However, the requirement to be reliant on an infusion pump is cumbersome for patients, and it would be a significant improvement if a continuous infusion-like exposure to PTH could be achieved with a single daily injection.

In order to address this issue reversible polymer conjugates of PTH were developed (WO2017/148883A1), which provide a sustained continuous release of PTH with daily injections. As both hypo- and hypercalcemia is associated with significant morbidity, it is paramount that the starting dose of such daily therapy is properly selected to ensure that patients receive both a clinical benefit while reducing the risk of adverse effects. So far, no information regarding suitable and safe starting doses for such PTH conjugates is available.

Thus, there is a need for identifying a safe and efficacious starting dose of a long acting PTH conjugates. This is the objective of the present disclosure.

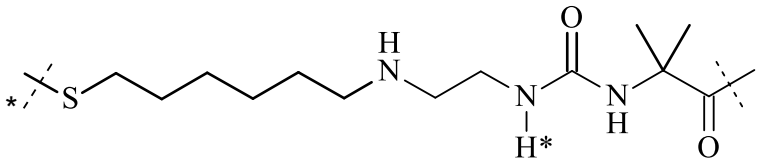
This object is achieved with a PTH conjugate, in which a PTH moiety is reversibly conjugated to a polymeric moiety or fatty acid-based moiety, or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising said PTH conjugate or pharmaceutically acceptable salt thereof for use in the treatment, control, delay or prevention of a disease that can be treated, controlled, delayed or prevented with PTH, wherein the starting dose ranges from 0.8 to 4.9 nmol/day. In certain examples the starting dose ranges from 0.8 to 3.9 nmol/day.

In another example the present disclosure relates to a method of treating, controlling, delaying or preventing in a patient suffering from a disease which can be treated, controlled, delayed or prevented with PTH, comprising administering an effective amount of a PTH conjugate, in which a PTH moiety is reversibly conjugated to a polymeric moiety or fatty acid-based moiety, or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising said PTH conjugate or pharmaceutically acceptable salt thereof to the patient in a starting dose ranging from 0.8 to 4.9 nmol/day. In certain examples the starting dose ranges from 0.8 to 3.9 nmol/day.

It was surprisingly found that a dose in the range 0.8 to 4.9 nmol/day, was able to induce suppression of endogenous PTH(1-84) secretion, while not inducing hypercalcemia and that a

dose in the range 0.8 to 3.9 nmol/day was able to increase serum calcium, while not completely suppressing endogenous PTH(1-84) secretion.

In one aspect, the present disclosure relates to use of a PTH conjugate, in which a PTH moiety is reversibly conjugated to a polymeric moiety or fatty acid-based moiety, or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising said PTH conjugate or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of hypoparathyroidism, wherein the medicament is to be administered at a starting dose that ranges from 0.8 to 4.9 nmol/day and wherein the PTH conjugate is of formula (IIf-i):

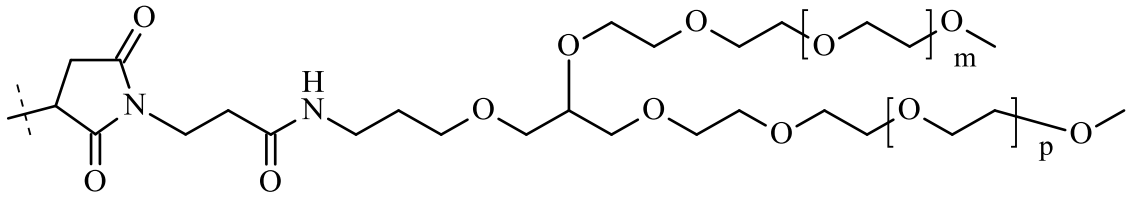


(IIf-i),

wherein

the unmarked dashed line indicates the attachment to the N-terminal amine functional group of a PTH moiety having the sequence of SEQ ID NO:51 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.

Within the present invention the terms are used having the meaning as follows.

As used herein the term “starting dose” refers to the dose of the PTH conjugate of the present invention that is administered to a patient when first initiating therapy with a PTH conjugate, i.e. such patient has not previously received a dose of said PTH conjugate. It is understood, that such starting dose may be continued for a period of time, such as several weeks or months, to allow the patient to stabilize and adjust other medication, such as oral calcium and active vitamin D.

As used herein the term “PTH” refers to all PTH polypeptides, preferably from mammalian species, more preferably from human and primate species, more preferably from human, as well as their variants, analogs, orthologs, homologs, and derivatives and fragments thereof, that are characterized by raising serum calcium and renal phosphorus excretion and lowering serum phosphorus and renal calcium excretion. The term “PTH” also refers to all PTHrP polypeptides, such as the polypeptide of SEQ ID NO:121, that bind to and activate the common PTH/PTHrP1 receptor. Preferably, the term “PTH” refers to the PTH polypeptide of SEQ ID NO:51 as well as its variants, homologs and derivatives exhibiting essentially the same biological activity, i.e. raising serum calcium and renal phosphorus excretion, and lowering serum phosphorus and renal calcium excretion.

Preferably, the term “PTH” refers to a polypeptide sequence selected from the group consisting of:

SEQ ID NO:1 (PTH 1-84)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE DNVLVESHEKSLGEADKADVNVLTKAKSQ

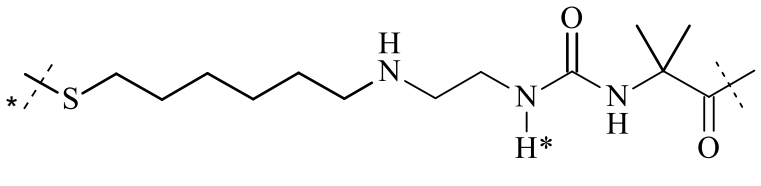
SEQ ID NO:2 (PTH 1-83)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE DNVLVESHEKSLGEADKADVNVLTKAKS

SEQ ID NO:3 (PTH 1-82)

Claims

1. Use of a PTH conjugate, in which a PTH moiety is reversibly conjugated to a polymeric moiety or fatty acid-based moiety, or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising said PTH conjugate or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of hypoparathyroidism, wherein the medicament is to be administered at a starting dose that ranges from 0.8 to 4.9 nmol/day and wherein the PTH conjugate is of formula (IIf-i):

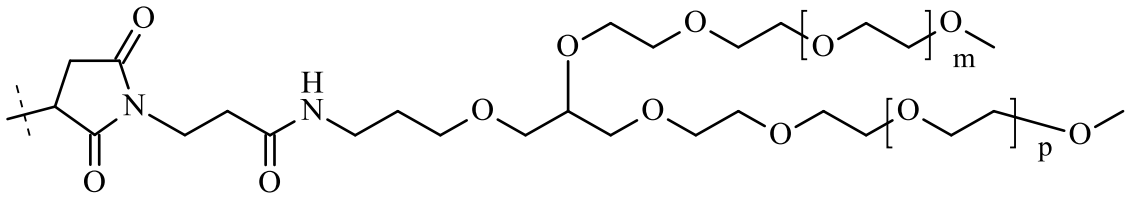


(IIf-i),

wherein

the unmarked dashed line indicates the attachment to the N-terminal amine functional group of a PTH moiety having the sequence of SEQ ID NO:51 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..

2. The use of claim 1, wherein the starting dose ranges from 2.9 to 4.5 nmol/day.

3. The use of claim 1, wherein the starting dose ranges from 3.6 to 4.4 nmol/day.

4. The use of claim 1, wherein the starting dose ranges from 0.8 to 3.9 nmol/day.

5. The use of claim 1 or 4, wherein the starting dose ranges from 1.5 to 3.4 nmol/day.

6. The use of any one of claims 1, 4 or 5, wherein the starting dose is 2.9 ± 0.3 nmol/day.

7. The use of claim 1, wherein the starting dose is 4.3 ± 0.3 nmol/day.

8. The use of claim 1 or 7, wherein the starting dose is 4.3 ± 0.2 nmol/day.

9. The use of claim 1 or 7, wherein the starting dose is 4.3 ± 0.1 nmol/day.

10. The use of any one of claims 1 to 9, wherein the starting dose is to be administered to a patient as one subcutaneous injection.