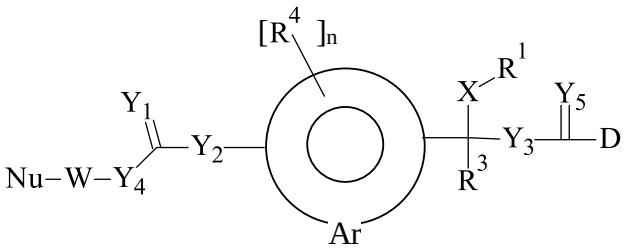
Claims

1. A container comprising a polymeric human growth hormone (hGH) prodrug or a pharmaceutically acceptable salt thereof of formula (Ia)



(Ia),

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;

$=Y_1$ is selected from the group consisting of =O and =S;

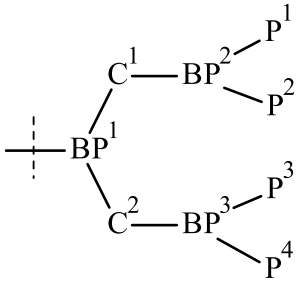
$-Y_2-$ is selected from the group consisting of -O- and -S-;

$-Y_3-$ is selected from the group consisting of -O- and -S-;

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

$=Y_5$ is selected from the group consisting of =O and =S;

$-R^1$ is a water-soluble PEG-based moiety comprising a moiety of formula (II)



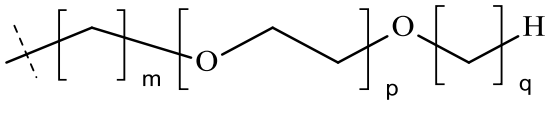
(II),

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 of formula (IIb)



(IIb),

wherein

the dashed line indicates attachment the remainder of R^1, i.e. to BP^2 or BP^3, respectively,

m is 0 or 1,

p is an integer ranging from 180 to 240,

q is selected from the group consisting of 1, 2, 3, 4, 5, and 6;

$-C^1-$, $-C^2-$ 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;

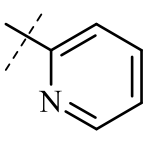
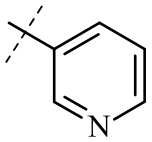
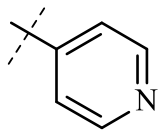
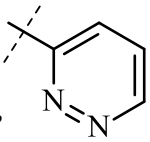
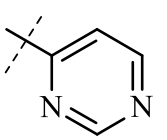
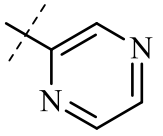
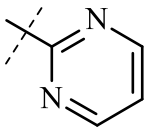
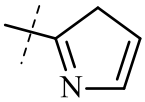
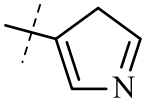
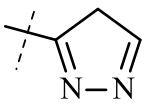
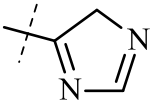
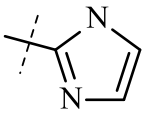
$-R^3$, $-R^5$, $-R^6$, $-R^{6a}$ are independently of each other selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl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

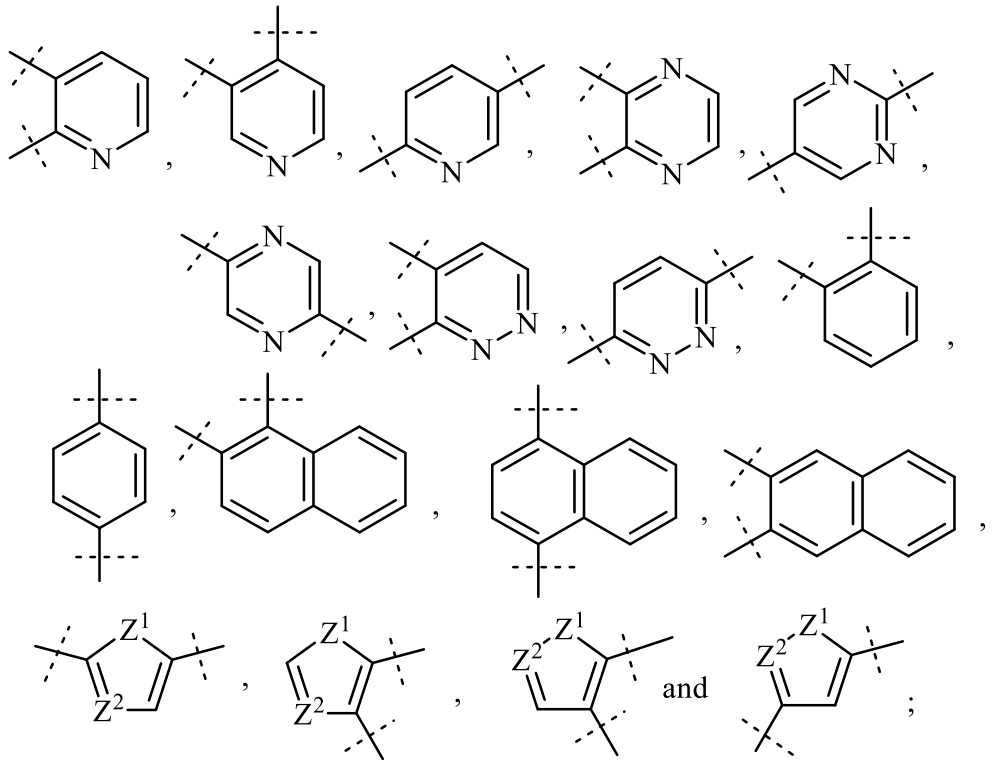
dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylpropyl;

-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.

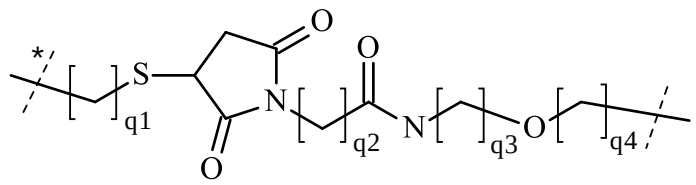
2. The container of claim 1, wherein BP^1 of formula (II) is –N<.

3. The container of claim 1 or 2, wherein BP^2 and BP^3 of formula (II) are both –CH<.

4. The container of any one of claims 1 to 3, wherein the first branching point BP^1 and the attachment site of X are separated by no more than 60 atoms.

5. The container of any one of claims 1 to 4, wherein C^1 and C^2 of formula (II) are C_{1-50} alkyl interrupted by one or more of the groups selected from the group consisting of -O-, $-C(O)N(R^{10})-$ and 3- to 10 membered heterocyclyl; wherein the 3- to 10 membered heterocyclyl is substituted with at least one oxo (=O).

6. The container of any one of claims 1 to 5, wherein C^1 and C^2 are of formula (IIa)



(IIa),

wherein

the dashed line marked with the asterisk indicates attachment to BP^1;

the unmarked dashed line indicates attachment to BP^2 or BP^3, respectively;

q1 is 1, 2, 3, 4, 5, 6, 7 or 8;

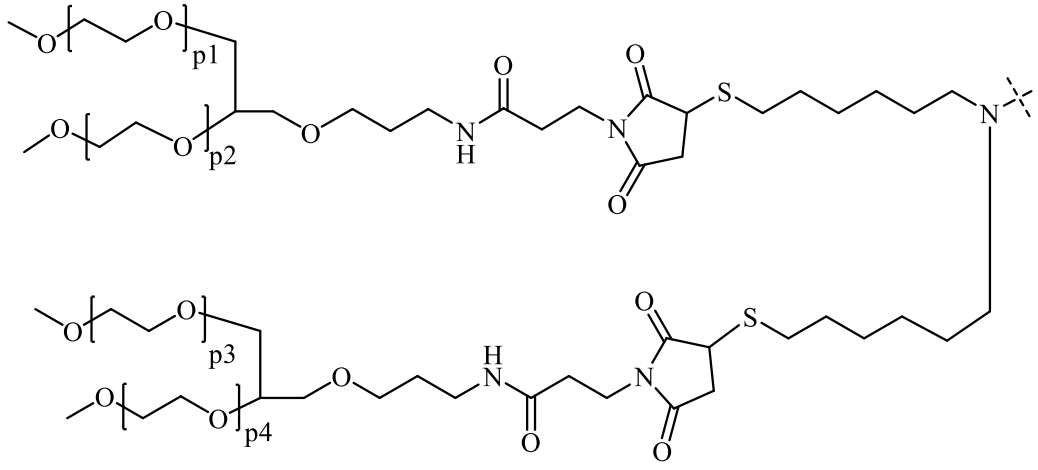
q2 is 1, 2, 3, 4, or 5;

q3 is 1, 2, 3, 4, 5, 6, 7 or 8;

q4 is 1, 2 or 3.

7. The container of any one of claims 1 to 6, wherein p is an integer ranging from 210 to 240.

8. The container of any one of claims 1 to 7, wherein $-R^1$ comprises a moiety of formula (IIc):



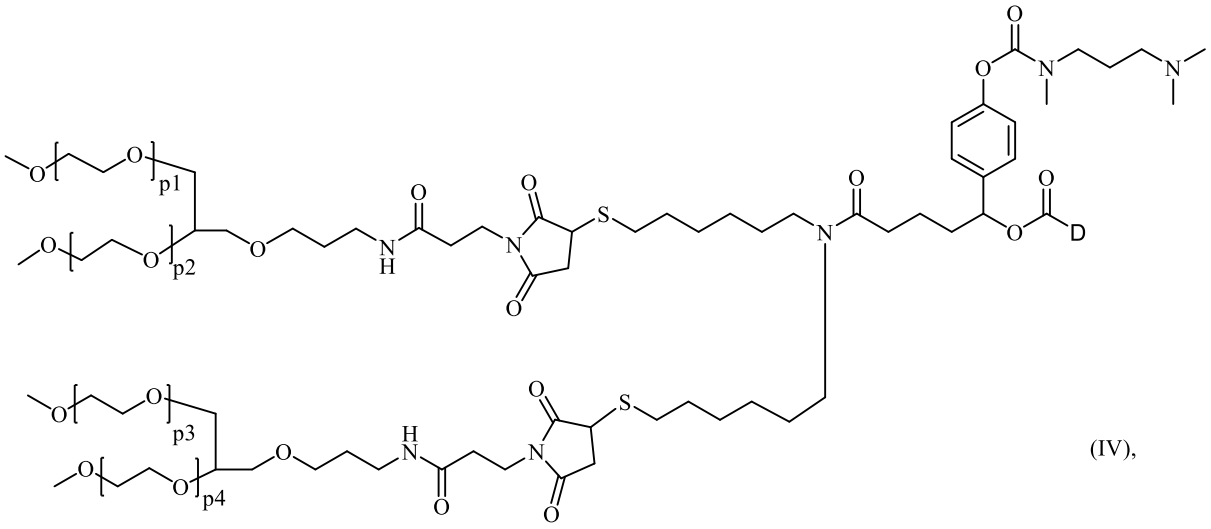
(IIc),

wherein

p1, p2, p3, p4 are independently an integer ranging from 180 to 240.

9. The container of one of claims 1 to 8, wherein p is an integer ranging from 210 to 240.

10. The container of any one of claims 1 to 9, wherein the polymeric hGH prodrug is of formula (IV)



(IV),

wherein

D is an 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 180 to 240.

11. The container of claim 10, wherein pl, p2, p3, and p4 are independently an integer ranging from 200 to 240.

12. The container of any one of claims 1 to 11, wherein-D is connected to the rest of the molecule through an amine provided by a lysine side chain.

13. The container of any one of claims 1 to 12, wherein the-D is an hGH moiety of SEQ ID NO: 1.

14. The container of any one of claims 1 to 13, which further comprises at least one excipient.

15. The container of any one of claims 1 to 14, which comprises a liquid formulation and from 3 to 300 mg/ml of the prodrug.

16. The container of claim 15, wherein the liquid formulation comprises

polymeric hGH prodrug	3-300 mg/ml
succinic acid	5-50 mM
optionally trehalose dihydrate	25-150 mg/ml

optionally methionine 1-50 mM;
and has a pH ranging from pH 4.0 to 6.0 which is titrated using a suitable buffer.

17. The container of any one of claims 1 to 14, which comprises a dry formulation and from 1 to 99.9% (w/w) of the prodrug.

18. The container of claim 17, wherein the dry formulation comprises from 9 to 71% (w/w) of the prodrug.

19. The container of claim 17 or 18, wherein the dry formulation comprises from 32 to 34% (w/w) or 50 to 54% (w/w) of the prodrug.

20. The container of any one of claims 17 to 19, wherein the dry formulation is obtained by a process comprising the steps of
    (a) providing a liquid formulation comprising
        polymeric hGH prodrug 3-300 mg/ml
        succinic acid 5-50 mM
        optionally trehalose dihydrate 25-150 mg/ml
        and having a pH ranging from pH 4.0 to pH 6.0 which is titrated using a suitable buffer, and
    (b) drying the liquid formulation of step (a).

21. The container of any one of claims 17 to 20, wherein the dry formulation comprises based on the total weight of the formulation:

polymeric hGH prodrug	14-65% (w/w)
succinic acid	0.5-2.5% (w/w)
trehalose dihydrate	31-84% (w/w)
Tris	0.4-4% (w/w)

22. The container of any one of claims 1 to 21, wherein the container is selected from the group consisting of syringes, dual-chamber syringes, vials, vials with stopper and seal, ampoules, cartridges, and dual-chamber cartridges.

23. The container of claim 22, wherein the vial is a glass vial.

24. The container of claim 22, wherein the container is a dual-chamber cartridge.