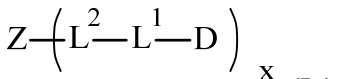
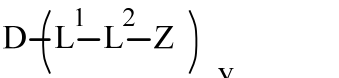
Claims

1. Use of a pharmaceutical composition comprising at least one controlled-release PTH compound or a pharmaceutically acceptable salt, hydrate or solvate thereof, in the manufacture of a medicament for the treatment of hypoparathyroidism, wherein said pharmaceutical composition is to be administered to a human patient no more frequently than once every 24 hours with a dosage of the controlled-release PTH compound that corresponds to no more than 40% of the molar equivalent dose of PTH 1-84 of SEQ ID NO:1 administered subcutaneously every 24 hours required to maintain serum calcium level of above 8.5 mg/dL and below 10.5 mg/dL over said 24 hour period in humans and wherein the controlled-release PTH compound is a water-soluble conjugate of formula (Ia) or (Ib)



(Ia)



(Ib),

or a water-insoluble compound comprising a conjugate D-L, wherein -D is a PTH moiety; and -L comprises a reversible prodrug linker moiety -L^1-, which moiety -L^1- is connected to the PTH moiety -D through a functional group of PTH; wherein -L^1- is substituted with -L^2-Z' and is optionally further substituted;

wherein

-D is a PTH moiety having a sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52,

SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120 and SEQ ID NO:121;

$-L^1-$ is a reversible prodrug linker moiety reversibly and covalently connected to the PTH moiety -D through a functional group of PTH;

$-L^2-$ is a single chemical bond or a spacer moiety;

-Z is a water-soluble carrier moiety;

-Z' is a water-insoluble carrier moiety to which a multitude of moieties $-L^2-L^1-D$ is connected;

x is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16; and

y is an integer selected from the group consisting of 1, 2, 3, 4 and 5;

from which PTH is released in its unmodified form with a release half-life of at least 12 hours in aqueous buffer with a pH of 7.4 and at 37°C.

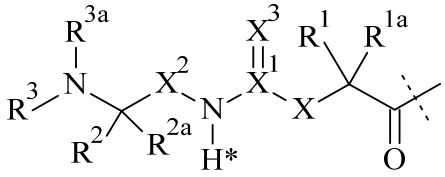
2. The use of claim 1, wherein the pharmaceutical composition is to be administered once every 24 hours.

3. The use of claim 1, wherein the pharmaceutical composition is to be administered once every week.

4. The use of any one of claims 1 to 3, wherein the dosage of the controlled-release PTH compound corresponds to no more than 30% of the molar equivalent dose of PTH 1-84.

5. The use of any one of claims 1 to 4, wherein the pharmaceutical composition is to be administered with a pen injector.

6. The use of any one of claims 1 to 5, wherein $-L^1-$ is of formula (II)


(II)

,

wherein the dashed line indicates the attachment to a nitrogen of -D which is a PTH moiety;

-X- is selected from the group consisting of $-C(R^4R^{4a})-$; $-N(R^4)-$; -O-; $-C(R^4R^{4a})-C(R^5R^{5a})-$; $-C(R^5R^{5a})-C(R^4R^{4a})-$; $-C(R^4R^{4a})-N(R^6)-$; $-N(R^6)-C(R^4R^{4a})-$; $-C(R^4R^{4a})-O-$; $-O-C(R^4R^{4a})-$; and $-C(R^7R^{7a})-$;

X^1 is selected from the group consisting of C; and S(O);

$-X^2-$ is selected from the group consisting of $-C(R^8R^{8a})-$; and $-C(R^8R^{8a})-C(R^9R^{9a})-$;

$=X^3$ is selected from the group consisting of =O; =S; and =N-CN;

$-R^1$, $-R^{1a}$, $-R^2$, $-R^{2a}$, $-R^4$, $-R^{4a}$, $-R^5$, $-R^{5a}$, $-R^6$, $-R^8$, $-R^{8a}$, $-R^9$ and $-R^{9a}$ are independently selected from the group consisting of -H; and C_{1-6} alkyl;

$-R^3$ and $-R^{3a}$ are independently selected from the group consisting of -H; and C_{1-6} alkyl, provided that in case one of $-R^3$ and $-R^{3a}$ or both are other than -H they are connected to N to which they are attached through an sp^3-hybridized carbon atom;

$-R^7$ is selected from the group consisting of $-N(R^{10}R^{10a})$; and $-NR^{10}-(C=O)-R^{11}$;

$-R^{7a}$, $-R^{10}$, $-R^{10a}$ and $-R^{11}$ are independently of each other selected from the group consisting of -H; and C_{1-6} alkyl;

optionally, one or more of the pairs $-R^{1a}/-R^{4a}$, $-R^{1a}/-R^{5a}$, $-R^{1a}/-R^{7a}$, $-R^{4a}/-R^{5a}$ and $-R^{8a}/-R^{9a}$ form a chemical bond;

optionally, one or more of the pairs $-R^1/-R^{1a}$, $-R^2/-R^{2a}$, $-R^4/-R^{4a}$, $-R^5/-R^{5a}$, $-R^8/-R^{8a}$ and $-R^9/-R^{9a}$ are joined together with the atom to which they are attached to form a C_{3-10} cycloalkyl; or 3- to 10-membered heterocyclyl;

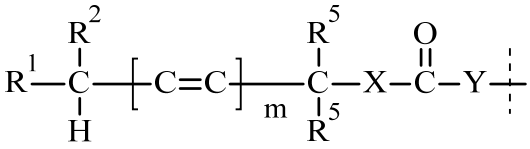
optionally, one or more of the pairs -R^1/-R^4, -R^1/-R^5, -R^1/-R^6, -R^1/-R^{7a}, -R^4/-R^5, -R^4/-R^6, -R^8/-R^9 and -R^2/-R^3 are joined together with the atoms to which they are attached to form a ring A;

optionally, R^3/R^{3a} are joined together with the nitrogen atom to which they are attached to form a 3- to 10-membered heterocycle;

A is selected from the group consisting of phenyl; naphthyl; indenyl; indanyl; tetralinyl; C_{3-10} cycloalkyl; 3- to 10-membered heterocyclyl; and 8- to 11-membered heterobicyclyl; and

wherein -L^1- is substituted with -L^2-Z or -L^2-Z' and wherein -L^1- is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (II) is not replaced by -L^2-Z or -L^2-Z' or a substituent.

7. The use of any one of claims 1 to 5, wherein -L^1- is of formula (IV):



(IV),

wherein

the dashed line indicates attachment to -D which is a PTH moiety and wherein attachment is through a functional group of -D selected from the group consisting of -OH, -SH and -NH_2;

m is 0 or 1;

at least one or both of -R^1 and -R^2 is/are independently of each other selected from the group consisting of -CN, -NO_2, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkenyl, optionally substituted alkynyl, -$C(O)R^3$, -$S(O)R^3$, -$S(O)_2R^3$, and -SR^4;

one and only one of -R^1 and -R^2 is selected from the group consisting of -H, optionally substituted alkyl, optionally substituted arylalkyl, and optionally substituted heteroarylalkyl;

-R^3 is selected from the group consisting of -H, optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, -OR^9 and -$N(R^9)_2$;

-R^4 is selected from the group consisting of optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

each -R^5 is independently selected from the group consisting of -H, optionally substituted alkyl, optionally substituted alkenylalkyl, optionally substituted alkynylalkyl,

optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

$-R^9$ is selected from the group consisting of -H and optionally substituted alkyl;

-Y- is absent and –X- is -O- or -S-; or

-Y- is -N(Q)CH2- and -X- is -O-;

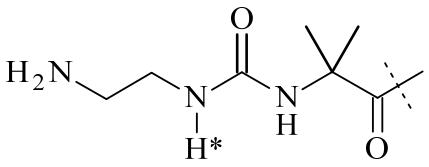
Q is selected from the group consisting of optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

optionally, $-R^1$ and $-R^2$ may be joined to form a 3 to 8-membered ring;

optionally, both $-R^9$ together with the nitrogen to which they are attached form a heterocyclic ring; and

wherein $-L^1-$ is substituted with $-L^2-Z$ or $-L^2-Z'$ and wherein $-L^1-$ is optionally further substituted.

8. The use of any one of claims 1 to 6, wherein $-L^1-$ is of formula (IIb-iii):



(IIb-iii),

wherein

the dashed line indicates the attachment to a nitrogen of -D by forming an amide bond; and

wherein $-L^1-$ is substituted with $-L^2-Z$ or $-L^2-Z'$ and wherein $-L^1-$ is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (IIb-iii) is not replaced by $-L^2-Z$ or $-L^2-Z'$ or a substituent.

9. The use of any one of claims 1 to 8, wherein $-L^2-$ is selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, $-C(O)N(R^{y1})-$, $-S(O)_2N(R^{y1})-$, $-S(O)N(R^{y1})-$, $-S(O)_2-$, -S(O)-, $-N(R^{y1})S(O)_2N(R^{y1a})-$, -S-, $-N(R^{y1})-$, $-OC(OR^{y1})(R^{y1a})-$, $-N(R^{y1})C(O)N(R^{y1a})-$, $-OC(O)N(R^{y1})-$, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein -T-, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more $-R^{y2}$, 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^{y3})-, -S(O)$_2$N(R^{y3})-, -S(O)N(R^{y3})-, -S(O)$_2$-, -S(O)-, -N(R^{y3})S(O)$_2$N(R^{y3a})-, -S-, -N(R^{y3})-, -OC(OR^{y3})(R^{y3a})-, -N(R^{y3})C(O)N(R^{y3a})-, and -OC(O)N(R^{y3})-;

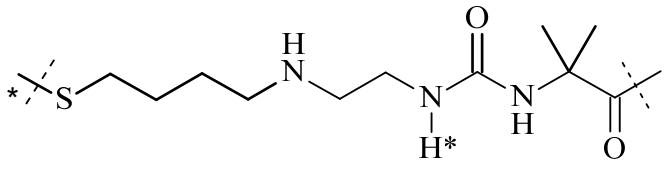
-R^{y1} and -R^{y1a} are independently of each other selected from the group consisting of -H, -T, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein -T, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more -R^{y2}, which are the same or different, 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^{y4})-, -S(O)$_2$N(R^{y4})-, -S(O)N(R^{y4})-, -S(O)$_2$-, -S(O)-, -N(R^{y4})S(O)$_2$N(R^{y4a})-, -S-, -N(R^{y4})-, -OC(OR^{y4})(R^{y4a})-, -N(R^{y4})C(O)N(R^{y4a})-, and -OC(O)N(R^{y4})-;

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^{y2}, which are the same or different;

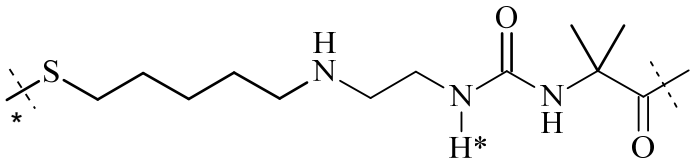
each -R^{y2} is independently selected from the group consisting of halogen, -CN, oxo (=O), -COOR^{y5}, -OR^{y5}, -C(O)R^{y5}, -C(O)N($R^{y5}R^{y5a}$), -S(O)$_2$N($R^{y5}R^{y5a}$), -S(O)N($R^{y5}R^{y5a}$), -S(O)$_2$$R^{y5}$, -S(O)$R^{y5}$, -N($R^{y5}$)S(O)$_2$N($R^{y5}aR^{y5b}$), -S$R^{y5}$, -N($R^{y5}R^{y5a}$), -NO$_2$, -OC(O)$R^{y5}$, -N($R^{y5}$)C(O)$R^{y5a}$, -N($R^{y5}$)S(O)$_2$$R^{y5a}$, -N(Ry^5)S(O)$R^{y5a}$, -N($R^{y5}$)C(O)O$R^{y5a}$, -N($R^{y5}$)C(O)N($R^{y5a}R^{y5b}$), -OC(O)N($R^{y5}R^{y5a}$), 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^{y3}, -R^{y3a}, -R^{y4}, -R^{y4a}, -R^{y5}, -R^{y5a} and -R^{y5b} 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.

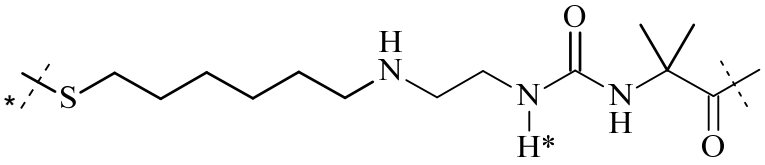
10. The pharmaceutical composition for use of any one of claims 1 to 6, 8 or 9, wherein -L^1-L^2- is selected from the group consisting of



(IIcb-i),



(IIcb-ii) and



(IIcb-iii);

wherein

the unmarked dashed line indicates the attachment to a nitrogen of -D which is a PTH moiety by forming an amide bond; and

the dashed line marked with the asterisk indicates attachment to -Z or -Z'.

11. The pharmaceutical composition for use of any one of claims 1 to 10, wherein -Z is a branched PEG-based polymer.

12. The pharmaceutical composition for use of any one of claims 1 to 10, wherein -Z' is a hydrogel.

13. The use of any one of claims 1 to 12, wherein -D has the sequence of SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114 or SEQ ID NO:115.

14. The use of any one of claims 1 to 13, wherein -D has the sequence of SEQ ID NO:51.

15. The use of any one of claims 1 to 11, 13 or 14, wherein the controlled-release PTH compound is of formula (Ia) with x = 1.

16. The use of any one of claims 1 to 15, wherein the pharmaceutical composition has a pH ranging from and including pH 3 to pH 8.