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, ~~and~~ 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 buffering agent is selected from the group consisting of succinic acid, citric acid, lactic acid, acetic acid, glutamic acid, fumaric acid, aspartic acid, glutaric acid, phosphoric acid, histidine, gluconic acid, tartaric acid, malic acid and mixtures thereof.~~

~~3. The liquid pharmaceutical formulation of claim 1 or 2, wherein the buffering agent is selected from the group consisting of succinic acid, lactic acid, acetic acid, glutamic acid, fumaric acid, aspartic acid, glutaric acid, phosphoric acid, histidine, gluconic acid, tartaric acid, malic acid and mixtures thereof.~~

~~4. The liquid pharmaceutical formulation of any one of claims 1 to 3, wherein the buffering agent is succinic acid.~~

~~5. The liquid pharmaceutical formulation of any one of claims 1 to 4, wherein the isotonicity agent is selected from the group consisting of mannitol, trehalose, sucrose, raffinose, gelatin, lactose, dibasic calcium phosphate, sorbitol, xylitol, glycine, histidine, ethanol, hydroxyethylstarch, potassium chloride, sodium chloride, dextrose, dextran, propylene glycol and mixtures thereof.~~

~~6. The liquid pharmaceutical formulation of any one of claims 1 to 5, wherein the isotonicity agent is mannitol.~~

~~7. The liquid pharmaceutical formulation of any one of claims 1 to 6, wherein the preservative is selected from the group consisting of m-cresol, benzylalcohol, benzoic acid, phenol, methylparaben, ethylparaben, propylparaben, butylparaben, potassium sorbate, chlorobutanol, benzyl alcohol, phenylmercuric nitrate, thimerosal, sorbic acid, potassium sorbate, chlorocresol, benzalkonium chloride, 2-ethoxyethanol, chlorhexidine, chlorobutanol, phenylethyl alcohol, phenylmercuric acetate and mixtures thereof.~~

~~8. The liquid pharmaceutical formulation of any one of claims 1 to 7, wherein the preservative is m-cresol.~~

~~9. The liquid pharmaceutical formulation of any one of claims 1 to 8, wherein the antioxidant is selected from the group consisting of methionine, butylhydroxytoluene, butylhydroxyanisol, tocopherol, propylgallate, ascorbic acid, sodium bisulfite, ethylenediaminetetraacetic acid, cysteine, glutathione, monothioglycerol, poly(ethylenimine), vitamin E, ectoine, morin and mixtures thereof.~~

~~10. The liquid pharmaceutical formulation of any one of claims 1 to 9, wherein the antioxidant is methionine.~~

~~11. The liquid pharmaceutical formulation of any one of claims 1 to 10, wherein the pharmaceutical formulation further comprises a pH-adjusting agent.~~

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.

~~12~~10. The liquid pharmaceutical formulation of any one of claims 1 to ~~11~~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.

~~13~~11. The liquid pharmaceutical formulation of any one of claims 1 to ~~12~~10, wherein the PTH moiety has the sequence SEQ ID NO:51.

~~14~~12. The liquid pharmaceutical formulation of any one of claims 1 to ~~13~~11, wherein the water-soluble carrier comprises a polymer.

~~15~~13. The liquid pharmaceutical formulation of claim ~~14~~12, wherein the polymer is selected from the group consisting of ~~2-methacryloyl-oxyethyl phosphoyl cholins,~~ 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.

~~16. The liquid pharmaceutical formulation of any one of claims 1 to 15, wherein the pharmaceutical formulation comprises the PTH conjugate, succinic acid, mannitol, m-cresol and optionally an antioxidant.~~

~~17. The liquid pharmaceutical formulation of any one of claims 1 to 16, wherein the pharmaceutical formulation comprises~~

~~PTH conjugate, of which PTH moiety~~	~~0.05 - 5.0 mg/ml~~
~~succinic acid~~	~~0.25 - 24 mg/ml~~
~~D-mannitol~~	~~10 - 200 mg/ml~~
~~m-cresol~~	~~1 - 10 mg/ml~~

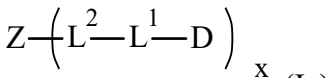
~~and wherein the pH ranges from 3.0 to 6.0.~~

~~18. The liquid pharmaceutical formulation of any one of claims 1 to 17, wherein the pharmaceutical formulation comprises~~

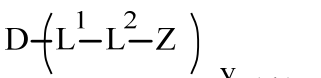
~~PTH conjugate, of which PTH moiety~~	~~0.1 - 5.0 mg/ml~~
~~succinic acid~~	~~0.25 - 24 mg/ml~~
~~D-mannitol~~	~~10 - 200 mg/ml~~
~~m-cresol~~	~~1 - 10 mg/ml~~

~~and wherein the pH ranges from 3.0 to 6.0.~~

~~19~~14. The liquid pharmaceutical formulation of any one of claims 1 to ~~18~~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.

~~20~~15. The liquid pharmaceutical formulation of claim ~~19~~14, wherein x of formula (Ia) is an integer selected from the group consisting of 1, 2, 3, 4, 6 and 8.

~~21~~16. The liquid pharmaceutical formulation of claim ~~19~~15, wherein y of formula (Ib) is an integer selected from the group consisting of 2, 3, 4 and 5.

~~22~~17. The liquid pharmaceutical formulation of claim ~~19~~14 or ~~20~~15, wherein the PTH conjugate is of formula (Ia) and x is 1.

~~23~~18. The liquid pharmaceutical formulation of any one of claims ~~19~~14 to ~~22~~17, wherein -D is connected to -L^1- through a nitrogen by forming an amide bond.

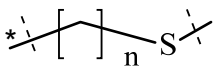
~~24~~19. The liquid pharmaceutical formulation of any one of claims ~~19~~14 to ~~23~~18, wherein -L^1- is directly conjugated to the N-terminal amine functional group of -D.

~~25~~20. The liquid pharmaceutical formulation of any one of claims ~~19~~14 to ~~24~~19, wherein -L^2- is a spacer moiety.

~~26~~21. The liquid pharmaceutical formulation of any one of claims ~~19~~14 to ~~25~~20, wherein -L^2- has a molecular weight in the range of from 14 g/mol to 750 g/mol.

~~27~~22. The liquid pharmaceutical formulation of any one of claims ~~19~~14 to ~~26~~21, wherein -L^2- has a chain length of 1 to 20 atoms.

~~28~~23. The liquid pharmaceutical formulation of any one of claims ~~19~~14 to ~~27~~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.

~~29~~24. The liquid pharmaceutical formulation of claim ~~28~~23, wherein n is selected from the group consisting of 3, 4, 5, 6, 7, 8 and 9.

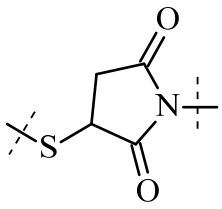
~~30~~25. The liquid pharmaceutical formulation of any one of claims ~~19~~14 to ~~29~~24, wherein -Z comprises a C_{8-24} alkyl or a polymer.

~~31~~26. The liquid pharmaceutical formulation of any one of claims ~~19~~14 to ~~30~~25, wherein -Z comprises a polymer.

~~32~~27. The liquid pharmaceutical formulation of any one of claims ~~19~~14 to ~~31~~26, wherein -Z comprises a polymer selected from the group consisting of ~~2-methacryloyl-oxyethyl phosphoyl cholins,~~ 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.

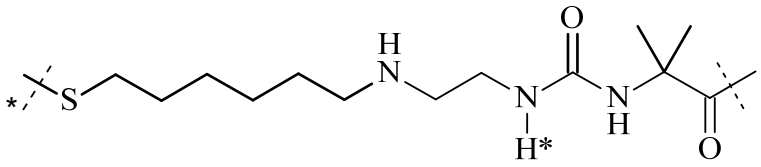
~~33~~28. The liquid pharmaceutical formulation of any one of claims ~~19~~14 to ~~32~~27, wherein -Z has a molecular weight ranging from 5 to 200 kDa.

~~34~~29. The liquid pharmaceutical formulation of any one of claims ~~19~~14 to ~~33~~28, wherein -Z comprises a moiety:



.

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

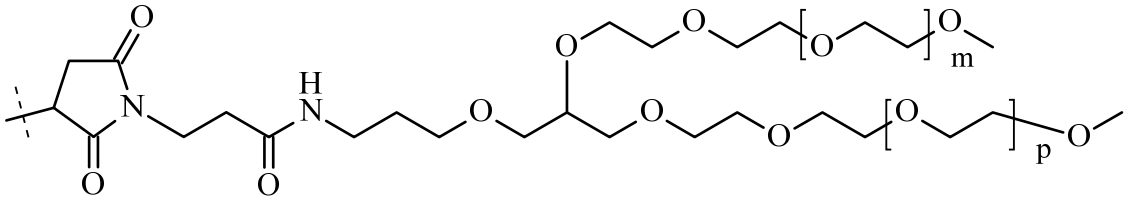


(IIf-i),

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.

~~35~~31. Method of manufacturing the liquid pharmaceutical formulation of any one of claims 1 to 4 or 10 to ~~34~~30, wherein the method comprises the steps of

(i) admixing the PTH conjugate with at least ~~a buffering agent, an isotonicity agent, a preservative and optionally an~~

~~antioxidant~~succinic 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.

~~36~~32. Method of manufacturing the liquid pharmaceutical formulation of any one of claims 1 to ~~34~~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;~~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.

~~37~~34. The method of manufacturing of any one of claims ~~35~~31 to 33 ~~or 36~~, wherein steps (ii) and (iii) are not reversed.

~~38. The method of manufacturing of claim 36, wherein the PTH conjugate in step (i) is admixed with succinic acid, mannitol, m-cresol and optionally an antioxidant.~~

~~39~~35. The liquid pharmaceutical formulation of any one of claims 1 to ~~34~~30 for use as a medicament.

~~40~~36. Use of the liquid pharmaceutical formulation of any one of claims 1 to ~~34~~30 for the manufacture of a medicament for the treatment, control, delay or prevention of one or more diseases ~~which can be treated, controlled, delayed or prevented with PTH~~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.

~~41. The use of claim 40, wherein the disease is selected from the group consisting of hypoparathyroidism, hyperphosphatemia, osteoporosis, fracture repair, osteomalacia, osteomalacia and osteoporosis in patients with hypophosphatasia, steroid-induced osteoporosis, male osteoporosis, arthritis, osteoarthritis, osteogenesis imperfecta, fibrous dysplasia, rheumatoid arthritis, Paget's disease, humoral hypercalcemia associated with malignancy, 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.~~

~~42~~37. The use of claim ~~40 or 41~~36, wherein the disease is hypoparathyroidism.