expression of CYP27B1 in the kidney and, thereby, increases conversion of calcifediol to calcitriol. When serum calcitriol levels are restored to adequate levels, PTH secretion decreases. If serum calcitriol levels cannot be corrected, as in the case of a calcifediol supply shortage (i.e., vitamin D insufficiency), plasma PTH remains elevated causing continuous mobilization of calcium from bone. A recent study (Berruti et al. (2012) *Oncologist* 17, 645-652) reported that 82% to 90% of subjects with prostate cancer metastatic to bone and receiving zoledronic acid exhibited elevated PTH, compared to 17% of patients receiving placebo. The elevated PTH was negatively associated with survival. The prevalence and persistence of SHPT in patients on antiresorptive therapies even though supplemented with Vitamin D and calcium indicates that appropriate supplementation regimens have not yet been clearly defined for this patient population, and the efficacy of antiresorptive agents can be limited by even mild hypocalcemia and/or SHPT.

[0017] Clearly, an alternative approach to currently available Vitamin D supplementation is needed in patients with cancer and in patients treated with an agent that increases the risk of hypocalcemia.

SUMMARY

[0018] The present disclosure relates to 25-hydroxyvitamin D therapy as adjunctive therapy and/or to treat cancer in a patient.
[0018a] In one aspect, the present disclosure relates to a pharmaceutical formulation for oral administration comprising (a) a core region comprising a 25-hydroxyvitamin D compound in a matrix that releasably binds and controllably releases the 25-hydroxyvitamin D compound and (b) an outer region comprising an agent that increases the risk of hypocalcemia, wherein the agent that increases the risk of hypocalcemia comprises cinacalcet or a salt thereof.

[0019] In one example, a method of treating or preventing iatrogenic hypocalcemia and/or secondary hyperparathyroidism in a patient treated with an agent that increases the risk of hypocalcemia comprises administering to the patient an effective amount of 25-hydroxyvitamin D, for example, administering a pharmaceutical formulation comprising (a) a first region comprising a 25-hydroxyvitamin D compound and (b) a second region comprising an agent that increases the risk of hypocalcemia, optionally cinacalcet or a pharmaceutically acceptable salt thereof, described herein.

[0020] In another exapmle, a method of increasing bone mineral density in a patient treated with an agent that increases the risk of hypocalcemia comprises administering to the patient an effective amount of 25-hydroxyvitamin D.

[0021] In another example, a method of decreasing the blood level of a bone resorption marker in a patient treated with an agent that increases the risk of hypocalcemia comprises administering to the patient an effective amount of 25-hydroxyvitamin D. In another example, a method of treating bone pain in a patient treated with an agent that increases the risk of hypocalcemia comprises administering to the patient an effective amount of 25-hydroxyvitamin D.

[0022] In another example, a method of increasing the time to the first post-treatment skeletal-related event in a patient treated with an agent that increases the risk of hypocalcemia comprises administering to the patient an effective amount of 25-hydroxyvitamin D. In another example, a method of treating a patient treated with an agent that increases the risk of hypocalcemia comprises administering to the patient an effective amount of 25-hydroxyvitamin D to effectively and safely restore blood 25-hydroxyvitamin D levels to at least 30 ng/mL and to maintain blood 25-hydroxyvitamin D levels at such optimal levels.

[0023] In any of the methods disclosed herein, the agent that increases the risk of hypocalcemia is optionally selected from the group consisting of an antiresorptive agent, an anti-convulsant agent, a corticosteroid, an antihypercalcemia agent, an antimicrobial agent, and combinations thereof. In one example, the agent that increases the risk of hypocalcemia is an antiresorptive agent, optionally selected from the group consisting of bisphosphonates (e.g., zoledronic acid, alendronate, risedronate, ibandronate, etidronate, and pamidronate), selective estrogen receptor modulators (e.g., raloxifene), calcitonin, hormones (e.g., estrogen), and monoclonal antibodies (e.g., denosumab). In another example, the agent that increases the risk of hypocalcemia is an antihypercalcemia agent, for example, cinacalcet.

[0024] In one example, a method of treating secondary hyperparathyroidism in Chronic Kidney Disease in a patient on dialysis comprises administering to said patient an effective amount of a 25-hydroxyvitamin D compound by modified release and an effective dose of cinacalcet or a pharmaceutically acceptable salt thereof in an amount of less than about 360 mg daily, wherein said effective amount of cinacalcet or a pharmaceutically acceptable salt thereof is a reduced dose compared to the effective dose of cinacalcet or a pharmaceutically acceptable salt thereof in the absence of said 25-hydroxyvitamin D administration.
[0024a] In another apect, the present disclosure relates to use of the formulation of claim 1 in the manufacture of a medicament for treating secondary hyperparathyroidism in Chronic Kidney Disease in a patient on dialysis, wherein the use comprises that the medicament is to be administered to said patient an effective amount of a 25-hydroxyvitamin D compound by modified release and an effective dose of cinacalcet or a salt thereof in an amount of less than 360 mg daily, and wherein said effective amount of cinacalcet is a reduced dose compared to the effective dose of cinacalcet in the absence of said 25-hydroxyvitamin D administration.

[0025] In another example, a method of treating hypercalcemia in a patient with parathyroid carcinoma comprises administering to said patient an effective amount of a 25-

hydroxyvitamin D compound by modified release and an effective dose of cinacalcet or a pharmaceutically acceptable salt thereof in an amount of less than about 360 mg daily, wherein said effective amount of cinacalcet or a pharmaceutically acceptable salt thereof is a reduced dose compared to the effective dose of cinacalcet or a pharmaceutically acceptable salt thereof in the absence of said 25-hydroxyvitamin D administration.

[0025a] In another aspect, the present disclosure relates to use of the formulation of claim 1 in the manufacture of a medicament for treating hypercalcemia in a patient with parathyroid carcinoma, wherein the use comprises that the medicament is to be administered to said patient an effective amount of a 25-hydroxyvitamin D compound by modified release and an effective dose of cinacalcet or a salt thereof in an amount of less than 360 mg daily, and wherein said effective amount of cinacalcet or a salt thereof is a reduced dose compared to the effective dose of cinacalcet in the absence of said 25-hydroxyvitamin D administration.

[0026] In still another example, a method of treating severe hypercalcemia in a patient with primary hyperparathyroidism who is unable to undergo parathyroidectomy comprises administering to said patient an effective amount of a 25-hydroxyvitamin D compound by modified release and an effective dose of cinacalcet or a pharmaceutically acceptable salt thereof in an amount of less than about 360 mg daily, wherein said effective amount of cinacalcet or a pharmaceutically acceptable salt thereof is a reduced dose compared to the effective dose of cinacalcet or a pharmaceutically acceptable salt thereof in the absence of said 25-hydroxyvitamin D administration.

[0026a] In another aspect, the present disclosure relates to use of the formulation of claim 1 in the manufacture of a medicament for treating severe hypercalcemia in a patient with primary hyperparathyroidism who is unable to undergo parathyroidectomy, wherein the use comprises that the medicament is to be administered to said patient an effective amount of a 25-hydroxyvitamin D compound by modified release and an effective dose of cinacalcet or a salt thereof in an amount of less than 360 mg daily, and wherein said effective amount of cinacalcet or a salt thereof is a reduced dose compared to the effective dose of cinacalcet in the absence of said 25-hydroxyvitamin D administration.

[0027] In another example, a method of lowering elevated serum parathyroid hormone levels in a patient having a bone metastasis and treated with an antiresorptive agent comprises administering an effective amount of 25-hydroxyvitamin D. In another example, a method of stabilizing serum calcium levels in a patient having a bone metastasis and treated with an antiresorptive agent comprises administering an effective amount of 25-hydroxyvitamin D. In still another example, a method of treating hungry bone syndrome comprises administering an effective amount of 25-hydroxyvitamin D to a patient in need of thereof.

[0028] In any of the methods of the present disclosure, the patient optionally has osteoporosis and/or cancer. In one example, a method of managing iatrogenic hypocalcemia and secondary hyperparathyroidism in a patient with a bone metastasis treated with an antiresorptive agent comprises administering an effective amount of 25-hydroxyvitamin D to prevent or reverse the iatrogenic hypocalcemia and lower the patient's serum parathyroid hormone level. In another example, a method of mitigating cancer progression and/or a skeletal related event in a patient with a bone tumor, optionally a bone metastasis from a solid tumor, comprises treating the patient with (a) an anticancer agent; (b) an antiresorptive agent; and (c) a 25-hydroxyvitamin D compound, wherein the combination of (a), (b), and (c) is effective to slow tumor growth and/or metastasis and/or increase the time to the first post-treatment skeletal-related event. In still another example, a method of treating a patient having cancer

and a bone metastasis comprises the administration of (a) a prophylactic and continuing course of an effective amount of 25-hydroxyvitamin D to stabilize 25-hydroxyvitamin D levels and calcium levels in the patient without causing or exacerbating hypercalcemia; followed by (b) treatment with an agent known to increase the risk of iatrogenic hypocalcemia, wherein the treatment in step (a) prevents and/or treats the iatrogenic hypocalcemia in the patient.

[0028a] In another aspect, the present disclosure relates to use of a pharmaceutical formulation of claim 1 in the manufacture of a medicament for managing iatrogenic hypocalcemia and secondary hyperparathyroidism in a patient receiving therapy with cinacalcet or a salt thereof.

[0029] In another example, a method of mitigating the progression of cancer in the bone in a patient comprises administering an effective amount of 25-hydroxyvitamin D. In another example, a method of inhibiting the proliferation and migration of cancer cells comprises administering an effective amount of 25-hydroxyvitamin D to a patient in need thereof. In another example, a method of treating cancer in a patient comprises administering to the patient an effective amount of a combination of 25-hydroxyvitamin D and an anticancer agent. In any of the foregoing methods, the patient optionally has a cancer selected from the group consisting of bone cancer, bladder cancer, breast cancer, colon cancer, endometrial cancer, kidney cancer, leukemia, lung cancer, lymphoma, pancreatic cancer, prostate cancer, skin cancer, thyroid cancer, and metastatic forms thereof.

[0030] The present disclosure also relates to the use of 25-hydroxyvitamin D, optionally in a modified release formulation, as adjunctive therapy to treat hypocalcemia in a patient in need thereof. In one example, the disclosure provides a pharmaceutical composition comprising (a) 25-hydroxyvitamin D and (b) an agent that increases the risk of hypocalcemia and/or an anticancer agent. In one example, the disclosure provides a pharmaceutical formulation for oral administration comprising (a) a 25-hydroxyvitamin D compound and (b) an agent that increases the risk of hypocalcemia, optionally cinacalcet or a pharmaceutically acceptable salt thereof. For example, in one example, the pharmaceutical formulation comprises a first region comprising a 25-hydroxyvitamin D compound and a second region comprising an agent that increases the risk of hypocalcemia, optionally cinacalcet or a pharmaceutically acceptable salt thereof.

[0031] In another example, the disclosure provides a kit comprising (a) 25-hydroxyvitamin D; (b) an agent that increases the risk of hypocalcemia and/or an anticancer agent; and (c) instructions for co-administering effective amounts of (a) and (b) to a patient in need thereof.

[0032] In another example, a method or pharmaceutical formulation according to the present disclosure comprises 25-hydroxyvitamin D in a modified release formulation, optionally an oral modified release formulation. In another example, the 25-hydroxyvitamin D is administered in a sterile intravenous formulation. In various examples, the 25-hydroxyvitamin D can be selected from the group consisting of 25-hydroxyvitamin D_2, 25-hydroxyvitamin D_3, 25-hydroxyvitamin D_4, 25-hydroxyvitamin D_5, 25-hydroxyvitamin D_7 and combinations thereof. In another example, a method or pharmaceutical formulation according to the present disclosure comprises cinacalcet or a pharmaceutically acceptable salt thereof in an immediate release formulation, optionally an oral rapidly dissolving formulation.

[0033] For the compositions and methods described herein, optional features, including but not limited to components, compositional ranges thereof, substituents, conditions, and steps, are contemplated to be selected from the various examples provided herein.

[0034] Further examples and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description. While the compositions and methods are susceptible of examples in various forms, the description hereafter includes specific examples with the understanding that the disclosure is illustrative and is not intended to limit the disclosure to the specific examples described herein.

DETAILED DESCRIPTION

[0035] The present disclosure relates to 25-hydroxyvitamin D therapy as adjunctive therapy and in the treatment of cancer. In various embodiments, the disclosure provides methods for dosing a subject receiving treatment with an agent that increases the risk of hypocalcemia and/or an anticancer agent with an effective amount of 25-hydroxyvitamin D, optionally as a modified release oral formulation or administered in intravenous form. The administration of 25-hydroxyvitamin D to a patient, for example, in a pharmaceutical formulation comprising 25-hydroxyvitamin D and an agent that increases the risk of hypocalcemia, such as cinacalcet or a pharmaceutically acceptable salt thereof, according to the present disclosure effectively achieves one or more of the following: (a) treats or prevents hypocalcemia, e.g., iatrogenic hypocalcemia; (2) treats or prevents secondary hyperparathyroidism, e.g., in a patient having Chronic Kidney Disease; (3) increases bone mineral density; (4) decreases the blood level of a bone resorption marker; (5) decreases bone

What is claimed is:

1. A pharmaceutical formulation for oral administration comprising (a) a core region comprising a 25-hydroxyvitamin D compound in a matrix that releasably binds and controllably releases the 25-hydroxyvitamin D compound and (b) an outer region comprising an agent that increases the risk of hypocalcemia, wherein the agent that increases the risk of hypocalcemia comprises cinacalcet or a salt thereof.

2. The pharmaceutical formulation of claim 1, wherein the matrix comprising the 25-hydroxyvitamin D compound comprises a wax, an emulsifier, an absorption enhancer, and a stabilizing agent.

3. The pharmaceutical formulation of claim 2, wherein the matrix comprising the 25-hydroxyvitamin D compound includes 20 wt% paraffin, 20 wt% to 25 wt% glycerol monostearate, 10 wt% a mixture of lauroyl macrogolglycerides and lauroyl polyoxylglycerides, 30 wt% to 35 wt% mineral oil, and 10 wt% to 15 wt% hydroxyl propyl methylcellulose.

4. The pharmaceutical formulation of claim 1, characterized by an in vitro dissolution profile providing release of the 25-hydroxyvitamin D compound of 20% to 40% at 2 hours, at least 35% at 6 hours, and at least 70% at 12 hours.

5. The pharmaceutical formulation of claim 4, characterized by an in vitro dissolution profile providing release of the agent that increases the risk of hypocalcemia of at least 50% at 30 minutes.

6. The pharmaceutical formulation of claim 1, wherein the formulation comprises a capsule having a hard shell.

7. The pharmaceutical formulation of claim 1, wherein the formulation comprises a soft capsule.

8. The pharmaceutical formulation of claim 1, comprising the agent that increases the risk of hypocalcemia disposed in a first capsule shell and the 25-hydroxyvitamin D compound is disposed in second capsule shell, the second capsule shell being disposed within the first capsule shell.

9. The pharmaceutical formulation of claim 1, comprising the agent that increases the risk of hypocalcemia in granular form.

10. The pharmaceutical formulation of claim 1, wherein the agent that increases the risk of hypocalcemia is disposed within a coating.

11. The pharmaceutical formulation of claim 1, wherein the agent that increases the risk of hypocalcemia is formulated for rapid release.

12. The pharmaceutical formulation of claim 1, wherein the 25-hydroxyvitamin D compound is 25-hydroxyvitamin D_2, 25-hydroxyvitamin D_3, or a combination thereof.

13. The pharmaceutical formulation of claim 12, wherein the 25-hydroxyvitamin D compound is 25-hydroxyvitamin D_3.

14. The pharmaceutical formulation of claim 1, comprising the 25-hydroxyvitamin D compound in an amount between 1 mcg and 1000 mcg.

15. The pharmaceutical formulation of claim 1, comprising the 25-hydroxyvitamin D compound in an amount between 1 mcg and 100 mcg.

16. The pharmaceutical formulation of claim 1, comprising the agent that increases the risk of hypocalcemia in an amount between 1 mg and 100 mg.

17. The pharmaceutical formulation of claim 1, wherein the cinacalcet or salt thereof comprises cinacalcet HCl.

18. The pharmaceutical formulation of claim 1, further comprising a disintegrant, optionally in an amount of 1 wt% to 10 wt%.

19. The pharmaceutical formulation of claim 1, wherein the region comprising the agent that increases the risk of hypocalcemia comprises from 10% to 40% by weight of cinacalcet or a salt thereof, from 45% to 85% by weight of at least one diluent, and from 1% to 10% by weight of at least one disintegrant, optionally further comprising from 1% to 5% by weight of at least one binder, wherein the percentage by weight is relative to the total weight of the region.

20. The pharmaceutical formulation of claim 1, wherein the region comprising the agent that increases the risk of hypocalcemia comprises:
(a) from 10% to 40% by weight of cinacalcet or salt thereof;
(b) from 40% to 75% by weight of microcrystalline cellulose;
(c) from 5% to 35% by weight of starch;
(d) from 1% to 10% by weight of crospovidone;
(e) from 0.05% to 1.5% by weight of colloidal silicon dioxide; and
(f) from 0.05% to 1.5% by weight of magnesium stearate;
wherein the percentage by weight is relative to the total weight of the region.

21. The pharmaceutical formulation of claim 1, wherein the region comprising the agent that increases the risk of hypocalcemia comprises:
(a) from 10% to 40% by weight of cinacalcet or salt thereof;
(b) from 40% to 75% by weight of microcrystalline cellulose;
(c) from 1% to 5% by weight of povidone;
(d) from 5% to 35% by weight of starch;
(e) from 0.05% to 1.5% by weight of colloidal silicon dioxide; and
(f) from 0.05% to 1.5% by weight of magnesium stearate;
wherein the percentage by weight is relative to the total weight of the region.

22. The pharmaceutical formulation of claim 1, wherein the region comprising the agent that increases the risk of hypocalcemia comprises:
(a) from 10% to 40% by weight of cinacalcet or salt thereof;
(b) from 40% to 75% by weight of microcrystalline cellulose;
(c) from 15% to 50% by weight of starch;
(d) from 0.05% to 1.5% by weight of colloidal silicon dioxide; and
(e) from 0.05% to 1.5% by weight of magnesium stearate;
wherein the percentage by weight is relative to the total weight of the region.

23. The pharmaceutical formulation of claim 1, wherein the region comprising the agent that increases the risk of hypocalcemia comprises:
(a) from 10% to 40% by weight of cinacalcet or salt thereof;
(b) from 40% to 75% by weight of microcrystalline cellulose;
(c) from 1% to 5% by weight of povidone;

(d) from 1% to 10% by weight of a disintegrant selected from the group consisting of croscarmellose, sodium starch glycolate, crosslinked cellulose, crosslinked polymers, crosslinked starches, and combinations thereof;
(e) from 0.05% to 1.5% by weight of colloidal silicon dioxide; and
(f) from 0.05% to 1.5% by weight of magnesium stearate;
wherein the percentage by weight is relative to the total weight of the region.

24. The pharmaceutical formulation of claim 1, wherein the region comprising the agent that increases the risk of hypocalcemia comprises:
(a) from 10% to 40% by weight of cinacalcet or salt thereof;
(b) from 40% to 75% by weight of microcrystalline cellulose;
(c) from 1% to 5% by weight of a binder selected from the group consisting of gelatin, acacia, tragacanth, alginic acid, cellulose, methyl cellulose, ethyl cellulose, HPMC, HPC, sodium carboxy methyl cellulose, PEG, PVA, polymethacrylate, polyvinylcaprolactam, and combinations thereof;
(d) from 5% to 35% by weight of starch;
(e) from 1% to 10% by weight of crospovidone;
(f) from 0.05% to 1.5% by weight of colloidal silicon dioxide; and
(g) from 0.05% to 1.5% by weight of magnesium stearate;
wherein the percentage by weight is relative to the total weight of the region.

25. Use of a pharmaceutical formulation of claim 1 in the manufacture of a medicament for managing iatrogenic hypocalcemia and secondary hyperparathyroidism in a patient receiving therapy with cinacalcet or a salt thereof.

26. The use of claim 25, wherein the patient has impaired renal function, optionally associated with Chronic Kidney Disease Stage 1, 2, 3, 4, or 5.

27. The use of claim 25, wherein the patient is receiving dialysis.

28. The use of claim 25, wherein the patient is not on dialysis.

29. The use of claim 25, wherein the effective amount of 25-hydroxyvitamin D is effective to restore or maintain the patient's serum calcium level to at least 8.0 mg/dL, optionally in a range of 8.3 mg/dL to 11.6 mg/dL.

30. The use of claim 25, wherein the effective amount of 25-hydroxyvitamin D is effective to safely increase the patient's serum level of 25-hydroxyvitamin D to at least 30 ng/mL, optionally in a range of 30 ng/mL to 100 ng/mL.

31. The use of claim 25, wherein the effective amount of 25-hydroxyvitamin D is effective to decrease the patient's serum parathyroid hormone level, optionally by 30% or more.

32. The use of claim 25, wherein the effective amount of 25-hydroxyvitamin D is to be administered in an oral modified release formulation, optionally a sustained release formulation.

33. The use of claim 25, wherein the 25-hydroxyvitamin D comprises 25-hydroxyvitamin D_3, 25-hydroxyvitamin D_2, or a combination thereof.

34. The use of claim 33, wherein the 25-hydroxyvitamin D comprises 25-hydroxyvitamin D_3.

35. The use of claim 25, wherein the 25-hydroxyvitamin D is to be administered in a dosage of 1 mcg to 1000 mcg per day.

36. The use of claim 25, wherein the cinacalcet or salt thereof comprises cinacalcet HCl.

37. The use of claim 25, wherein the patient is receiving cinacalcet to be administered in a dosage of 1 mg to 400 mg per day.

38. Use of the formulation of claim 1 in the manufacture of a medicament for treating secondary hyperparathyroidism in Chronic Kidney Disease in a patient on dialysis, wherein the use comprises that the medicament is to be administered to said patient an effective amount of a 25-hydroxyvitamin D compound by modified release and an effective dose of cinacalcet or a salt thereof in an amount of less than 360 mg daily, and wherein said effective amount of cinacalcet is a reduced dose compared to the effective dose of cinacalcet in the absence of said 25-hydroxyvitamin D administration.

39. The use of claim 38, comprising an initial dose of cinacalcet in a range of 20 mg to 25 mg once daily.

40. Use of the formulation of claim 1 in the manufacture of a medicament for treating hypercalcemia in a patient with parathyroid carcinoma, wherein the use comprises that the medicament is to be administered to said patient an effective amount of a 25-hydroxyvitamin D compound by modified release and an effective dose of cinacalcet or a salt thereof in an amount of less than 360 mg daily, and wherein said effective amount of cinacalcet or a salt thereof is a reduced dose compared to the effective dose of cinacalcet in the absence of said 25-hydroxyvitamin D administration.

41. Use of the formulation of claim 1 in the manufacture of a medicament for treating severe hypercalcemia in a patient with primary hyperparathyroidism who is unable to undergo parathyroidectomy, wherein the use comprises that the medicament is to be administered to said patient an effective amount of a 25-hydroxyvitamin D compound by modified release and an effective dose of cinacalcet or a salt thereof in an amount of less than 360 mg daily, and wherein said effective amount of cinacalcet or a salt thereof is a reduced dose compared to the effective dose of cinacalcet in the absence of said 25-hydroxyvitamin D administration.

42. The use of claim 40, comprising an initial dose of cinacalcet in a rage of 20 mg to 25 mg once daily.

43. The use of claim 40, wherein the effective amount of 25-hydroxyvitamin D is in a range of 100 mcg to 300 mcg.