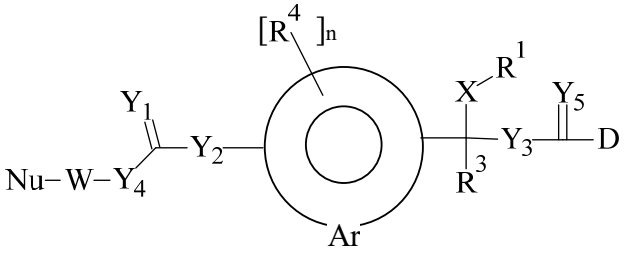
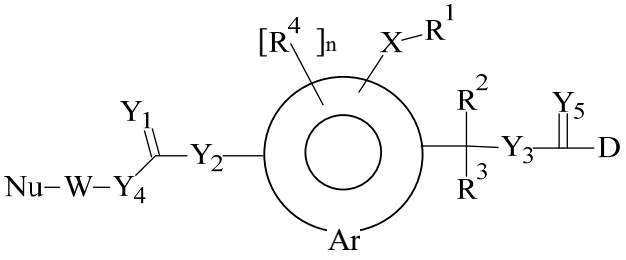
Claims

1. Use of a long-acting growth hormone or a pharmaceutical formulation comprising such long-acting growth hormone in the preparation of a medicament for treating growth hormone deficiency in a patient, wherein the patient is a non-responder, wherein the patient has previously been treated with daily growth hormone, and wherein the long-acting growth hormone is of formula (Ia) or (Ib)



(Ia),



(Ib),

wherein

-D is a hGH moiety connected to the rest of the molecule through an amine functional group;

n is 0, 1, 2, 3, or 4;

-X- is a chemical bond or a spacer;

$=Y_1$, $=Y_5$ are selected independently from the group consisting of =O and =S;

$-Y_2-$, $-Y_3-$ are selected from the group consisting of -O- and -S-;

$-Y_4-$ is selected from the group consisting of -O-, $-NR^5-$ and $-C(R^6R^{6a})-$;

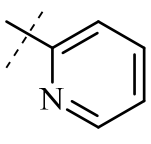
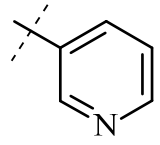
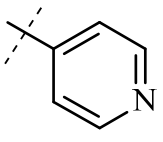
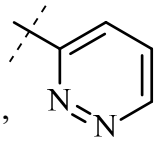
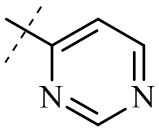
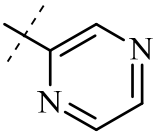
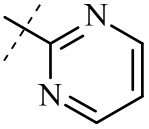
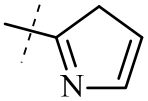
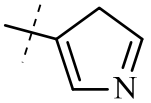
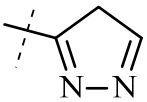
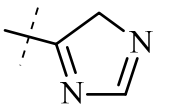
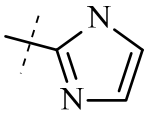
$-R^1$ is a carrier, preferably a water-soluble PEG-based moiety comprising at least 40% PEG;

$-R^2$, $-R^3$, $-R^5$, $-R^6$, $-R^{6a}$ are independently of each other selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylpropyl;

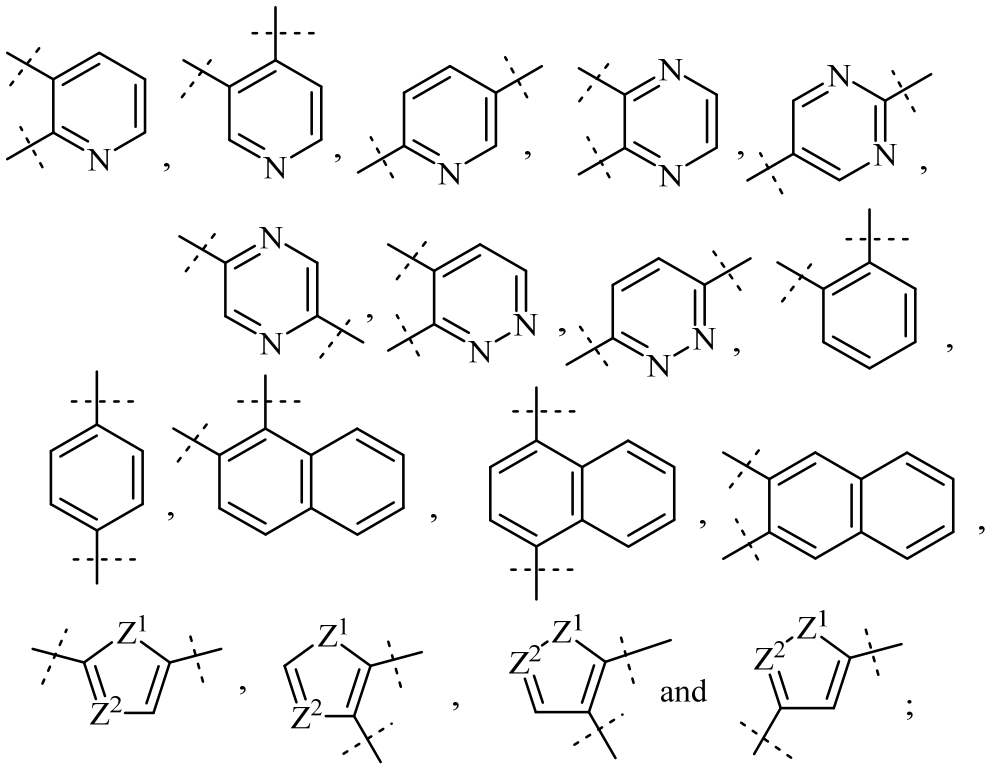
-R^4 is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylpropyl;

-W- is selected from the group consisting of C_{1-20} alkyl optionally interrupted by one or more groups selected from the group consisting of C_{3-10} cycloalkyl, 8- to 30-membered carbopolycyclyl, 3- to 10-membered heterocyclyl, -C(O)-, -C(O)N(R^7)-, -O-, -S- and -N(R^7)-;

-Nu is a nucleophile selected from the group consisting of -N(R^7R^{7a}), -N(R^7OH), -N(R^7)-N($R^{7a}R^{7b}$), -S(R^7), -COOH,


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and

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-Ar- is selected from the group consisting of



wherein

dashed lines indicate attachment to the rest of the prodrug,

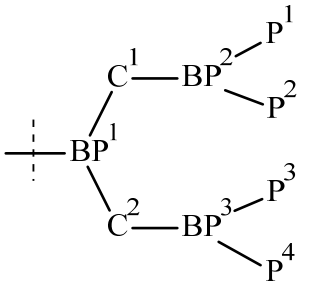
$-Z^1-$ is selected from the group consisting of -O-, -S- and $-N(R^7)-$, and

$-Z^2-$ is $-N(R^7)-$; and

$-R^7$, $-R^{7a}$, $-R^{7b}$ are independently of each other selected from the group consisting of -H, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl;

wherein the prodrug of formula (Ia) and (Ib) is optionally further substituted.

2. The use of claim 1, wherein $-R^1$ of formula (Ia) and (Ib) comprises a moiety of formula (II)



(II),

wherein

-BP^1<, -BP^2<, -BP^3< are independently of each other selected from the group consisting of -N< and -$C(R^8)$<;

R^8 is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl;

-P^1, -P^2, -P^3, -P^4 are independently of each other a PEG-based chain comprising at least 40% PEG and having a molecular weight ranging from 5 to 30 kDa;

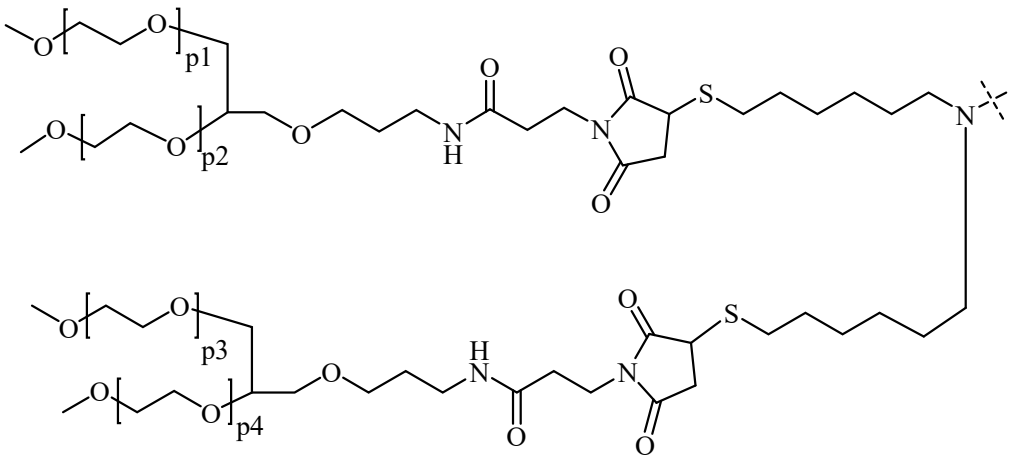
-C^1-, -C^2- are independently of each other selected from the group consisting of C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more R^9, which are the same or different and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -$C(O)N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$S(O)N(R^{10})$-, -$S(O)_2$-, -S(O)-, -$N(R^{10})S(O)_2N(R^{10a})$-, -S-, -$N(R^{10})$-, -$OC(OR^{10})(R^{10a})$-, -$N(R^{10})C(O)N(R^{10a})$-, and -$OC(O)N(R^{10})$-;

each T is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8-to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl; wherein each T is independently optionally substituted with one or more R^9, which are the same or different;

each R^9 is independently selected from the group consisting of halogen, -CN, oxo (=O), -$COOR^{11}$, -OR^{11}, -$C(O)R^{11}$, -$C(O)N(R^{11}R^{11a})$, -$S(O)_2N(R^{11}R^{11a})$, -$S(O)N(R^{11}R^{11a})$, -$S(O)_2R^{11}$, -$S(O)R^{11}$, -$N(R^{11})S(O)_2N(R^{11a}R^{11b})$, -$SR^{11}$, -$N(R^{11}R^{11a})$, -$NO_2$, -$OC(O)R^{11}$, -$N(R^{11})C(O)R^{11a}$, -$N(R^{11})S(O)_2R^{11a}$, -$N(R^{11})S(O)R^{11a}$, -$N(R^{11})C(O)OR^{11a}$, -$N(R^{11})C(O)N(R^{11a}R^{11b})$, -$OC(O)N(R^{11}R^{11a})$, and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different; and

each R^{10}, R^{10a}, R^{11}, R^{11a} and R^{11b} is independently selected from the group consisting of -H, and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

3. The use of claim 1 or 2, wherein -R^1 comprises a moiety of formula (IIc):

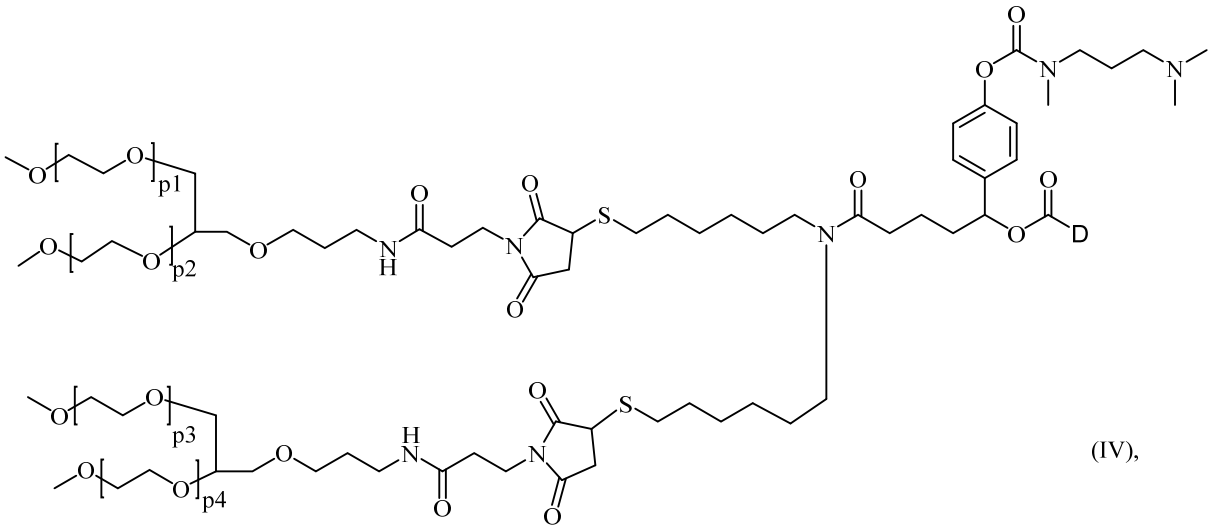


(IIc),

wherein

p1, p2, p3, p4 are independently an integer ranging from 170 to 284.

4. The use of any one of claims 1 to 3, wherein the long-acting growth hormone is a polymeric hGH prodrug of formula (IV)



(IV),

wherein

D is a hGH moiety connected to the rest of the molecule through an amine functional group; and

p1, p2, p3, p4 are independently an integer ranging from 170 to 284.

5. The use of claim 3 or 4, wherein p1, p2, p3, p4 are independently an integer ranging from 198 to 255.

6. The use of any one of claims 1 to 5, wherein the hGH moiety is a polypeptide of SEQ ID NO:1.

7. The use of any one of claims 1 to 6, wherein the growth hormone deficiency is growth hormone deficiency in children.

8. The use of any one of claims 1 to 7, wherein the long-acting growth hormone is to be administered no more than once per week.

9. The use of any one of claims 1 to 8, wherein the time between two consecutive administrations is 1 week.

10. The use of claim 8 or 9, wherein each administration is with a dose of the long-acting growth hormone of at least 0.16 mg/kg/week.

11. The use of claim 10, wherein the dose ranges from 0.24 mg/kg/week to 0.3 mg/kg/week.

12. The use of any one of claims 1 to 11, wherein the pharmaceutical formulation is a dry formulation.

13. The use of any one of claims 1 to 11, wherein the pharmaceutical formulation is a liquid formulation.

14. The use of any one of claims 1 to 13, wherein the growth hormone deficiency is treated for a time period of at least 6 months.

15. The use of any one of claims 1 to 14, wherein the long-acting growth hormone is to be administered using an autoinjector pen.

16. The use of any one of claims 1 to 15, wherein the long-acting growth hormone is to be administered using a dual chamber cartridge that is loaded into a pen device or electronic injector.