IOWA | Health and Human Services

PDL DRUG REVIEW

Proprietary Name: Yorvipath®
Common Name: palopegteriparatide
PDL Category: Endocrine Metabolic Agents

Comparable Products	Preferred Drug List Status
Calcium/Vit D	Preferred with Conditions
Calcitriol	Preferred

Pharmacology/Usage: Palopegteriparatide, the active ingredient of Yorvipath®, is a parathyroid hormone analog (PTH(1-34)). Palopegteriparatide is a prodrug of teriparatide (PTH(1-34)), consisting of PTH(1-34) transiently conjugated to an inert carrier via a proprietary TransCon Linker. PTH(1-34) is identical to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone. The carrier is a branched 40 kDa methoxy polyethylene glycol (mPEG) moiety.

At physiological conditions, palopegteriparatide releases PTH(1-34) to maintain a continuous systemic exposure. Endogenous PTH maintains extracellular calcium and phosphate homeostasis by increasing serum calcium and decreasing serum phosphate. These effects are mediated by stimulating bone turnover to mobilize calcium and phosphate from bone, promoting renal calcium reabsorption and phosphate excretion, and facilitating active vitamin D synthesis, in turn increasing intestinal absorption of calcium and phosphate. Similar to endogenous PTH, PTH(1-34) released from palopegteriparatide exerts these effects through its main receptor, parathyroid hormone 1 receptor (PTH1R), which is highly expressed on osteoblasts, osteocytes, renal tubular cells, and in several other tissues.

Indication: For the treatment of hypoparathyroidism in adults.

Limitations of use include that Yorvipath® was not studied for acute post-surgical hypoparathyroidism. In addition, Yorvipath's® titration scheme was only evaluated in adults who first achieved an albumin-corrected serum calcium of at least 7.8mg/dL using calcium and active vitamin D treatment.

There is no pregnancy category for this medication; however, the risk summary indicates that available data from reports of pregnancies in the clinical trials from drug development are not sufficient to identify a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are disease-associated risks to the mother and fetus related to hypocalcemia in pregnancy. If Yorvipath® is administered during pregnancy, or if a patient becomes pregnant while receiving Yorvipath®, healthcare providers should report Yorvipath® exposure by calling 1-844-442-7236. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Solution in single-patient-use prefilled pens for injection, in three presentations. Refer to the table below, which was adapted from the prescribing information. Refrigerate until the first use.

Pen type and strength	Labeled dose (mcg)	Range of deliverable dose (minimum-maximum) (mcg)
Prefilled pen with blue push button (168mcg/0.56ml)	6	4.5 - 7.5
	9	7.5 - 10.5

Pen type and strength	Labeled dose (mcg)	Range of deliverable dose (minimum-maximum) (mcg)
	12	10.5 – 13.5
Prefilled pen with orange push button (294mcg/0.98ml)	15	13.1 – 16.5
	18	16.1 – 19.5
	21	19.1 – 22.5
Prefilled pen with burgundy push button (420mcg/1.4ml)	24	21.6 – 25.5
	27	24.6 – 28.5
	30	27.6 – 31.5

Recommended Dosage: The following includes an overview of dosage and monitoring:

- Use only one injection to achieve the once daily recommended dosage. (Using two Yorvipath® injections to achieve the recommended once daily dosage increases the variability of the total delivered dose, which can cause unintended changes in serum calcium levels, including hypercalcemia and hypocalcemia.)
- The maximum recommended dosage is 30mcg SC QD. If an adequate response is not achieved with a maximum Yorvipath® dosage, consider adding or restarting calcium and/or active vitamin D therapy and/or seek other treatment options.
- Yorvipath's® once daily SC dosage is individualized. The recommended starting dosage is 18mcg QD and is titrated in 3mcg increments or decrements with the goal of maintaining serum calcium within the normal range without the need for active vitamin D (e.g., calcitriol) or therapeutic calcium doses (elemental calcium >600mg/day). Calcium supplementation sufficient to meet daily dietary requirements may be continued.
- Do not increase the Yorvipath® dosage more often than every 7 days. Do not decrease the Yorvipath® dosage more often than every 3 days. The recommended dosage range of Yorvipath® is 6 to 30mcg QD.
- Advise patients to monitor daily for clinical signs and symptoms of hypocalcemia or hypercalcemia.
- Measure serum calcium 7 to 10 days after the first Yorvipath® dose and after any dose change in Yorvipath®, active vitamin D, or calcium supplements, and monitor for clinical signs and symptoms of hypocalcemia or hypercalcemia. Once the Yorvipath® maintenance dosage is achieved, measure serum calcium levels at a minimum every 4 to 6 weeks or as indicated for symptoms of hypocalcemia or hypercalcemia.
- Adjust Yorvipath®, active vitamin D, and/or calcium supplements. Some patients may require an increase in the Yorvipath® dose over time to maintain the same therapeutic effect.

Within two weeks before the first dose of Yorvipath®, confirm serum 25(OH) vitamin D is within the normal range and albumin-corrected serum calcium is ≥7.8mg/dL.

On the day of initiation or up-titration of Yorvipath®, adjust the dose of active vitamin D and calcium supplements based on albumin-corrected serum calcium and current active vitamin D intake. Refer to the prescribing information for the dosage adjustments to active vitamin D (calcitriol) and calcium supplements with initiation or up-titration of Yorvipath®.

The maintenance dosage is individualized and should be the Yorvipath® dose that achieves serum calcium within the normal range, without the need for active vitamin D or therapeutic doses of calcium. Calcium supplementation sufficient to meet daily dietary requirements may be continued. Once the maintenance dosage is achieved, monitor for clinical signs and symptoms of hypocalcemia or hypercalcemia and measure serum calcium levels as indicated, and at a minimum every 4 to 6 weeks, as some patients may need further dose titration. If calcium levels remain low with the maximum recommended dosage of 30mcg QD, consider adding or restarting calcium and/or active vitamin D therapy and/or seek other treatment.

Refer to the prescribing information for information on titration recommendations for albumin-corrected serum calcium less than 12mg/dL and for titration recommendations for albumin-corrected serum calcium 12mg/dL or greater.

Take Yorvipath® as soon as possible if a dose is missed by less than 12 hours. Skip the missed dose if the dose has been missed by more than 12 hours. Take the next dose as scheduled. If Yorvipath® treatment is delayed or interrupted for 3 days or more, assess patients for signs and symptoms of hypocalcemia and consider measuring serum calcium. If indicated, resume treatment with, or increase the dose of, calcium supplements and active vitamin D. Resume Yorvipath® at the previously prescribed dose as soon as possible after an interruption then measure serum calcium within 7 to 10 days and adjust doses of Yorvipath®, active vitamin D, and/or calcium supplements per the prescribing information.

Patients and caregivers who will administer Yorvipath® should receive appropriate training by a healthcare professional prior to the first use. Administer Yorvipath® subcutaneously to the abdomen or front of the thigh, with rotating the injection site daily. In addition, Yorvipath® should be administered initially when the patient can sit or lie down due to the potential of orthostatic hypotension.

Dose adjustments are not required with mild, moderate, or severe renal impairment. In a dedicated renal impairment study, patients with severe renal impairment (eGFR 15 to 30 ml/min/1.73m^2) had no clinically significant difference in total PTH compared to subjects with normal renal function upon treatment with Yorvipath®.

Drug Interactions: Yorvipath® increases serum calcium, thus concomitant use with digoxin (which has a narrow therapeutic index) may predispose patients to digitalis toxicity if hypercalcemia develops. Digoxin efficacy may be reduced if hypocalcemia is present. When Yorvipath® is used concomitantly with digoxin, measure serum calcium and digoxin levels, and monitor for signs and symptoms of digoxin toxicity. Adjustment of the digoxin and/or Yorvipath® dose may be needed.

Drugs that affect serum calcium may alter the therapeutic response to Yorvipath®. Measure serum calcium more frequently when Yorvipath® is used concomitantly with these drugs, especially after these drugs are initiated, discontinued, or dose-adjusted.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Yorvipath®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included injection site reactions (34%), vasodilatory signs and symptoms (28%), headache (11%), diarrhea (5%), back pain (8%), hypercalcemia (8%), and oropharyngeal pain (7%).

Serious events of hypercalcemia requiring hospitalization have been reported with Yorvipath®. The risk is greatest when starting or increasing the dose of Yorvipath® but may occur at any time. Measure serum calcium 7 to 10 days after any dose change or if there are signs or symptoms of hypercalcemia, and at a minimum of every 4 to 6 weeks once the maintenance dose is achieved. Treat hypercalcemia if needed. If albumin-corrected serum calcium is greater than 12mg/dL, withhold Yorvipath® for at least 2-3 days. For less serious hypercalcemia, adjust the dose of Yorvipath®, active vitamin D, and/or calcium supplements.

Serious events of hypocalcemia have been observed with PTH products, including Yorvipath®. The risk is highest when Yorvipath® is abruptly discontinued, but may occur at any time, even in patients who have been on stable doses of Yorvipath®. Measure serum calcium 7 to 10 days after any dose change or if there are signs or symptoms of hypocalcemia, and at a minimum of every 4 to 6 weeks once the maintenance dosage is achieved. Treat

hypocalcemia if needed, and adjust the dose of Yorvipath®, active vitamin D, and/or calcium supplements if hypocalcemia occurs.

Yorvipath® is a PTH analog. An increased incidence of osteosarcoma has been reported in male and female rats treated with PTH analogs, including teriparatide. Osteosarcoma occurrence in rats is dependent on teriparatide or PTH dose and treatment duration. Osteosarcoma has been reported in patients treated with teriparatide in the post marketing setting; however, an increased risk of osteosarcoma has not been observed in observational studies in humans. There are limited data assessing the risk of osteosarcoma beyond 2 years of teriparatide use. Yorvipath® is not recommended in patients who are at increased risk of osteosarcoma, such as patients with:

- Open epiphyses. Yorvipath® is not approved in pediatric patients.
- Metabolic bone diseases other than hypoparathyroidism, including Paget's disease of bone.
- Unexplained elevations of alkaline phosphatase.
- Bone metastases or a history of skeletal malignancies.
- History of external beam or implant radiation therapy involving the skeleton.
- Hereditary disorders predisposing to osteosarcoma.

Instruct patients to promptly report clinical symptoms (e.g., persistent localized pain) and signs (e.g., soft tissue mass tender to palpation) that could be consistent with osteosarcoma.

Orthostatic hypotension has been reported with Yorvipath®. Associated signs and symptoms may include decreased blood pressure, dizziness, palpitations, tachycardia, presyncope, or syncope. Such symptoms can be managed by dosing at bedtime, while reclining. Yorvipath® should be administered initially when the patient can sit or lie down due to the potential of orthostatic hypotension.

Contraindications: In patients with severe hypersensitivity to palopegteriparatide or to any of its excipients. Hypersensitivity reactions, including anaphylaxis, angioedema, and urticaria, have been observed with parathyroid hormone (PTH) analogs.

Manufacturer: Ascendis Pharma

Analysis: The safety and efficacy of Yorvipath® was assessed in a randomized, double-blind, placebo-controlled, phase 3 study of 26 weeks duration that included adults (N=82) with hypoparathyroidism. Before randomization, all patients underwent about a 4-week screening period in which calcium and active vitamin D supplements were adjusted to achieve an albumin-corrected serum calcium concentration between 7.8 and 10.6mg/dL, a magnesium concentration ≥1.3mg/dL and below the upper limit of the reference range, and a 25(OH) vitamin D concentration between 20 to 80ng/mL. During the double-blind period, subjects were randomized to either Yorvipath® (N=61) or placebo (N=21), at a starting dose of 18mcg/day, co-administered with conventional therapy (calcium & active vitamin D). Study drug and conventional therapy were subsequently titrated per albumin-corrected serum calcium levels.

The mean age at enrollment into the study was 49 years (range 19 to 78 years), while 78% were female and 93% were Caucasian. In addition, 85% of subjects had hypoparathyroidism acquired from neck surgery. Of the subjects with other etiologies of hypoparathyroidism, 7 patients (8.5%) had idiopathic disease, 2 had autoimmune polyglandular syndrome type 1 (APS-1), 1 had autosomal dominant hypocalcemia type 1 (ADH1, CaSR mutation), 1 had DiGeorge Syndrome, and 1 had hypoparathyroidism, sensorineural deafness and renal dysplasia (HDR) syndrome (*GATA3* mutation). At baseline, the median duration of hypoparathyroidism was 8.5 years (range 1 to 56 years), while the baseline mean albumin-corrected serum calcium was 8.8mg/dL for Yorvipath® and 8.6mg/dL for the placebo group. In addition, the mean 24-hour urine calcium was 392mg/day for Yorvipath® and 329mg/day for placebo. The mean baseline dose of elemental calcium was 1,839mg/day, while the mean baseline doses of active vitamin D were 0.75mcg/day in calcitriol-treated subjects (N=70) and 2.3mcg/day in alfacalcidol-treated subjects (N=12).

Efficacy was assessed per the proportion of subjects who achieved all of the following at week 26, including:

- Albumin-corrected serum calcium in the normal range (8.3 to 10.6mg/dL),
- Independence from conventional therapy (defined as requiring no active vitamin D and ≤600mg/day of calcium supplementation, including no use of pro re nata [PRN] doses) since week 22,
- No increase in the study drug dose since week 22,
- No missing active vitamin D and calcium data since week 22, and
- Study drug dose of 30mcg or less once daily during the 26-week treatment period.

In the Yorvipath® group, 68.9% met the efficacy endpoint at week 26 compared with 4.8% in the placebo group. The treatment difference was 64.2%. Results are provided in the table below, which was adapted from the prescribing information.

	Yorvipath® (N=61)	Placebo (N=21)	Response rate difference
Overall Response at week 26, n (%)	42 (68.9%)	1 (4.8%)	64.2%
NNT *calculated by Optum Rx*	2		
Response for each component:			
Normal albumin-corrected serum calcium	49 (80.3%)	10 (47.6%)	32.7%
Independence from active vitamin D	58 (95.1%)	5 (23.8%)	71.3%
Independence from therapeutic dose of calcium	53 (86.9%)	1 (4.8%)	82.2%
No increase in study drug dose since week 22	57 (93.4%)	12 (57.1%)	36.4%
Study drug dose ≤30mcg/day up to week 26	56 (91.8%)	Not applicable	Not applicable

The proportion of subjects randomized to Yorvipath® who met the efficacy endpoint decreased over time as follows: 68.9% (42/61) at week 26 and 39.3% (24/61) at both week 52 and week 78 during the open-label extension period. Allowing for dose up-titration, the proportion of subjects who were able to maintain normocalcemia and independence from active vitamin D and therapeutic dose of calcium was 64% (39/61) at week 52 and 66% (40/61) at week 78.

Place in Therapy: Yorvipath® is a parathyroid hormone analog (PTH(1-34)) indicated for the treatment of hypoparathyroidism in adults. Limitations of use include that it was not studied for acute post-surgical hypoparathyroidism. In addition, Yorvipath's® titration scheme was only evaluated in adults who first achieved an albumin-corrected serum calcium of at least 7.8mg/dL using calcium and active vitamin D treatment. First line therapy for patients with hypoparathyroidism is a combination of active vitamin D and oral calcium, rather than PTH. For persistent symptoms despite first line therapy or intolerance to first line therapy, Yorvipath® would be recommended.[2] Within two weeks before the first dose of Yorvipath®, confirm serum 25(OH) vitamin D is within the normal range and albumin-corrected serum calcium is ≥7.8mg/dL. The efficacy of Yorvipath® was assessed in a randomized, double-blind, placebo-controlled, phase 3 study that included adults with hypoparathyroidism (N=82). Results suggested that at week 26, 68.9% of the Yorvipath® group met the efficacy endpoint as compared with 4.8% of the placebo group (*CHC calculated* NNT = 2). Yorvipath® is the only FDA-approved agent for the treatment of adults with hypoparathyroidism and may be a good agent to be used for patients with persistent hypocalcemia, hypercalciuria, or intolerance to conventional therapy.

Summary

It is recommended that Yorvipath® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Yorvipath [package insert]. Princeton, NJ: Ascendis Pharma Endocrinology, Inc; 2024.
[2] UpToDate online. Hypoparathyroidism. Accessed February 2025.

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