xOEG-γGlu), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-6xOEG-γGlu), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-6xOEG-γGlu-γGlu), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-5xOEG-γGlu-γGlu), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-βAsp-5xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-βAsp-6xOEG),

desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-αGlu-5xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-αGlu-6xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-αGlu-αGlu-5xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-αGlu-αGlu-6xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-αAsp-5xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-αAsp-6xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-γGlu-7xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-γGlu-8xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-γGlu-γGlu-7xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-γGlu-γGlu-8xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-7xOEG-γGlu), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-8xOEG-γGlu), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-8xOEG-γGlu-γGlu), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-7xOEG-γGlu-γGlu), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-βAsp-7xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-βAsp-8xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-αGlu-7xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-αGlu-8xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-αGlu-αGlu-7xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-αGlu-αGlu-8xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-αAsp-7xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-αAsp-8xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-heneicosanoyl-γGlu-5xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-heneicosanoyl-γGlu-6xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-heneicosanoyl-γGlu-7xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-heneicosanoyl-γGlu-8xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-tricosanesanoyl-γGlu-5xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-tricosanesanoyl-γGlu-6xOEG), desB30 human

insulin; A14E, B16H, B25H, B29K(N(ε)-tricosanesanoyl-γGlu-7xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-tricosanesanoyl-γGlu-8xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-tetracosanedioyl-γGlu-5xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-tetracosanedioyl-γGlu-6xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-tetracosanedioyl-γGlu-7xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-tetracosanedioyl-γGlu-8xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-γGlu-9xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-γGlu-9xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-hexacosanedioyl-γGlu-6xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-γGlu-5xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-γGlu-6xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-γGlu-γGlu-5xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-γGlu-γGlu-6xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-5xOEG-γGlu), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-6xOEG-γGlu), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-6xOEG-γGlu-γGlu), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-5xOEG-γGlu-γGlu), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-βAsp-5xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-βAsp-6xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-αGlu-5xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-αGlu-6xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-αGlu-αGlu-5xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-αGlu-αGlu-6xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-αAsp-5xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-αAsp-6xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-γGlu-7xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-γGlu-8xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-γGlu-γGlu-7xOEG), desB30 human insulin; A14E,

B16E, B25H, B29K(N(ε)-eicosanedioyl-γGlu-γGlu-8xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-7xOEG-γGlu), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-8xOEG-γGlu), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-8xOEG-γGlu-γGlu), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-7xOEG-γGlu-γGlu), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-βAsp-7xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-βAsp-8xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-αGlu-7xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-αGlu-8xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-αGlu-αGlu-7xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-αGlu-αGlu-8xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-αAsp-7xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-αAsp-8xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-γGlu-5xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-γGlu-6xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-γGlu-γGlu-5xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-γGlu-γGlu-6xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-5xOEG-γGlu), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-6xOEG-γGlu), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-6xOEG-γGlu-γGlu), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-5xOEG-γGlu-γGlu), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-βAsp-5xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-βAsp-6xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-αGlu-5xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-αGlu-6xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-αGlu-αGlu-5xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-αGlu-αGlu-6xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-αAsp-5xOEG), desB30 human insulin; A14E, B16E,

B25H, B29K(N(ε)-docosanedioyl-αAsp-6xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-γGlu-7xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-γGlu-8xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-γGlu-γGlu-7xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-γGlu-γGlu-8xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-7xOEG-γGlu), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-8xOEG-γGlu), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-8xOEG-γGlu-γGlu), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-7xOEG-γGlu-γGlu), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-βAsp-7xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-βAsp-8xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-αGlu-7xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-αGlu-8xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-αGlu-αGlu-7xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-αGlu-αGlu-8xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-αAsp-7xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-αAsp-8xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-heneicosanoyl-γGlu-5xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-heneicosanoyl-γGlu-6xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-heneicosanoyl-γGlu-7xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-heneicosanoyl-γGlu-8xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-tricosanesanoyl-γGlu-5xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-tricosanesanoyl-γGlu-6xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-tricosanesanoyl-γGlu-7xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-tricosanesanoyl-γGlu-8xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-tetracosanedioyl-γGlu-5xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-tetracosanedioyl-γGlu-6xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-tetracosanedioyl-γGlu-7xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-tetracosanedioyl-γGlu-

8xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-γGlu-9xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-γGlu-9xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-γGlu-12xPEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-γGlu-12xPEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-γGlu-13xPEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-γGlu-13xPEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-γGlu-14xPEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-γGlu-14xPEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-γGlu-15xPEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-γGlu-15xPEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-γGlu-16xPEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-γGlu-16xPEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-γGlu-17xPEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-γGlu-17xPEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-γGlu-18xPEG), desB30 human insulin; and B29K(N(ε)-eicosanedioyl-γGlu-18xPEG), desB30 human insulin.

~~13. The insulin derivative according to claim 4 or 5 wherein, the the acylated insulin is selected from the group consisting of B29K(N(ε)-eicosanedioyl-γGlu-5xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-γGlu-6xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-γGlu-5xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-γGlu-6xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-γGlu-7xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-γGlu-8xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-γGlu-7xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-γGlu-8xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-γGlu-9xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-γGlu-9xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-γGlu-5xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-γGlu-6xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-γGlu-5xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-γGlu-6xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-γGlu-7xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-γGlu-8xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-**

γGlu-7xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-γGlu-8xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-γGlu-9xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-γGlu-9xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-hexacosanedioyl-γGlu-6xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-γGlu-5xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-γGlu-6xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-γGlu-5xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-γGlu-6xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-γGlu-7xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-γGlu-8xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-γGlu-7xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-γGlu-8xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-eicosanedioyl-γGlu-9xOEG), desB30 human insulin; A14E, B16E, B25H, B29K(N(ε)-docosanedioyl-γGlu-9xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-γGlu-12xPEG), desB30 human insulin; and B29K(N(ε)-eicosanedioyl-γGlu-12xPEG), desB30 human insulin.

14. The insulin derivative according to claim 4 or 5 wherein, the the acylated insulin is selected from the group consisting of B29K(*N*(ε)-eicosanedioyl-γGlu-5×OEG), desB30 human insulin; B29K(*N*(ε)-eicosanedioyl-γGlu-6×OEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-5×OEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-6×OEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-γGlu-8xOEG), desB30 human insulin; B29K(N(ε)-docosanedioyl-γGlu-8xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-γGlu-6xOEG), desB30 human insulin; and A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-γGlu-6xOEG), desB30 human insulin.

1512. A pharmaceutical composition, comprising the insulin derivative according to any one of claims 1–14–11 and one or more pharmaceutically acceptable excipients.;

16. The pharmaceutical composition according to claim 15, wherein the pharmaceutical composition comprises at least 1.5 moles of zinc ions/6 moles of the

insulin derivative; preferably at least 2.2 moles of zinc ions/6 moles of the insulin derivative; preferably at least 3.5 moles of zinc ions/6 moles of the insulin derivative; preferably at least 4.5 moles of zinc ions/6 moles of the insulin derivative; preferably 4.5–12 moles of zinc ions/6 moles of the insulin derivative; more preferably 4.5–10 moles of zinc ions/6 moles of the insulin derivative; more preferably 4.5–8 moles of zinc ions/6 moles of the insulin derivative; more preferably 4.5–7.5 moles of zinc ions/6 moles of the insulin derivative; more preferably 4.5–7.0 moles of zinc ions/6 moles of the insulin derivative; or more preferably 4.5–6.5 moles of zinc ions/6 moles of the insulin derivative; and/or

the pharmaceutical composition has a pH value in the range from 6.5 to 8.5; preferably, the pH value is 6.8–8.2; preferably, the pH value is 7.0–8.2; preferably, the pH value is 7.2–7.6; more preferably, the pH value is 7.4 or 7.6~~.~~;

~~17. The pharmaceutical composition according to claim 16,~~ wherein the pharmaceutical composition further comprises glycerol, phenol, *m*-cresol, NaCl and/or Na_2HPO_4; preferably, the pharmaceutical composition further comprises glycerol, phenol and NaCl; preferably, the pharmaceutical composition further comprises glycerol, phenol, *m*-cresol and NaCl; preferably, the pharmaceutical composition further comprises glycerol, phenol, NaCl and Na_2HPO_4; more preferably, the pharmaceutical composition further comprises glycerol, phenol, *m*-cresol, NaCl and Na_2HPO_4~~.~~;

~~18. The pharmaceutical composition according to claim 17,~~ wherein the content of glycerol is no more than about 2.5% (w/w), preferably no more than about 2% (w/w), preferably about 0.3% to about 2% (w/w), preferably about 0.5% to about 1.8% (w/w), preferably about 0.7% to about 1.8% (w/w), more preferably about 1% to about 1.8% (w/w); and/or

the content of phenol is about 16–80 mM, preferably about 25–75 mM, preferably about 45–70 mM, preferably about 45–65 mM, preferably about 45 mM, about 46 mM, about 47 mM, about 48 mM, about 49 mM, about 50 mM, about 51 mM, about 52 mM, about 53 mM, about 54 mM, about 55 mM, about 56 mM, about 57 mM, about 58 mM, about 59 mM, about 60 mM, about 61 mM, about 62 mM, about 63 mM, about 64 mM or about 65 mM; and/or

the content of *m*-cresol is about 0–35 mM, preferably about 0–19 mM, preferably

about 0–15 mM, preferably about 0 mM, about 1 mM, about 2 mM, about 3 mM, about 4 mM, about 5 mM, about 6 mM, about 7 mM, about 8 mM, about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM or about 15 mM; and/or

the content of NaCl is about 0–150 mM, preferably about 5–120 mM, preferably about 10–120 mM, preferably about 10–100 mM, more preferably about 10–75 mM, more preferably about 10–50 mM, or more preferably about 10–30 mM; and/or

the content of Na_2HPO_4 is about 0–75 mM, preferably about 5–60 mM, preferably less than about 50 mM, more preferably less than about 25 mM, more preferably less than about 15 mM; and/or

the content of insulin derivative is more than about 0.3 mM, preferably more than about 0.6 mM, preferably about 0.3–12 mM, preferably about 0.6–9.0 mM, preferably about 0.6–8.4 mM, preferably about 0.6–7.2 mM, preferably about 0.6–6.0 mM, preferably about 0.6–4.2 mM, preferably about 0.6–3.6 mM, preferably about 0.6–3.0 mM, preferably about 0.6–2.4 mM, preferably about 0.6–2.1 mM, preferably about 0.6–1.2 mM.

~~19. The pharmaceutical composition according to any one of claims 15-18, wherein the insulin derivative is B29K(*N*(ε)-eicosanedioyl-γGlu-5×OEG), desB30 human insulin; B29K(*N*(ε)-eicosanedioyl-γGlu-6×OEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-5×OEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-6×OEG), desB30 human insulin; B29K(*N*(ε)-eicosanedioyl-γGlu-8×OEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-8×OEG), desB30 human insulin; A14E, B16H, B25H, B29K(*N*(ε)-eicosanedioyl-γGlu-6×OEG), desB30 human insulin; or A14E, B16H, B25H, B29K(*N*(ε)-docosanedioyl-γGlu-6×OEG), desB30 human insulin.~~

13~~20~~. A pharmaceutical composition, comprising about 0.6–4.2 mM insulin derivative according to any one of claims 1–114, about 1% to about 1.8% (w/w) glycerol, about 45–65 mM phenol, about 4.5–6.5 moles of zinc ions/6 moles of the insulin derivative, about 10–120 mM sodium chloride and about 0–15 mM *m*-cresol and having a pH value of about 7.0–8.2, wherein preferably, the insulin derivative is B29K(*N*(ε)-eicosanedioyl-γGlu-5×OEG), desB30 human insulin; B29K(*N*(ε)-eicosanedioyl-γGlu-6×OEG), desB30 human insulin; B29K(*N*(ε)-

docosanedioyl-γGlu-5×OEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-6×OEG), desB30 human insulin; B29K(*N*(ε)-eicosanedioyl-γGlu-8×OEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-8×OEG), desB30 human insulin; A14E, B16H, B25H, B29K(*N*(ε)-eicosanedioyl-γGlu-6×OEG), desB30 human insulin; or A14E, B16H, B25H, B29K(*N*(ε)-docosanedioyl-γGlu-6×OEG), desB30 human insulin.

~~21~~14. A pharmaceutical composition, comprising about 0.6 mM or 1.2 mM insulin derivative according to any one of claims 1–~~14~~11, 1.7% (w/w) glycerol, about 45 mM phenol, about 10 mM *m*-cresol, about 6.5 moles of zinc ions/6 moles of the insulin derivative and about 20 mM sodium chloride and having a pH value of about 7.0–8.0, wherein preferably, the insulin derivative is B29K(*N*(ε)-eicosanedioyl-γGlu-5×OEG), desB30 human insulin; B29K(*N*(ε)-eicosanedioyl-γGlu-6×OEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-5×OEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-6×OEG), desB30 human insulin; B29K(*N*(ε)-eicosanedioyl-γGlu-8×OEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-8×OEG), desB30 human insulin; A14E, B16H, B25H, B29K(*N*(ε)-eicosanedioyl-γGlu-6×OEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-γGlu-12xPEG), desB30 human insulin; or A14E, B16H, B25H, B29K(*N*(ε)-docosanedioyl-γGlu-6×OEG), desB30 human insulin;

preferably, the insulin derivative is B29K(N(ε)-eicosanedioyl-γGlu-6xOEG), desB30 human insulin; B29K(N(ε)- docosanedioyl-γGlu-6xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-γGlu-6xOEG), desB30 human insulin; B29K(N(ε)-eicosanedioyl-γGlu-12xPEG), desB30 human insulin or A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-γGlu-6xOEG), desB30 human insulin.

~~22~~15. A pharmaceutical composition, comprising about 0.6–4.2 mM insulin derivative according to any one of claims 1–~~14~~11, about 1% to about 2% (preferably about 1.5%–1.7%) (w/w) glycerol, about 15–60 mM (preferably about 30–60 mM, more preferably about 45–60 mM) phenol, about 1.5–7.0 (preferably about 2.2–4.5) moles of zinc ions/6 moles of the insulin derivative, about 10–120 mM (preferably about 20–50 mM) sodium chloride and about 0–25 mM (preferably about 0–10 mM) *m*-cresol and having a pH value of about 7.0–8.2, wherein preferably, the insulin

derivative is B29K(*N*(ε)-eicosanedioyl-γGlu-5×OEG), desB30 human insulin; B29K(*N*(ε)-eicosanedioyl-γGlu-6×OEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-5×OEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-6×OEG), desB30 human insulin; B29K(*N*(ε)-eicosanedioyl-γGlu-8×OEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-8×OEG), desB30 human insulin; A14E, B16H, B25H, B29K(*N*(ε)-eicosanedioyl-γGlu-6×OEG), desB30 human insulin; or A14E, B16H, B25H, B29K(*N*(ε)-docosanedioyl-γGlu-6×OEG), desB30 human insulin.

~~23~~16. A pharmaceutical composition, comprising about 1.2–1.5 mM insulin derivative according to any one of claims 1–~~14~~11, about 1.5%–1.7% (w/w) glycerol, about 45–60 mM phenol, about 2.2–4.5 moles of zinc ions/6 moles of the insulin derivative and about 20 mM sodium chloride, about 0–10 mM *m*-cresol and having a pH value of about 7.0–8.0, wherein preferably the insulin derivative is B29K(N(ε)-eicosanedioyl-γGlu-5xOEG), desB30 human insulin; B29K(*N*(ε)-eicosanedioyl-γGlu-6×OEG), desB30 human insulin; B29K(N(ε)- docosanedioyl-γGlu-5xOEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-6×OEG), desB30 human insulin; B29K(*N*(ε)-eicosanedioyl-γGlu-8×OEG), desB30 human insulin; B29K(N(ε)- docosanedioyl-γGlu-8xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)- eicosanedioyl -γGlu-6xOEG), desB30 human insulin; or A14E, B16H, B25H, B29K(*N*(ε)-docosanedioyl-γGlu-6×OEG), desB30 human insulin.

~~24~~17. The pharmaceutical composition according to any one of claims ~~15~~12-~~23~~16, further comprising an insulinotropic GLP-1 compound, wherein preferably, the pharmaceutical composition further comprises an insulinotropic GLP-1 compound selected from the group consisting of *N*-ε^{26}-(17-carboxyheptadecanoylamino)-4(*S*)-carboxybutanoyl-[Arg34]GLP-1-(7-37) peptide, *N*-ε^{26}-(17-carboxyheptadecanoylamino)-4(*S*)-carboxybutanoyl-[Gly8, Arg34]GLP-1-(7-37) peptide, *N*-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(17-carboxyheptadecanoylamino)-4(*S*)-carboxybutanoylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8, Arg34]GLP-1-(7-37) peptide, and *N*-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(17-carboxyheptadecanoylamino)-4(*S*)-carboxybutanoylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Gly8, Arg34]GLP-1-(7-37) peptide.

~~25~~18. The pharmaceutical composition according to any one of claims ~~15~~12-~~23~~16, further comprising an insulinotropic GLP-1 compound shown as formula (B) or a pharmaceutically acceptable salt, amide or ester thereof:

$[Acy-(L1)_r-(L2)_q]-G1$ (B),

wherein G1 is a GLP-1 analogue having Arg and Ala or Gly, respectively, at positions corresponding to position 34 and position 8, respectively, of GLP-1(7-37) (SEQ ID NO: 15), and $[Acy-(L1)_r-(L2)_q]$ is a substituent linked to an ε amino group of the Lys residue at position 26 of the GLP-1 analogue, wherein

r is an integer from 1 to 10, and q is 0 or an integer from 1 to 10;

Acy is a fatty diacid containing 20–24 carbon atoms, wherein formally, a hydroxyl group has been removed from one of the carboxyl groups in the fatty diacid;

L1 is an amino acid residue selected from the group consisting of γGlu, αGlu, βAsp, αAsp, γ-D-Glu, α-D-Glu, β-D-Asp and α-D-Asp;

L2 is a neutral and alkylene glycol-containing amino acid residue;

Acy, L1 and L2 are linked by amide bonds; and

the order of L1 and L2 presented in the formula (B) can be interchanged independently.

~~26~~19. The pharmaceutical composition according to claim ~~25~~18, wherein,

G1 is a [Gly8, Arg34]GLP-1-(7-37) peptide (SEQ ID NO: 16) or a [Arg34]GLP-1-(7-37) peptide (SEQ ID NO: 17), and preferably is a [Gly8, Arg34]GLP-1-(7-37) peptide; and/or

r is 1, 2, 3, 4, 5 or 6; preferably, r is 1, 2, 3 or 4; preferably, r is 1 or 2; preferably, r is 1; and/or

q is 0, 1, 2, 3, 4, 5, 6, 7 or 8; preferably, q is 0, 1, 2, 3 or 4; more preferably, q is 0, 1 or 2; and/or

Acy is a fatty diacid containing 20–23 carbon atoms, and preferably Acy is a fatty diacid containing 20, 21 or 22 carbon atoms, wherein formally, a hydroxyl group has been removed from one of the carboxyl groups in the fatty diacid.

~~27~~20. The pharmaceutical composition according to claim ~~25 or 26~~18 or 19, wherein

L2 is: $-HN-(CH_2)_2-O-(CH_2)_2-O-CH_2-CO-$, $-HN-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-CO-$, $-HN-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-$

$(CH_2)_2$-O-$(CH_2)_2$-CO-, -HN-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-CO-, -HN-$(CH_2)_3$-O-$(CH_2)_4$-O-$(CH_2)_3$-NH-CO-, -HN-$(CH_2)_3$-O-$(CH_2)_4$-O-$(CH_2)_3$-NH-CO-CH_2-O-CH_2-CO-, -HN-$(CH_2)_3$-O-$(CH_2)_4$-O-$(CH_2)_3$-NH-CO-$(CH_2)_2$-CO-, -HN-$(CH_2)_2$-O-$(CH_2)_2$-O-CH_2-CO-CH_2-O-CH_2-CO-, -HN-$(CH_2)_3$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_3$-NH-CO-$(CH_2)_2$-CO-, -HN-$(CH_2)_3$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_3$-NH-CO-CH_2-O-CH_2-CO-, -HN-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-NH-CO-$(CH_2)_2$-CO-, -HN-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-NH-CO-CH_2-O-CH_2-CO-, -HN-$(CH_2)_3$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_3$-NH-CO-CH_2-O-CH_2-CO-, -HN-$(CH_2)_3$-O-$(CH_2)_3$-O-CH_2-CO-, or -HN-$(CH_2)_4$-O-$(CH_2)_4$-O-CH_2-CO-; preferably, L2 is -HN-$(CH_2)_2$-O-$(CH_2)_2$-O-CH_2-CO-; and/or

L1 is selected from γGlu and βAsp; preferably, L1 is γGlu; and/or

Acy is HOOC-$(CH_2)_{18}$-CO-, HOOC-$(CH_2)_{19}$-CO-, HOOC-$(CH_2)_{20}$-CO-, HOOC-$(CH_2)_{21}$-CO- or HOOC-$(CH_2)_{22}$-CO-; preferably, Acy is HOOC-$(CH_2)_{18}$-CO-, HOOC-$(CH_2)_{20}$-CO- or HOOC-$(CH_2)_{22}$-CO-.

~~28~~21. The pharmaceutical composition according to any one of claims ~~25-27~~18-20, wherein the Acy, L1 and L2 in the formula (B) are sequentially linked by amide bonds, and the C-terminal of L2 is linked to the ε amino group of the Lys residue at position 26 of the GLP-1 analogue.

~~29~~22. The pharmaceutical composition according to any one of claims ~~25-27~~18-20, wherein the insulinotropic GLP-1 compound is selected from the group consisting of:

N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(19-carboxynonadecanoylamino)-4(*S*)-carboxybutanoylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Gly8, Arg34]GLP-1-(7-37) peptide,

N-ε^{26}-[2-(2-[2-(4-[19-carboxynonadecanoylamino]-4(*S*)-carboxybutanoylamino)ethoxy]ethoxy)acetyl][Gly8, Arg34]GLP-1-(7-37) peptide,

N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(21-carboxyheneicosanoylamino)-4(*S*)-carboxybutanoylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Gly8, Arg34]GLP-1-(7-37) peptide,

N-ε^{26}-[2-(2-[2-(4-[21-carboxyheneicosanoylamino]-4(*S*)-carboxybutanoylamino)ethoxy]ethoxy)acetyl][Gly8, Arg34]GLP-1-(7-37) peptide,

N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(23-carboxytricosanoylamino)-4(*S*)-carboxybutanoylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Gly8, Arg34]GLP-1-(7-37) peptide,
N-ε^{26}-[2-(2-[2-(4-[23-carboxytricosanoylamino]-4(*S*)-carboxybutanoylamino)ethoxy]ethoxy)acetyl][Gly8, Arg34]GLP-1-(7-37) peptide,
N-ε^{26}-(23-carboxytricosanoylamino)-4(*S*)-carboxybutanoyl-[Gly8, Arg34]GLP-1-(7-37) peptide,
N-ε^{26}-(19-carboxynonadecanoylamino)-4(*S*)-carboxybutanoyl-[Gly8, Arg34]GLP-1-(7-37) peptide,
N-ε^{26}-(21-carboxyheneicosanoylamino)-4(*S*)-carboxybutanoyl-[Gly8, Arg34]GLP-1-(7-37) peptide,
N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(19-carboxynonadecanoylamino)-4(*S*)-carboxybutanoylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Arg34]GLP-1-(7-37) peptide,
N-ε^{26}-[2-(2-[2-(4-[19-carboxynonadecanoylamino]-4(*S*)-carboxybutanoylamino)ethoxy]ethoxy)acetyl][Arg34]GLP-1-(7-37) peptide,
N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(21-carboxyheneicosanoylamino)-4(*S*)-carboxybutanoylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Arg34]GLP-1-(7-37) peptide,
N-ε^{26}-[2-(2-[2-(4-[21-carboxyheneicosanoylamino]-4(*S*)-carboxybutanoylamino)ethoxy]ethoxy)acetyl][Arg34]GLP-1-(7-37) peptide,
N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(23-carboxytricosanoylamino)-4(*S*)-carboxybutanoylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Arg34]GLP-1-(7-37) peptide,
N-ε^{26}-[2-(2-[2-(4-[23-carboxytricosanoylamino]-4(*S*)-carboxybutanoylamino)ethoxy]ethoxy)acetyl][Arg34]GLP-1-(7-37) peptide,
N-ε^{26}-(23-carboxytricosanoylamino)-4(*S*)-carboxybutanoyl-[Arg34]GLP-1-(7-37) peptide,
N-ε^{26}-(19-carboxynonadecanoylamino)-4(*S*)-carboxybutanoyl-[Arg34]GLP-1-(7-37) peptide,
N-ε^{26}-(21-carboxyheneicosanoylamino)-4(*S*)-carboxybutanoyl-[Arg34]GLP-1-(7-37) peptide,

N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(20-carboxyeicosanoylamino)-4(*S*)-carboxybutanoylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Gly8, Arg34]GLP-1-(7-37) peptide,
N-ε^{26}-[2-(2-[2-(4-[20-carboxyeicosanoylamino]-4(*S*)-carboxybutanoylamino)ethoxy]ethoxy)acetyl][Gly8, Arg34]GLP-1-(7-37) peptide,
N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(22-carboxydocosanoylamino)-4(*S*)-carboxybutanoylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Gly8, Arg34]GLP-1-(7-37) peptide,
N-ε^{26}-[2-(2-[2-(4-[22-carboxydocosanoylamino]-4(*S*)-carboxybutanoylamino)ethoxy]ethoxy)acetyl][Gly8, Arg34]GLP-1-(7-37) peptide,
N-ε^{26}-(20-carboxyeicosanoylamino)-4(*S*)-carboxybutanoyl-[Gly8, Arg34]GLP-1-(7-37) peptide,
N-ε^{26}-(22-carboxydocosanoylamino)-4(*S*)-carboxybutanoyl-[Gly8, Arg34]GLP-1-(7-37) peptide,
N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(20-carboxyeicosanoylamino)-4(*S*)-carboxybutanoylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Arg34]GLP-1-(7-37) peptide,
N-ε^{26}-[2-(2-[2-(4-[20-carboxyeicosanoylamino]-4(*S*)-carboxybutanoylamino)ethoxy]ethoxy)acetyl][Arg34]GLP-1-(7-37) peptide,
N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(22-carboxydocosanoylamino)-4(*S*)-carboxybutanoylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Arg34]GLP-1-(7-37) peptide,
N-ε^{26}-[2-(2-[2-(4-[22-carboxydocosanoylamino]-4(*S*)-carboxybutanoylamino)ethoxy]ethoxy)acetyl][Arg34]GLP-1-(7-37) peptide,
N-ε^{26}-(20-carboxyeicosanoylamino)-4(*S*)-carboxybutanoyl-[Arg34]GLP-1-(7-37) peptide, and
N-ε^{26}-(22-carboxydocosanoylamino)-4(*S*)-carboxybutanoyl-[Arg34]GLP-1-(7-37) peptide.

~~30. The pharmaceutical composition according to claim 25, wherein the insulinotropic GLP-1 compound is selected from the group consisting of~~

~~*N*-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(19-carboxynonadecanoylamino)-4(*S*)-carboxybutanoylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Gly8, Arg34]GLP-1-(7-37) peptide,~~

~~*N*-ε^{26}-[2-(2-[2-(4-[19-carboxynonadecanoylamino]-4(*S*)-carboxybutanoylamino)ethoxy]ethoxy)acetyl][Gly8, Arg34]GLP-1-(7-37) peptide,~~

~~*N*-ε^{26}-(19-carboxynonadecanoylamino)-4(*S*)-carboxybutanoyl-[Gly8, Arg34]GLP-1-(7-37) peptide,~~

~~*N*-ε^{26}-(19-carboxynonadecanoylamino)-4(*S*)-carboxybutanoyl-[Arg34]GLP-1-(7-37) peptide,~~

~~*N*-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(21-carboxyheneicosanoylamino)-4(*S*)-carboxybutanoylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Gly8, Arg34]GLP-1-(7-37) peptide, and~~

~~*N*-ε^{26}-[2-(2-[2-(4-[21-carboxyheneicosanoylamino]-4(*S*)-carboxybutanoylamino)ethoxy]ethoxy)acetyl][Gly8, Arg34]GLP-1-(7-37) peptide; preferably, the insulinotropic GLP-1 compound is:~~

~~*N*-ε^{26}-[2-(2-[2-(4-[19-carboxynonadecanoylamino]-4(*S*)-carboxybutanoylamino)ethoxy]ethoxy)acetyl][Gly8, Arg34]GLP-1-(7-37) peptide, or *N*-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(21-carboxyheneicosanoylamino)-4(*S*)-carboxybutanoylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Gly8, Arg34]GLP-1-(7-37) peptide.~~

~~31~~23. The pharmaceutical composition according to any one of claims ~~15~~12 ~~23~~-16, further comprising a rapid-acting insulin.

~~32~~24. The pharmaceutical composition according to claim ~~31~~23, wherein the rapid-acting insulin is one or more insulins selected from Asp^{B28} human insulin, Lys^{B28}Pro^{B29} human insulin, Lys^{B3}Glu^{B29} human insulin, human insulin and desB30 human insulin; preferably, the rapid-acting insulin is Asp^{B28} human insulin, Lys^{B28}Pro^{B29} human insulin, Lys^{B3}Glu^{B29} human insulin, human insulin or desB30 human insulin.

~~33~~25. The pharmaceutical composition according to claim ~~31 or 32~~23 or 24, wherein the molar ratio of the insulin derivative to the rapid-acting insulin is about 60:3 to about 0.5:3, preferably about 57:3 to about 1:3, preferably about 55:3 to about 1.2:3, preferably about 50:3 to about 1.5:3, preferably about 40:3 to about 1.5:3, preferably

about 30:3 to about 1.5:3, preferably about 27:3 to about 1.5:3, preferably about 25:3 to about 1.5:3, preferably about 22:3 to about 1.5:3, preferably about 20:3 to about 1.5:3, preferably about 17:3 to about 1.5:3, preferably about 15:3 to about 1.5:3, preferably about 12:3 to about 1.5:3, preferably about 10:3 to about 1.5:3, preferably about 9:3 to about 1.5:3, preferably about 8:3 to about 1.5:3, preferably about 7:3 to about 1.5:3, preferably about 6.9:3 to about 1.5:3, preferably about 6.8:3 to about 1.5:3, preferably about 6.5:3 to about 1.5:3, preferably about 6.3:3 to about 1.5:3, preferably about 6:3 to about 1.5:3, preferably about 5.8:3 to about 1.5:3, preferably about 5.5:3 to about 1.5:3, preferably about 5.3:3 to about 1.5:3, preferably about 5:3 to about 1.5:3, preferably about 4.8:3 to about 1.5:3, preferably about 4.5:3 to about 1.5:3, preferably about 4.2:3 to about 1.5:3, preferably about 4:3 to about 1.5:3, preferably about 3.9:3 to about 1.5:3, preferably about 3.8:3 to about 1.5:3, preferably about 3.5:3 to about 1.5:3, preferably about 3.2:3 to about 1.5:3, preferably about 3:3 to about 1.5:3, preferably about 2.8:3 to about 1.5:3, preferably about 2.5:3 to about 1.5:3, preferably about 15:3 to about 2:3, preferably about 12:3 to about 2:3, preferably about 10:3 to about 2:3, preferably about 9:3 to about 2:3, preferably about 8:3 to about 2:3, preferably about 7:3 to about 2:3, preferably about 6.9:3 to about 2:3, preferably about 6.8:3 to about 2:3, preferably about 6.5:3 to about 2:3, preferably about 6.3:3 to about 2:3, preferably about 6:3 to about 2:3, preferably about 5.8:3 to about 2:3, preferably about 5.5:3 to about 2:3, preferably about 5.3:3 to about 2:3, preferably about 5:3 to about 2:3, preferably about 4.8:3 to about 2:3, preferably about 4.5:3 to about 2:3, preferably about 4.2:3 to about 2:3, preferably about 4:3 to about 2:3, preferably about 3.9:3 to about 2:3, preferably about 3.8:3 to about 2:3, preferably about 3.5:3 to about 2:3, preferably about 3.2:3 to about 2:3, preferably about 3:3 to about 2:3, preferably about 15:3 to about 2.4:3, preferably about 12:3 to about 2.4:3, preferably about 10:3 to about 2.4:3, preferably about 9:3 to about 2.4:3, preferably about 8:3 to about 2.4:3, preferably about 7:3 to about 2.4:3, preferably about 6.9:3 to about 2.4:3, preferably about 6.8:3 to about 2.4:3, preferably about 6.5:3 to about 2.4:3, preferably about 6.3:3 to about 2.4:3, preferably about 6:3 to about 2.4:3, preferably about 5.8:3 to about 2.4:3, preferably about 5.5:3 to about 2.4:3, preferably about 5.3:3 to about 2.4:3, preferably about 5:3 to about 2.4:3, preferably about 4.8:3 to about 2.4:3,

preferably about 4.5:3 to about 2.4:3, preferably about 4.2:3 to about 2.4:3, preferably about 4:3 to about 2.4:3, preferably about 3.9:3 to about 2.4:3, preferably about 3.8:3 to about 2.4:3, preferably about 3.5:3 to about 2.4:3, preferably about 3.2:3 to about 2.4:3, preferably about 3:3 to about 2.4:3, more preferably about 1.5:3, more preferably about 2:3, more preferably about 2.5:3, more preferably about 2.75:3, more preferably about 3:3.

~~34~~26. The pharmaceutical composition according to any one of claims ~~31-33~~23-25, wherein the insulin derivative is the insulin derivative according to ~~any one of~~ claim~~s~~ ~~12-14~~11; preferably, the insulin derivative is B29K(*N*(ε)-eicosanedioyl-γGlu-5×OEG), desB30 human insulin; B29K(*N*(ε)-eicosanedioyl-γGlu-6×OEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-5×OEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-6×OEG), desB30 human insulin; B29K(*N*(ε)-eicosanedioyl-γGlu-7×OEG), desB30 human insulin; B29K(*N*(ε)-eicosanedioyl-γGlu-8×OEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-7×OEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-8×OEG), desB30 human insulin; B29K(*N*(ε)-eicosanedioyl-γGlu-9×OEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-9×OEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-γGlu-5xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-γGlu-6xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(*N*(ε)-docosanedioyl-γGlu-5×OEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-γGlu-6xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(*N*(ε)-eicosanedioyl-γGlu-7×OEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-γGlu-8xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-γGlu-7xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-γGlu-8xOEG), desB30 human insulin; A14E, B16H, B25H, B29K(N(ε)-eicosanedioyl-γGlu-9xOEG), desB30 human insulin; or A14E, B16H, B25H, B29K(N(ε)-docosanedioyl-γGlu-9xOEG), desB30 human insulin; more preferably, the insulin derivative is B29K(N(ε)- docosanedioyl-γGlu-6xOEG), desB30 human insulin or B29K(*N*(ε)-eicosanedioyl-γGlu-6×OEG), desB30 human insulin.

~~35~~27. The pharmaceutical composition according to any one of claims ~~31-34~~23-26, comprising about 0.09–0.36 mM insulin derivative, about 0.18 mM Asp^{B28} human insulin, about 0.85% to about 2.0% (w/w) glycerol, about 15–70 mM phenol, about 8–14 moles of zinc ions/6 moles of the insulin derivative, about 10–120 mM sodium chloride and about 0–15 mM *m*-cresol and having a pH value of about 7.0–8.2, wherein the insulin derivative is B29K(*N*(ε)-eicosanedioyl-γGlu-5×OEG), desB30 human insulin; B29K(*N*(ε)-eicosanedioyl-γGlu-6×OEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-5×OEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-6×OEG), desB30 human insulin; B29K(*N*(ε)-eicosanedioyl-γGlu-8×OEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-8×OEG), desB30 human insulin; A14E, B16H, B25H, B29K(*N*(ε)-eicosanedioyl-γGlu-6×OEG), desB30 human insulin; or A14E, B16H, B25H, B29K(*N*(ε)-docosanedioyl-γGlu-6×OEG), desB30 human insulin.

~~36~~28. The pharmaceutical composition according to any one of claims ~~31-35~~23-27, comprising about 0.165–0.18 mM insulin derivative, about 0.18 mM Asp^{B28} human insulin, about 1.5%–1.7% (w/w) glycerol, about 20–30 mM phenol, about 9–12 moles of zinc ions/6 moles of the insulin derivative, about 20–75 mM sodium chloride and about 10–15 mM *m*-cresol and having a pH value of about 7.0–8.2, wherein the insulin derivative is B29K(*N*(ε)-eicosanedioyl-γGlu-5×OEG), desB30 human insulin; B29K(*N*(ε)-eicosanedioyl-γGlu-6×OEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-5×OEG), desB30 human insulin; B29K(*N*(ε)-docosanedioyl-γGlu-6×OEG), desB30 human insulin; B29K(*N*(ε)-eicosanedioyl-γGlu-8×OEG), desB30 human insulin; or B29K(*N*(ε)-docosanedioyl-γGlu-8×OEG), desB30 human insulin.

~~37. An insulin derivative according to any one of claims 1–14 or a pharmaceutical composition according to any one of claims 15-36 for use as a medicament.~~

~~38~~29. An insulin derivative according to any one of claims 1–~~14~~–11 or a pharmaceutical composition according to any one of claims ~~15~~12-~~36~~ 28for use as a medicament for treating or preventing diabetes, hyperglycemia, and/or impaired glucose tolerance.

~~39. An insulin derivative according to any one of claims 1–14 or a pharmaceutical~~

~~composition according to any one of claims 15-36 for use in treating or preventing diabetes, hyperglycemia, and/or impaired glucose tolerance.~~

~~40. Use of the insulin derivative according to any one of claims 1-14 or the pharmaceutical composition according to any one of claims 15-36 for the manufacture of a medicament, wherein preferably, the medicament is used for treating or preventing diabetes, hyperglycemia, and/or impaired glucose tolerance.~~

~~41. The use according to claim 40, wherein the medicament is used for treating diabetes; the insulin derivative is administered to the same patient every other day or at a lower frequency, and on average, the insulin derivative is not administered to the same patient at a higher frequency during a period of at least 1 month, 6 months or 1 year.~~

~~42. The use according to any one of claim 40 or 41, wherein the medicament is used for treating diabetes; the insulin derivative is administered twice a week or at a lower frequency, and on average, the insulin derivative is not administered to the same patient at a higher frequency during a period of at least 1 month, 6 months or 1 year.~~

~~43. The use according to any one of claims 40-42, wherein the medicament is used for treating diabetes; the insulin derivative is administered once a week or at a lower frequency, and on average, the insulin derivative is not administered to the same patient at a higher frequency during a period of at least 1 month, 6 months or 1 year.~~

~~44. A method for treating or preventing diabetes, hyperglycemia, and/or impaired glucose tolerance, wherein the method comprises administering a therapeutically effective amount of the insulin derivative according to any one of claims 1-14 or the pharmaceutical composition according to any one of claims 15-36.~~

~~45~~30. A method for increasing capability of an insulin derivative to bind to an insulin receptor in the presence of albumin or increasing potency of an insulin derivative, wherein the method comprises:

linking an albumin binding residue to a natural insulin or an insulin analogue via a linker Lin to obtain the insulin derivative, wherein linker Lin is a hydrophilic linker containing at least 10, preferably at least 15, preferably at least 25, preferably at least 30, preferably at least 36, preferably 25–90, preferably 30–80, preferably 30–59, or preferably 30–54 carbon atoms; the albumin binding residue contains 20–40

carbon atoms; preferably, the albumin binding residue comprises a linear or branched lipophilic group containing 20–40 carbon atoms; preferably, the albumin binding residue is a fatty acid or a fatty diacid containing 20–26 carbon atoms (more preferably a fatty acid or a fatty diacid containing 20–24 carbon atoms), wherein formally, a hydroxyl group has been removed from the carboxyl group in the fatty acid or one of the carboxyl groups in the fatty diacid;

or

modifying a natural insulin or an insulin analogue with formula (A) or formula (A') to obtain the insulin derivative,

$III\text{-}(II)_m\text{-}(I)_n\text{-}$ (A), wherein,

m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, and n is 5, 6, 7, 8, or 9;

I is a neutral and alkylene glycol-containing amino acid residue;

II is an acidic amino acid residue;

III is an albumin binding residue comprising a linear or branched lipophilic group containing 20–40 carbon atoms; preferably, III is a fatty acid or a fatty diacid containing 20–26 carbon atoms (more preferably a fatty acid or a fatty diacid containing 20–24 carbon atoms), wherein formally, a hydroxyl group has been removed from the carboxyl group in the fatty acid and one of the carboxyl groups in the fatty diacid;

III, II and I are linked by amide bonds; and

the order of II and I presented in the formula (A) can be interchanged independently;

$III\text{-}(II)_m\text{-}(I')_{n'}\text{-}$ (A'),

wherein,

m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, and n' is an integer;

I' is a neutral and alkylene glycol-containing amino acid residue;

II is an acidic amino acid residue;

III is an albumin binding residue comprising a linear or branched lipophilic group containing 20–40 carbon atoms; preferably, III is a fatty acid or a fatty diacid containing 20–26 carbon atoms (more preferably a fatty acid or a fatty diacid containing 20–24 carbon atoms), wherein formally, a hydroxyl group has been removed from the carboxyl group in the fatty acid and one of the carboxyl groups in the fatty diacid;

III, II and I' are linked by amide bonds;

the order of II and I' presented in the formula (A') can be interchanged independently; and

the total number of carbon atoms of $(I')_{n'}$ is 15–100, preferably 20–100, preferably 25–90, preferably 30–80, preferably 30–59, preferably 30-54.

~~46. A method for increasing potency of an insulin derivative, wherein the method comprises:~~

~~linking an albumin binding residue to a natural insulin or an insulin analogue via a linker Lin to obtain the insulin derivative, wherein the linker Lin is a hydrophilic linker containing at least 10, preferably at least 15, preferably at least 25, preferably at least 30, preferably at least 36, preferably 15-100, preferably 25-90, preferably 30-80, preferably 30-59, preferably 30-54 carbon atoms; the albumin binding residue contains 20-40 carbon atoms; preferably, the albumin binding residue contains a linear or branched lipophilic group containing 20-40 carbon atoms; preferably, the albumin binding residue is a fatty acid or a fatty diacid containing 20-26 carbon atoms (more preferably a fatty acid or a fatty diacid containing 20-24 carbon atoms), wherein formally, a hydroxyl group has been removed from the carboxyl group in the fatty acid or one of the carboxyl groups in the fatty diacid; or modifying a natural insulin or an insulin analogue with formula (A) or formula (A') to obtain the insulin derivative, III-$(II)_m$-$(I)_n$- (A), wherein,~~

~~m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, and n is 5, 6, 7, 8 or 9;~~

~~I is a neutral and alkylene glycol-containing amino acid residue;~~

~~II is an acidic amino acid residue;~~

~~III is an albumin binding residue comprising a linear or branched lipophilic group containing 20-40 carbon atoms; preferably, III is a fatty acid or a fatty diacid containing 20-26 carbon atoms (more preferably a fatty acid or a fatty diacid containing 20-24 carbon atoms), wherein formally, a hydroxyl group has been removed from the carboxyl group in the fatty acid and one of the carboxyl groups in the fatty diacid;~~

~~III, II and I are linked by amide bonds; and~~

~~the order of II and I presented in the formula (A) can be interchanged independently;~~

~~(A') is III-$(II)_m$-$(I')_{n'}$- (A'),~~

~~wherein,~~

~~m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, and n' is an integer;~~

~~I' is a neutral and alkylene glycol-containing amino acid residue;~~

~~II is an acidic amino acid residue;~~

~~III is an albumin binding residue comprising a linear or branched lipophilic group containing 20-40 carbon atoms; preferably, III is a fatty acid or a fatty diacid containing 20-26 carbon atoms (more preferably a fatty acid or a fatty diacid containing 20-24 carbon atoms), wherein formally, a hydroxyl group has been removed from the carboxyl group in the fatty acid and one of the carboxyl groups in the fatty diacid;~~

~~III, II and I' are linked by amide bonds;~~

~~the order of II and I' presented in the formula (A') can be interchanged independently; and~~

~~the total number of carbon atoms of $(I')_{n'}$ is 15-100, preferably 20-100, preferably 25-90, preferably 30-80, preferably 30-59, preferably 30-54.~~

~~47~~31. The method according to claim ~~45 or 46~~30, wherein m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and / or

III is a fatty diacid containing 20-24 carbon atoms, wherein formally, a hydroxyl group has been removed from one of the carboxyl groups in the fatty diacid.

~~48~~32. The method according to claim ~~45 or 46~~30, wherein the natural insulin or insulin analogue comprises at least one lysine residue, and the linker Lin, the formula (A) or the formula (A') is linked to an amino group of the lysine residue or the N-terminal amino acid residue of the natural insulin or an insulin analogue~~insulin parent~~.

~~49~~33. The method according to claim ~~45 or 46~~30, wherein,

n is 5, 6, 7 or 8; and/or

m is 1, 2, 3, 4, 5 or 6; preferably, preferably, m is 1, 2, 3 or 4; preferably, m is 1 or 2; preferably, m is 1; and/or

III is a fatty diacid containing 20–26 (preferably 20–23) carbon atoms, and preferably III is a fatty diacid comprising 20, 21 or 22 carbon atoms, wherein formally, a hydroxyl group has been removed from one of the carboxyl groups in the fatty diacid; and/or

the ~~insulin parent~~ natural insulin or an insulin analogue comprises one lysine residue.

~~50~~34. The method according to claim ~~45 or 46~~30, wherein,

I is: -HN-$(CH_2)_2$-O-$(CH_2)_2$-O-CH_2-CO-, -HN-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-CO-, -HN-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-CO-, -HN-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-CO-, -HN-$(CH_2)_3$-O-$(CH_2)_4$-O-$(CH_2)_3$-NH-CO-, -HN-$(CH_2)_3$-O-$(CH_2)_4$-O-$(CH_2)_3$-NH-CO-CH_2-O-CH_2-CO-, -HN-$(CH_2)_3$-O-$(CH_2)_4$-O-$(CH_2)_3$-NH-CO-$(CH_2)_2$-CO-, -HN-$(CH_2)_2$-O-$(CH_2)_2$-O-CH_2-CO-CH_2-O-CH_2-CO-, -HN-$(CH_2)_3$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_3$-NH-CO-$(CH_2)_2$-CO-, -HN-$(CH_2)_3$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_3$-NH-CO-CH_2-O-CH_2-CO-, -HN-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-NH-CO-$(CH_2)_2$-CO-, -HN-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-NH-CO-CH_2-O-CH_2-CO-, -HN-$(CH_2)_3$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_3$-NH-CO-CH_2-O-CH_2-CO-, -HN-$(CH_2)_3$-O-$(CH_2)_3$-O-CH_2-CO-, or -HN-$(CH_2)_4$-O-$(CH_2)_4$-O-CH_2-CO-; preferably, I is -HN-$(CH_2)_2$-O-$(CH_2)_2$-O-CH_2-CO-; or I' is -HN-$(CH_2$-CH_2-O$)_{10}$-CH_2-CO-, -HN-$(CH_2$-CH_2-O$)_{11}$-CH_2-CO-, -HN-$(CH_2$-CH_2-O$)_{12}$-CH_2-CO- or -HN-$(CH_2$-CH_2-CH_2-O$)_8$-CH_2-CO-; and/or

II is an amino acid residue selected from the group consisting of γGlu, αGlu, βAsp, αAsp, γ-D-Glu, α-D-Glu, β-D-Asp and α-D-Asp; preferably, II is selected from γGlu and βAsp; and/or

III is HOOC-$(CH_2)_{18}$-CO-, HOOC-$(CH_2)_{19}$-CO-, HOOC-$(CH_2)_{20}$-CO-, HOOC-$(CH_2)_{21}$-CO-, HOOC-$(CH_2)_{22}$-CO- or HOOC-$(CH_2)_{24}$-CO-; preferably, III is HOOC-$(CH_2)_{18}$-CO-, HOOC-$(CH_2)_{20}$-CO- or HOOC-$(CH_2)_{22}$-CO-.

~~51~~35. The method according to claim ~~45 or 46~~30, wherein the formula (A) is linked to an amino group of the lysine residue or the N-terminal amino acid residue of the natural insulin or insulin analogue via the C-terminal of I, or the formula (A') is linked to an amino group of the lysine residue or the N-terminal amino acid residue of the natural insulin or insulin analogue via the C-terminal of I'.

~~52~~36. The method according to any one of claims ~~45–51~~30-35, wherein the formula (A) or the formula (A') is linked to an ε amino group of the lysine residue of the natural insulin or an insulin analogue~~insulin parent.~~,

~~53. The method according to any one of claims 45-52,~~ wherein the lysine residue of

the natural insulin or insulin analogue is at position B29.

~~54~~37. The method according to any one of claims ~~45-53~~30-36, wherein the natural insulin or insulin analogue is selected from the group consisting of desB30 human insulin; A14E, B16H, B25H, desB30 human insulin; A14E, B16E, B25H, desB30 human insulin; human insulin; A21G human insulin; A21G, desB30 human insulin; and B28D human insulin; preferably, the insulin parent is desB30 human insulin or A14E, B16H, B25H, desB30 human insulin.