Palopegteriparatide (YORVIPATH) in Hypoparathyroidism
National Drug Mini-monograph
June 2025

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION		
	Description / MOA	Palopegteriparatide is a prodrug containing a 34 amino-acid subunit of parathyroid hormone (PTH 1-34) which is identical to the 34-N-terminal amino acid active region of endogenous human parathyroid hormone. PTH(1-34) is linked to a proprietary methoxypolyethyleneglycol (mPEG) TransCon linker. Autocleavage of the mPEG moiety results in sustained release of PTH(1-34) over a 24 hour period
	Indication Under Review[1]	Hypoparathyroidism in adults
	Dosage Regimen	Initial dose 18 mcg subcutaneously once daily. Dose adjust in 3 mcg increments based on serum calcium levels, supplemental calcitriol and supplemental calcium doses. Maximum dose 30 mcg/day
	Dosage Forms Under Review	Supplied in Pen-injectors containing 168mcg, 294 mcg, or 420 mcg per device. Store refrigerated until first dose. Device and any remaining solution should be discarded after 14 days.

EFFICACY CONSIDERATIONS	**Trial**	**PaTHway trial**	**PaTHway 52-week OLE**
	Design	26 week R, DB, PC with participants (n=84) randomized 3:1 to TransCon PTH or matched placebo co administered with conventional vit. D and calcium therapy. Primary endpoint was a composite that included normalized serum calcium and independence from therapeutic doses of calcium and vitamin D	1 year report of the 156-week open label extension of the original 26-week PaTHway trial assessing percent of patients who maintained normal calcium levels and avoidance of therapeutic VitD and Calcium as well as assessments of GFR and TEAEs
	Population	Adults with hypo-PTH Dx for at least 26 weeks and on stable doses of >/= 0.5mcg calcitriol and >800mg/d calcium	Adults with hypo-PTH continuing open label Tx from the original 26-week PaTHway study with placebo patients reallocated active Tx. Patients were prospectively stratified based on GFR< or >60
	Intervention	TransCon PTH	Continuation of TransConPTH
	Comparator	Placebo	N/A
	Results	After 26 weeks 79% of PTH treated patients achieved the primary composite endpoint compared to 5% of placebo treated patients	At week 52 85% of patients met the composite endpoint with 95% remaining VitD and Calcium Tx independent. Renal function improved slightly from baseline (avg 9 mL/min/1.73m2)

SAFETY CONSIDERATIONS		
	Boxed Warnings	None
	Contraindications	Severe hypersensitivity to palopegteriparatide or any of its excipients
	Other Warnings	Unintended changes in serum calcium levels related to number of daily injections – using two injections to achieve desired daily dose increased variability of the total delivered dose Serious hypercalcemia and hypocalcemia have occurred. Periodically measure serum calcium and monitor for s/sxs of hyper/hypocalcemia Palopegteriparitide is not recommend in patients at increased risk of osteosarcoma Orthostatic hypotension has been reported. Monitor for s/sxs of orthostatic hypotension Digoxin toxicity – concomitant use may predispose to digoxin toxicity if hypercalcemia occurs. Measure serum calcium and digoxin levels frequently and monitor for s/sxs of hypercalcemia and digoxin toxicity
	Top 5 AEs	Injection site reactions (39%), vasodilatory s/sxs (28%), Headache (21%), Diarrhea (10%), Hypercalcemia (8%), Back Pain (8%)
	Drug Interactions	Other drugs known to affect serum calcium levels. Measure serum calcium more frequently

VHA PLACE IN THERAPY		
	Potential Use in VHA	Hypoparathyroidism is a rare, but not exceedingly rare, condition that has historically been managed with therapeutic doses of calcium and active VitD to maintain normal serum calcium levels. Human recombinant PTH (NATPARA) was available until late 2024 but all-time use within VHA was very rare. Palopegteriparatide fills a similar niche to human rPTH with rare use expected only in patients refractory to standard care with therapeutic doses of calcium and calcitriol. Patients who may benefit can include patients with: *Hyperphosphatemia *corrected calcium below target levels or symptomatic hypocalcemia *Hypercalcuria or nephrolithiasis despite thiazide use *malabsorption syndromes *declining eGFR *ED visit or hospitalization for hypocalcemia or requiring IV calcium in any setting

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References

1 Palopegteriparatide (YORVIPATH) formulation [prescribing information online]. Princeton, NJ: Ascendis Pharma Bone Diseases. Aug 2024. Available at: https://ascendispharma.us/products/pi/yorvipath/yorvipath_pi.pdf Accessed April 2024

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