Claims

1. A liquid pharmaceutical formulation, wherein the pharmaceutical formulation comprises a PTH conjugate, a buffering agent, an isotonicity agent, a preservative and optionally an antioxidant, wherein the PTH conjugate comprises a PTH moiety that is covalently and reversibly conjugated to a water-soluble carrier and wherein the liquid formulation comprises

PTH conjugate, of which PTH moiety	0.1 - 5.0 mg/ml
succinic acid	0.25 - 24 mg/ml
D-mannitol	10 - 200 mg/ml
m-cresol	1 - 10 mg/ml

and wherein the pH ranges from 3.0 to 6.0.

2. The liquid pharmaceutical formulation of claim 1, wherein the pH-adjusting agent is a base.

3. The liquid pharmaceutical formulation of claim 1 or 2, wherein the pH-adjusting agent is selected from the group consisting of Tris (tris(hydroxymethyl)aminomethane), potassium hydroxide, lysine, sodium hydroxide and mixtures thereof.

4. The liquid pharmaceutical formulation of any one of claims 1 to 3, wherein the pH-adjusting agent is sodium hydroxide.

5. The liquid pharmaceutical formulation of any one of claims 1 to 4, wherein the liquid pharmaceutical formulation comprises

PTH conjugate, of which PTH moiety	0.1 - 1.5 mg/ml
succinic acid	0.6 - 6.0 mg/ml
D-mannitol	30 - 60 mg/ml
m-cresol	1.5 - 3.5 mg/ml

and wherein the pH ranges from 3.5 to 5.0.

6. The liquid pharmaceutical formulation of any one of claims 1 to 5, wherein the liquid pharmaceutical formulation comprises

PTH conjugate, of which PTH moiety	0.25 - 0.35 mg/ml
succinic acid	1.0 - 1.4 mg/ml
D-mannitol	36 - 48 mg/ml
m-cresol	2.0 - 3.0 mg/ml

and wherein the pH ranges from 3.5 to 5.0.

7. The liquid pharmaceutical formulation of any one of claims 1 to 6, wherein the liquid pharmaceutical formulation comprises

PTH conjugate, of which PTH moiety	0.25 - 0.35 mg/ml
succinic acid	1.0 - 1.4 mg/ml
D-mannitol	36 - 48 mg/ml
m-cresol	2.0 - 3.0 mg/ml

and wherein the pH ranges from 3.7 to 4.3.

8. The liquid pharmaceutical composition of any one of claims 1 to 7, wherein the liquid pharmaceutical composition comprises about 0.3 mg/ml PTH moiety, about 1.18 mg/ml succinic acid, about 41.7 mg/ml D-mannitol, about 2.5 mg/ml m-cresol and wherein the pH is about 4.0.

9. The liquid pharmaceutical composition of any one of claims 1 to 8, wherein the liquid pharmaceutical composition comprises 0.3 mg/ml PTH moiety, 1.18 mg/ml succinic acid, 41.7 mg/ml D-mannitol, 2.5 mg/ml m-cresol and wherein the pH is 4.0.

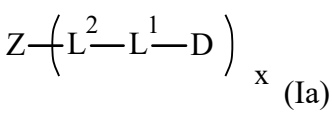
10. The liquid pharmaceutical formulation of any one of claims 1 to 9, wherein the PTH moiety has the sequence SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114 or SEQ ID NO:115.

11. The liquid pharmaceutical formulation of any one of claims 1 to 10, wherein the PTH moiety has the sequence SEQ ID NO:51.

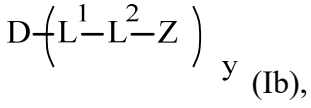
12. The liquid pharmaceutical formulation of any one of claims 1 to 11, wherein the water-soluble carrier comprises a polymer.

13. The liquid pharmaceutical formulation of claim 12, wherein the polymer is selected from the group consisting of poly(acrylic acids), poly(acrylates), poly(acrylamides), poly(alkyloxy) polymers, poly(amides), poly(amidoamines), poly(amino acids), poly(anhydrides), poly(aspartamides), poly(butyric acids), poly(glycolic acids), polybutylene terephthalates, poly(caprolactones), poly(carbonates), poly(cyanoacrylates), poly(dimethylacrylamides), poly(esters), poly(ethylenes), poly(ethyleneglycols), poly(ethylene oxides), poly(ethyl phosphates), poly(ethyloxazolines), poly(glycolic acids), poly(hydroxyethyl acrylates), poly(hydroxyethyl-oxazolines), poly(hydroxymethacrylates), poly(hydroxypropylmethacrylamides), poly(hydroxypropyl methacrylates), poly(hydroxypropyloxazolines), poly(iminocarbonates), poly(lactic acids), poly(lactic-co-glycolic acids), poly(methacrylamides), poly(methacrylates), poly(methyloxazolines), poly(organophosphazenes), poly(ortho esters), poly(oxazolines), poly(propylene glycols), poly(siloxanes), poly(urethanes), poly(vinyl alcohols), poly(vinyl amines), poly(vinylmethylethers), poly(vinylpyrrolidones), silicones, celluloses, carbomethyl celluloses, hydroxypropyl methylcelluloses, chitins, chitosans, dextrans, dextrins, gelatins, hyaluronic acids and derivatives, functionalized hyaluronic acids, mannans, pectins, rhamnogalacturonans, starches, hydroxyalkyl starches, hydroxyethyl starches and other carbohydrate-based polymers, xylans, and copolymers thereof.

14. The liquid pharmaceutical formulation of any one of claims 1 to 13, wherein the PTH conjugate is of formula (Ia) or (Ib):



(Ia)



(Ib),

wherein

-D is a PTH moiety;

-L^1- is a reversible linker moiety 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;
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 and 16; and
y is an integer selected from the group consisting of 1, 2, 3, 4 and 5.

15. The liquid pharmaceutical formulation of claim 14, wherein x of formula (Ia) is an integer selected from the group consisting of 1, 2, 3, 4, 6 and 8.

16. The liquid pharmaceutical formulation of claim 15, wherein y of formula (Ib) is an integer selected from the group consisting of 2, 3, 4 and 5.

17. The liquid pharmaceutical formulation of claim 14 or 15, wherein the PTH conjugate is of formula (Ia) and x is 1.

18. The liquid pharmaceutical formulation of any one of claims 14 to 17, wherein -D is connected to -L^1- through a nitrogen by forming an amide bond.

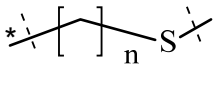
19. The liquid pharmaceutical formulation of any one of claims 14 to 18, wherein -L^1- is directly conjugated to the N-terminal amine functional group of -D.

20. The liquid pharmaceutical formulation of any one of claims 14 to 19, wherein -L^2- is a spacer moiety.

21. The liquid pharmaceutical formulation of any one of claims 14 to 20, wherein -L^2- has a molecular weight in the range of from 14 g/mol to 750 g/mol.

22. The liquid pharmaceutical formulation of any one of claims 14 to 21, wherein -L^2- has a chain length of 1 to 20 atoms.

23. The liquid pharmaceutical formulation of any one of claims 14 to 22, wherein -L^2- is of formula (i):


(i),

wherein

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

the unmarked dashed line indicates attachment to -Z;

n is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 and 18; and

wherein the moiety of formula (i) is optionally further substituted.

24. The liquid pharmaceutical formulation of claim 23, wherein n is selected from the group consisting of 3, 4, 5, 6, 7, 8 and 9.

25. The liquid pharmaceutical formulation of any one of claims 14 to 24, wherein -Z comprises a C_{8-24} alkyl or a polymer.

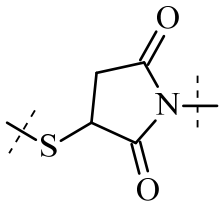
26. The liquid pharmaceutical formulation of any one of claims 14 to 25, wherein -Z comprises a polymer.

27. The liquid pharmaceutical formulation of any one of claims 14 to 26, wherein -Z comprises a polymer selected from the group consisting of poly(acrylic acids), poly(acrylates), poly(acrylamides), poly(alkyloxy) polymers, poly(amides), poly(amidoamines), poly(amino acids), poly(anhydrides), poly(aspartamides), poly(butyric acids), poly(glycolic acids), polybutylene terephthalates, poly(caprolactones), poly(carbonates), poly(cyanoacrylates), poly(dimethylacrylamides), poly(esters), poly(ethylenes), poly(ethyleneglycols), poly(ethylene oxides), poly(ethyl phosphates), poly(ethyloxazolines), poly(glycolic acids), poly(hydroxyethyl acrylates), poly(hydroxyethyl-oxazolines), poly(hydroxymethacrylates), poly(hydroxypropylmethacrylamides), poly(hydroxypropyl methacrylates), poly(hydroxypropyloxazolines), poly(iminocarbonates), poly(lactic acids), poly(lactic-co-glycolic acids), poly(methacrylamides), poly(methacrylates), poly(methyloxazolines), poly(organophosphazenes), poly(ortho esters), poly(oxazolines), poly(propylene glycols), poly(siloxanes), poly(urethanes), poly(vinyl alcohols), poly(vinyl amines), poly(vinylmethylethers), poly(vinylpyrrolidones), silicones, celluloses, carbomethyl celluloses, hydroxypropyl methylcelluloses, chitins, chitosans, dextrans, dextrins,

gelatins, hyaluronic acids and derivatives, functionalized hyaluronic acids, mannans, pectins, rhamnogalacturonans, starches, hydroxyalkyl starches, hydroxyethyl starches and other carbohydrate-based polymers, xylans, and copolymers thereof.

28. The liquid pharmaceutical formulation of any one of claims 14 to 27, wherein -Z has a molecular weight ranging from 5 to 200 kDa.

29. The liquid pharmaceutical formulation of any one of claims 14 to 28, wherein -Z comprises a moiety:



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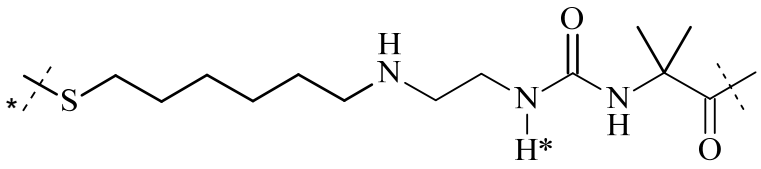
30. The liquid pharmaceutical formulation of any one of claims 1 to 29, wherein the PTH conjugate is of formula (IIf-i):

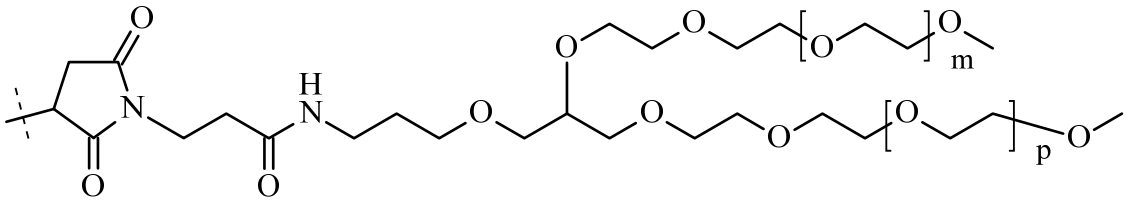


(IIf-i),

wherein

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

the dashed line marked with the asterisk indicates attachment to a moiety



wherein

m and p are independently an integer ranging from and including 400 to 500.

31. Method of manufacturing the liquid pharmaceutical formulation of any one of claims 1 to 4 or 10 to 30, wherein the method comprises the steps of

(i) admixing the PTH conjugate with at leastsuccinic acid, mannitol, m-cresol, optionally an antioxidant to yield a formulation comprising

PTH conjugate, of which PTH moiety	0.10 - 5.0 mg/ml
succinic acid	0.25 - 24 mg/ml
D-mannitol	10 - 200 mg/ml
m-cresol	1 - 10 mg/ml;

(ii) adjusting the pH of the admixture of step (i) to a pH ranging from pH 3.0 to 6.0 with NaOH and HCl;

(iii) optionally, filtering the admixture from step (ii);

(iv) transferring amounts of the admixture from step (ii) or (iii) equivalent to the desired number of dosages into a container;

(v) sealing the container; and

wherein the order of steps (ii) and (iii) may optionally be reversed.

32. Method of manufacturing the liquid pharmaceutical formulation of any one of claims 1 to 30, wherein the method comprises the steps of

(i) admixing the PTH conjugate with succinic acid, mannitol and m-cresol to yield a formulation comprising

PTH conjugate, of which PTH moiety	0.25 - 0.35 mg/ml
succinic acid	1.0 - 1.4 mg/ml
D-mannitol	36 - 48 mg/ml
m-cresol	2.0 - 3.0 mg/ml;

(ii) adjusting the pH of the admixture of step (i) to a pH ranging from 3.7 to 4.5;

(iii) optionally, filtering the admixture from step (ii);

(iv) transferring amounts of the admixture from step (ii) or (iii) equivalent to the desired number of dosages into a container;

(v) sealing the container; and

wherein the order of steps (ii) and (iii) may optionally be reversed.

33. Method of manufacturing the liquid pharmaceutical formulation of any one of claims 1 to 30, wherein the method comprises the steps of

(i) admixing the PTH conjugate with at least succinic acid, mannitol, m-cresol and optionally an antioxidant to yield a formulation comprising

PTH conjugate, of which PTH moiety	0.30 mg/ml
succinic acid	1.18 mg/ml
D-mannitol	41.7 mg/ml
m-cresol	2.5 mg/ml

(ii) adjusting the pH of the admixture of step (i) to a pH of about 4 with NaOH and HCl;

(iii) optionally, filtering the admixture from step (ii);

(iv) transferring amounts of the admixture from step (ii) or (iii) equivalent to the desired number of dosages into a container;

(v) sealing the container; and

wherein the order of steps (ii) and (iii) may optionally be reversed.

34. The method of manufacturing of any one of claims 31 to 33, wherein steps (ii) and (iii) are not reversed.

35. The liquid pharmaceutical formulation of any one of claims 1 to 30 for use as a medicament.

36. Use of the liquid pharmaceutical formulation of any one of claims 1 to 30 for the manufacture of a medicament for the treatment, control, delay or prevention of one or more diseases selected from the group consisting of hypoparathyroidism, osteoporosis, fracture repair, osteomalacia, osteomalacia and osteoporosis in patients with hypophasphatasia, steroid-induced osteoporosis, male osteoporosis, arthritis, osteoarthritis, osteogenenesis imperfecta, fibrous dysplasia, rheumatoid arthritis, osteopenia, periodontal disease, bone fracture, alopecia, chemotherapy-induced alopecia and thrombocytopenia, chronic periodontitis, osteonecrosis of jaw and poorly healing fractures due to ALPL gene mutations.

37. The use of claim 36, wherein the disease is hypoparathyroidism.