Claims

1. Use of a long-acting PTH compound in the manufacture of a medicament for the reduction of bone mineral density (BMD) in a patient having an increased BMD.

2. The use of claim 1, wherein the reduction in BMD is a reduction in the Z-score of at least 0.1.

3. The use of claim 1 or 2, wherein the reduction in BMD is a reduction of BMD in trabecular bones.

4. The use of any one of claims 1 to 3, wherein the reduction in BMD is measured in at least one region selected from the group consisting of lumbar spine L1 to L4, femoral neck and total hip.

5. The use of any one of claims 1 to 4, wherein no reduction in BMD is observed in the distal 1/3 radius.

6. The use of any one of claims 1 to 5, wherein the reduction in BMD does not result in a Z-score below 0.

7. The use of any one of claims 1 to 6, wherein the reduction in BMD is associated with an initial increase in bone turnover markers that trends towards age- and sex-appropriate norms with prolonged use of the long-acting PTH compound.

8. The use of any one of claims 1 to 7, wherein the patient having increased BMD is a patient having a disease selected from the group consisting of hypoparathyroidism; SAPHO syndrome; chronic infective osteomyelitis; osseous tuberous sclerosis; fluorosis; renal osteodystrophy; acromegaly; hepatitis C-associated osteosclerosis; myelofibrosis; mastocytosis; congenital conditions of reduced bone resorption such as osteopetrosis, pycnodysostosis, osteopoikilosis and melorheostosis; congenital conditions of increased bone formation such as sclerosteosis, van Buchem’s disease, LRP5 HBM, LRP4 HBM, craniometaphyseal dysplasia; and conditions of disturbed formation and resorption such as Camurati Engelmann disease and Ghosal syndrome.

9. The use of any one of claims 1 to 8, wherein the patient having increased BMD is a patient having hypoparathyroidism.

10. The use of claim 9, wherein the patient has had hypoparathyroidism for less than 5 years.

11. The use of claim 9 wherein the patient has had hypoparathyroidism for between 5 and 10 years.

12. The use of claim 9, wherein the patient has had hypoparathyroidism for more than 10 years.

13. The use of any one of claims 1 to 8, wherein the patient having increased BMD is a patient having osteopetrosis.

14. The use of any one of claims 1 to 13, wherein the long-acting PTH compound is to be administered to the patient in the form of a pharmaceutical composition comprising one or more long-acting PTH compound and at least one excipient.

15. The use of any one of claims 1 to 14, wherein the long-acting PTH compound is to be administered to the patient once daily.

16. The use of a long-acting PTH compound in the manufacture of a medicament for the treatment of hypoparathyroidism, wherein the medicament is to be administered in a dosage regimen, in which the dose of the long-acting PTH compound is increased in the course of the treatment and wherein such dosage regimen comprises the steps of

(i) titrating the dose of the long-acting PTH compound administered to the patient to result in normal serum calcium levels in the patient and maintaining the patient on such dose for a first time period;

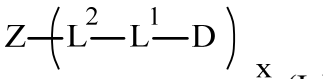
(ii) increasing the dose of the long-acting PTH compound for a second time period directly following the first time period by a factor of at least 1.1; and

(iii) optionally increasing the dose of the long-acting PTH compound for a third or further subsequent time period by a factor of at least 1.1.

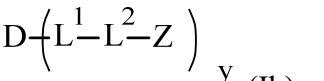
17. The use of claim 16, wherein the first time period is at least 5 months.

18. The use of claim 16 or 17, wherein the second time period is at least 1 month.

19. The use of any one of claims 1 to 18, wherein the long-acting PTH compound is of formula (Ia) or (Ib) or a pharmaceutically acceptable salt thereof



(Ia)



(Ib),

wherein

each -D is individually a PTH moiety;

each -L^1- is individually a linker moiety covalently and reversibly connected to -D;

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

each -Z is individually a carrier moiety, such as a fatty acid derivative or a polymer;

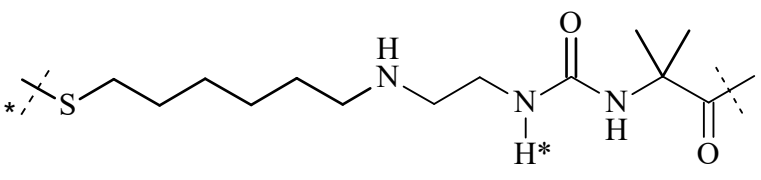
x is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 and 25; and

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

20. The use of claim 19, wherein the long-acting PTH compound is a compound of formula (Ia).

21. The use of claim 19 or 20, wherein the long-acting PTH compound is a compound of formula (Ia) with x = 1.

22. The use of any one of claims 19 to 21, wherein the long-acting PTH compound is of formula (IIf-i):

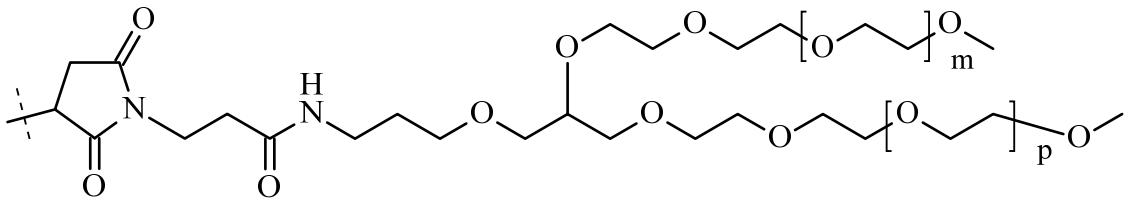


(IIf-i),

wherein

the unmarked dashed line indicates the attachment to a nitrogen of -D through 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.

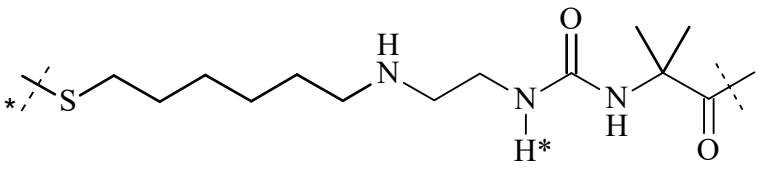
23. The use of claim 22, wherein the unmarked dashed line indicates attachment to the N-terminal amine of a PTH moiety of SEQ ID NO:51.

24. The use of any one of claims 1 to 23, wherein the long-acting PTH compound is to be administered to the patient in the form of a pharmaceutical composition comprising one or more long-acting PTH compound and at least one excipient.

25. The use of any one of claims 1 to 24, wherein the long-acting PTH compound is to be administered to the patient once daily.

26. The use of any one of claims 1 to 24, wherein the long-acting PTH compound is to be administered to the patient once a week.

27. A pharmaceutical composition comprising a compound of formula (IIf-ii)

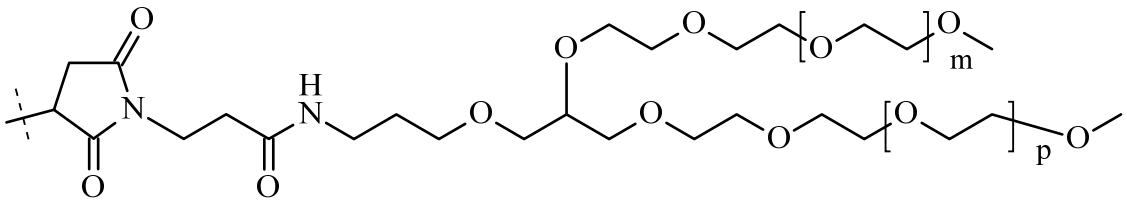


(IIf-ii),

wherein

the unmarked dashed line indicates the attachment to the N-terminal amine of a PTH moiety of SEQ ID NO:51; and

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



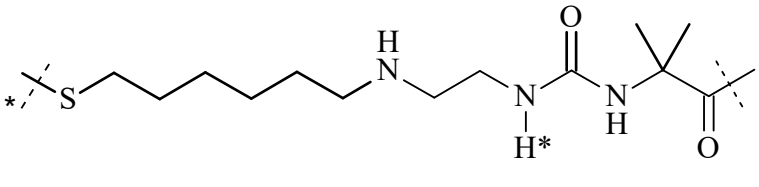
wherein

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

wherein 1 ml of the pharmaceutical composition comprises 3456 µg of the long-acting PTH compound of formula (IIf-ii), 1.18 mg succinic acid, 41.7 mg mannitol, 2.5 mg metacresol, 0.13 mg sodium hydroxide and water for injection.

28. The pharmaceutical composition of claim 27, wherein the pharmaceutical composition has a pH of 3.7 to 4.3.

29. Use of a compound of formula (IIf-ii)

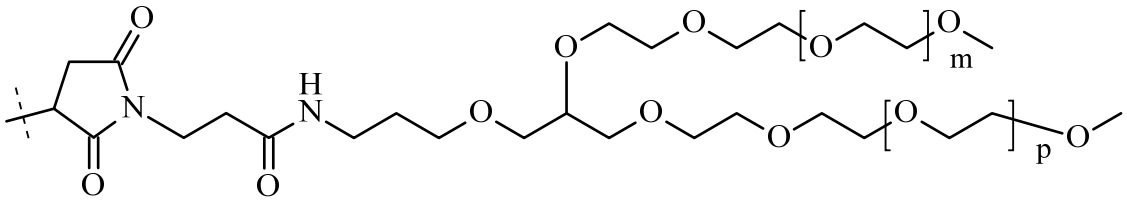


(IIf-ii),

wherein

the unmarked dashed line indicates the attachment to the N-terminal amine of a PTH moiety of SEQ ID NO:51; 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,

or a pharmaceutical composition comprising the compound of formula (IIf-ii), in the manufacture of a medicament for the treatment of hypoparathyroidism, wherein the treatment is initiated by

a) confirming that the serum 25(OH) vitamin D of the patient is within the normal range within two weeks before the first dose of the compound of formula (IIf-ii) is to be administered to the patient and serum calcium is ≥ 7.8 mg/dL at the initiation of treatment;

b) if the patient is taking active vitamin D at the time treatment with the compound of formula (IIf-ii) is initiated:

b-i) maintaining the same dose of calcium supplements and discontinue active vitamin D on the same day as the first dose of the compound of formula (IIf-ii) is to be administered, if serum calcium is ≥ 8.3 mg/dL; or

b-ii) reducing the dose of active vitamin D by ≥50% on the same day as the first dose of the compound of formula (IIf-ii) is to be administered and maintaining the same dose of calcium supplements, if serum calcium is < 8.3 mg/dL; or

if the patient is not taking active vitamin D at the time treatment with the compound of formula (IIf-ii) is initiated:

b-iii) decreasing calcium supplements by at least 1500 mg on the same day as the first dose of the compound of formula (IIf-ii) is to be administered; and

c) optionally continuing dietary calcium supplements at doses of ≤600 mg/day, if calcium supplements are indicated to meet dietary requirements.

30. The use of claim 29, wherein a starting dose of 18 µg PTH(1-34)/day in the form of the compound of formula (IIf-ii) is to be administered, followed by daily administrations of the same dose, and the treatment further comprises the steps of

d) measuring serum calcium within 7 to 14 days of the first administration of the compound of formula (IIf-ii); and

e) adjusting the dose of the compound of formula (IIf-ii), active vitamin D and/or calcium supplement.

31. The use of claim 30, wherein the dose adjusting of step f) are performed as follows:

f-i) if serum calcium is <8.3 mg/dL:

- if ≥7 days have passed since treatment with the compound of formula (IIf-ii) was started or the dose of the compound of formula (IIf-ii) was changed,

the same calcium supplement and active vitamin D doses are continued, and the dose of the compound of formula (IIf-ii) is increased by 3 μg; or

- if fewer than 7 days have passed since treatment with the compound of formula (IIf-ii) has started or the dose of the compound of formula (IIf-ii) was changed, calcium supplements and/or active vitamin D are increased toward prior doses based on physician's clinical judgement and the same dose of the compound of formula (IIf-ii) is continued;

f-ii) if serum calcium ranges from 8.3 to 10.6 mg/dL:

- if ≥7 days have passed since treatment with the compound of formula (IIf-ii) was started or since the dose of the compound of formula (IIf-ii) was changed and the patient is still taking active vitamin D, active vitamin D is discontinued, and the dose of the compound of formula (IIf-ii) is increased by 3 μg;
- if ≥7 days have passed since treatment with the compound of formula (IIf-ii) was started or since the dose of the compound of formula (IIf-ii) was changed and the patient is no longer taking active vitamin D, but is taking calcium supplements, wherein the calcium supplement is ≥1500 mg/day, the calcium supplement is decreased by ≥1500 mg and the dose of the compound of formula (IIf-ii) is increased by 3 μg;
- if ≥7 days have passed since treatment with the compound of formula (IIf-ii) was started or since the dose of the compound of formula (IIf-ii) was changed and the patient is no longer taking active vitamin D, but is taking calcium supplements, wherein the calcium supplement is less than 1500 mg/day, calcium supplements are discontinued, and the dose of the compound of formula (IIf-ii) is increased by 3 μg;
- if ≥7 days have passed since treatment with the compound of formula (IIf-ii) was started or since the dose of the compound of formula (IIf-ii) was changed and the patient is no longer taking active vitamin D and is no longer taking calcium supplements, the same dose of the compound of formula (IIf-ii) is continued; or
- if fewer than 7 days have passed since treatment with the compound of formula (IIf-ii) was started or since the dose of the compound of formula (IIf-ii) was changed, the same dose of the compound of formula (IIf-ii), of the calcium supplement and active vitamin D is continued;

f-iii) if serum calcium ranges from 10.7 to 11.9 mg/dL:

- if the patient is still taking active vitamin D, active vitamin D is discontinued and the same doses of the compound of formula (IIf-ii) and calcium supplement are continued;
- if the patient is not taking active vitamin D but takes calcium supplements at a dose of ≥1500 mg/day, calcium supplements are decreased by ≥1500 mg and the same dose of the compound of formula (IIf-ii) is continued;
- if the patient is not taking active vitamin D but takes calcium supplements, which calcium supplements are less than 1500 mg per day, calcium supplements are discontinued, and the same dose of the compound of formula (IIf-ii) is continued; or
- if the patient is not taking active vitamin D and does not take calcium supplements, the dose of the compound of formula (IIf-ii) is decreased by 3 μg; or

f-iv) if serum calcium is ≥ 12 mg/dL:

- withhold the compound of formula (IIf-ii) for 2 to 3 days, recheck serum calcium and
  - if subsequent serum calcium is <12 mg/dL, resume titration of the compound of formula (IIf-ii), active vitamin D and calcium supplements as described in steps f-i) to f-iii) using the most recent serum calcium value obtained; and
  - if serum calcium remains ≥ 12 mg/dL, withhold the compound of formula (IIf-ii) for an additional 2 to 3 days, recheck serum calcium and proceed as described in the previous step.

32. The use of any one of claims 29 to 31, wherein a daily maintenance dose is to be administered, and the treatment further comprises the step of

g) measuring serum calcium per standard of care.