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Reviewed: 10/09/24

Revised: 00/00/00

Subject: Palopegteriparatide (Yorvipath) SQ Injection

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DESCRIPTION:

Hypoparathyroidism (HP) is a rare condition caused by low or absent parathyroid hormone (PTH), which results in hypocalcemia and serum phosphate levels in the upper normal or elevated range. HP most commonly occurs in patients who had anterior neck surgery (75-80% of all cases) but may also be the result of an autoimmune or genetic disorder. Complications of HP due to chronic hypocalcemia and/or hyperphosphatemia may include neurologic signs (e.g., extrapyramidal signs, depression), dermatologic presentations (e.g., dry, brittle hair with hair loss, course skin), dental abnormalities (e.g., enamel hypoplasia, delay or lack of tooth eruption), ophthalmologic problems (e.g., blurred vision, cataracts), and gastrointestinal symptoms (e.g., constipation, abdominal cramps, steatorrhea). Management of chronic HP includes oral calcium (e.g., calcium carbonate, calcium citrate) at 1-2 g of elemental calcium daily and vitamin D supplementation to stimulate calcium absorption. The preferred vitamin D supplementation is calcitriol, its most active metabolite, at a starting dose of 0.25 mcg twice daily, with some patients requiring up to 2 mcg daily. Use of parathyroid hormone is recommended only for patients who are not well-controlled on calcium supplements and active forms of vitamin D alone. Parathyroid hormone (Natpara) injection was approved by the FDA in January 2015 as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism. In October 2022, the manufacturer announced it will discontinue manufacturing of parathyroid hormone (Natpara) injection by the end of 2024.

On August 9, 2024, the FDA approved palopegteriparatide (Yorvipath) subcutaneous injection, a parathyroid hormone analog (PTH(1-34)) indicated for the treatment of hypoparathyroidism in adults. Palopegteriparatide (Yorvipath) is a prodrug of teriparatide that releases PTH(1-34) to maintain a continuous systemic exposure.

The safety and efficacy of palopegteriparatide (Yorvipath) subcutaneous injection was evaluated in a randomized, double-blind, placebo-controlled, phase 3 study, which enrolled 82 patients with hypoparathyroidism. Prior to randomization, all patients underwent 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 10.6 mg/dL, a magnesium concentration ≥1.3 mg/dL and below the upper limit of the reference range, and a 25(OH) vitamin D concentration between 20 to 80 ng/mL. Following the screening period, patients were randomized 3:1 to either palopegteriparatide (N = 61) or placebo (N= 21), at a starting dose of 18 mcg/day SQ co-administered with conventional therapy (calcium and active vitamin D) and subsequently titrated according to the albumin-corrected serum calcium levels. The mean age at enrollment was 49 years (range: 19 to 78 years), 78% were female, and 93% were Caucasian. Eighty-five percent (85%) of subjects had hypoparathyroidism acquired from neck surgery. Of the subjects with other etiologies of hypoparathyroidism, 7 (8.5%) subjects 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: 1-56 years). Baseline mean albumin-corrected serum calcium was 8.8 mg/dL and 8.6 mg/dL and mean 24-hour urine calcium was 392 mg/day and 329 mg/day for palopegteriparatide (Yorvipath) and placebo, respectively. The mean baseline dose of elemental calcium was 1839 mg/day, and the mean baseline doses of active vitamin D were 0.75 mcg/day in calcitriol-treated subjects (n=70), and 2.3 mcg/day in alfacalcidol-treated subjects (n=12). Efficacy was assessed based on the proportion of subjects who achieved the parameters listed in Table 1 at Week 26.

Table 1: Efficacy at Week 26 in Adults with Hypoparathyroidism

	Palopegteriparatide (Yorvipath) (N=61)	**Placebo (N=21)**	**Response Rate Difference, % (95% CI)[e]**
Overall Response at Week 26	**42 (68.9%)**	**1 (4.8%)**	**64.2% (49.5%, 78.8%)**
Normal albumin-corrected serum calcium[a]	49 (80.3%)	10 (47.6%)	32.7% (9.2%, 56.3%)
Independence from active vitamin D[b]	58 (95.1%)	5 (23.8%)	71.3% (52.5%, 90.2%)
Independence from therapeutic dose of calcium[c]	53 (86.9%)	1 (4.8%)	82.2% (70.0%, 94.4%)
No increase in study drug dose since Week 22[d]	57 (93.4%)	12 (57.1%)	36.4% (14.2%, 58.5%)
Study drug dose ≤30 mcg/day up to Week 26[e]	56 (91.8%)	NA	NA

[a] Normal range for albumin-corrected serum calcium was 8.3 to 10.6 mg/dL.

[b] No daily standing doses of active vitamin D, no PRN doses, and no missing active vitamin D data within 4 weeks prior to Week 26 visit.

[c] Average daily standing dose of elemental calcium ≤600 mg, no PRN doses, and no missing calcium data within 4 weeks prior to Week 26 visit.

[d] No increase in study drug dose within 4 weeks prior to Week 26 visit.

[e] Subjects who received more than 30 mcg/day at any timepoint during the 26-week treatment period were considered as non-responders for the efficacy endpoint.

The most common adverse reactions with palopegteriparatide (Yorvipath) subcutaneous injection (reported in ≥ 5%) are injection site reactions, vasodilatory signs and symptoms, headache, diarrhea, back pain, hypercalcemia, and oropharyngeal pain.

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of palopegteriparatide (Yorvipath) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Age 18 years or older
2. Diagnosis of hypoparathyroidism
3. Does **NOT** have any of the following (“a”, “b”, and “c”):
    a. Acute post-surgical hypoparathyroidism
    b. Pseudohypoparathyroidism
    c. Hypoparathyroidism caused by calcium-sensing receptor (CaSR) mutations
4. Documentation of parathyroid hormone (PTH) concentrations below the lower limit of the normal reference range on two test dates at least 21 days apart within the past 12 months - laboratory documentation must be provided
5. The member has tried and had an inadequate response to maximally tolerated oral calcium AND vitamin D supplements (e.g., calcitriol)
6. Baseline (prior to the start of therapy) documentation that the serum 25 (OH) vitamin D is within the normal range and albumin-adjusted serum calcium is at least 7.8 mg/dL – laboratory documentation must be provided
7. Calcium and vitamin D supplementation will be continued while titrating to an appropriate dose of palopegteriparatide (Yorvipath)
8. Prescribed by, or in consultation with, an endocrinologist
9. Dose does not exceed 30 mcg subcutaneously once daily

Approval duration: 6 months

Continuation of palopegteriparatide (Yorvipath) **meets the definition of medical necessity** for members meeting the following criteria:

1. Authorization or reauthorization for palopegteriparatide (Yorvipath) has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of hypoparathyroidism (if another health plan, documentation of a health plan-paid claim for palopegteriparatide (Yorvipath) during the 90 days immediately before the authorization request must be submitted); **OR** the member previously met **ALL** indication-specific initiation criteria
2. The member has had a positive biochemical response to treatment as documented by one of the following ("a" or "b"): - documentation must be provided
    a. Albumin-corrected serum calcium within the normal reference range
    b. Increased albumin-corrected serum calcium as compared to baseline while continuing to titrate palopegteriparatide (Yorvipath) therapy with calcium and vitamin D supplementation
3. Prescribed by, or in consultation with, an endocrinologist
4. Dose does not exceed 30 mcg subcutaneously once daily

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Palopegteriparatide (Yorvipath) is a parathyroid hormone analog (PTH(1-34)) indicated for the treatment of hypoparathyroidism in adults.
- The dose should be individualized based on the albumin-corrected serum calcium level. Within two weeks before the first dose, confirm serum 25(OH) vitamin D is within the normal range and albumin-corrected serum calcium is ≥7.8 mg/dL. The recommended starting dosage is 18 mcg once daily and is titrated in 3 mcg 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 >600 mg/day). Calcium supplementation sufficient to meet daily dietary requirements may be continued.
- The recommended dosage range is 6 to 30 mcg subcutaneously once daily, as a single injection. Using two injections to achieve the recommended once daily dosage increases the risk of unintended changes in serum calcium levels, including hypocalcemia and hypercalcemia.
- Measure serum calcium 7 to 10 days after the first palopegteriparatide (Yorvipath) dose and after any dose change, active vitamin D, or calcium supplements, and monitor for clinical signs and symptoms of hypocalcemia or hypercalcemia. Once the 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.

Dose Adjustments

- Dosage adjustments are based on albumin-corrected serum calcium levels as well as active vitamin D and/or calcium supplementation.
- Some patients may require an increase in the palopegteriparatide (Yorvipath) dose over time to maintain the same therapeutic effect.

Drug Availability

- Palopegteriparatide (Yorvipath) is available in a prefill, disposable, 14-dose pen-injector. Each pen contains a clear and colorless solution of 3456 mcg/mL of palopegteriparatide equivalent to 300 mcg/mL of teriparatide. Each pack contains 2 prefilled pens and 28 needles for 28 injections (plus two spare needles).
    - 168 mcg/0.56 mL pen, labeled doses of 6, 9, or 12 mcg (73362-100-01)
    - 294 mcg/0.98 mL pen, labeled doses of 15, 18, or 21 mcg (73362-101-01)
    - 420 mcg/1.4 mL pen, labeled doses of 24, 27, or 30 mcg (73362-102-01)
- Palopegteriparatide (Yorvipath) must be refrigerated at 2°C to 8°C (36°F to 46°F) until first use.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- Known hypersensitivity to any component of the product

Precautions/Warnings

- **Unintended Changes in Serum Calcium Levels Related to Number of Daily Injections:** Use only one daily palopegteriparatide (Yorvipath) injection. Using two injections to achieve the recommended once daily dosage increases the variability of the total delivered dose.
- **Serious Hypercalcemia and Hypocalcemia:** Have occurred with palopegteriparatide (Yorvipath). Periodically measure serum calcium and monitor for signs and symptoms of hypercalcemia and hypocalcemia.
- **Potential Risk of Osteosarcoma:** Palopegteriparatide (Yorvipath) is not recommended in patients at increased risk of osteosarcoma.
- **Orthostatic Hypotension:** Has been reported with palopegteriparatide (Yorvipath). Monitor for signs and symptoms of orthostatic hypotension.
- **Digoxin Toxicity:** Concomitant use with digoxin may predispose to digitalis toxicity if hypercalcemia develops. With concomitant use, frequently measure serum calcium and digoxin levels, and monitor for signs and symptoms of digoxin toxicity.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J3590	Unclassified biologics
C9399	Unclassified drugs or biologicals

ICD-10 Diagnosis Codes That Support Medical Necessity

E20.0	Idiopathic hypoparathyroidism
E20.818	Other specified hypoparathyroidism due to impaired parathyroid hormone secretion
E20.818	Hypoparathyroidism due to impaired parathyroid hormone secretion, unspecified
E20.89	Other specified hypoparathyroidism
E20.9	Hypoparathyroidism, unspecified

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: The following National Coverage Determination (NCD) was reviewed on the last guideline revised date: Self-administered Drug List (A54770). No Local Coverage Determination (LCD) was found at the time of the last guideline revised date.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

1. Clinical Pharmacology powered by ClinicalKey [Internet]. Tampa, FL: Elsevier.; 2024. Available at: https://www.clinicalkey.com/pharmacology/. Accessed 9/26/24.
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3. DynaMed [database online]. Ipswich, MA: EBSCO Information Services.; 2024. URL http://www.dynamed.com. Accessed 9/26/24.

4. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2024 [cited 2024 Sept 26]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.
5. Yorvipath (palopegteriparatide) [package insert]. Princeton, NJ: Ascendis Pharma Endocrinology, Inc.; August 2024.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 10/09/24.

GUIDELINE UPDATE INFORMATION:

01/01/25	New Medical Coverage Guideline: Palopegteriparatide (Yorvipath) SQ injection for the treatment of hypoparathyroidism in adults who have tried and had an inadequate response to maximally tolerated calcium AND vitamin D supplements.