Paltusotine (PALSONIFY) in Acromegaly
National Drug Mini-Monograph
July 2026
VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services 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.

Abbreviations: AC, active-controlled; CO, crossover; DB, double-blind; F, Formulary; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; MC, multicenter; MN, multinational; NF, Non-Formulary; PC, placebo-controlled; Q, GRADE quality of evidence; RCT, randomized clinical trial; TBD, To be determined

Product specific abbreviations: ASD, Acromegaly Symptom Diary; DB, double-blind; EOR, end of randomized phase; GH, growth hormone; IGF-1, insulin-like growth factor-1; PC, placebo-controlled; PPI, proton pump inhibitor; QD, once daily; RCT, randomized clinical trial; SE, standard error; SRL, somatostatin receptor ligand; ULN, upper limit of normal.

FDA PRESCRIBING INFORMATION[1]

Description / MOA	Paltusotine is a nonpeptide, selective somatostatin receptor agonist which suppresses the secretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1)
Indication Under Review	Treatment of adults with acromegaly with inadequate response to surgery (or surgery is contraindicated)
Dosage Regimen	40 mg once daily; may be titrated to 60 mg once daily after 2 to 4 weeks based on IGF-1 levels
Dosage Forms Under Review	Tablets: 20 mg and 30 mg

EFFICACY CONSIDERATIONS

Trial	PATHFNDR-2	PATHFNDR-1
Design	Phase 3, multicenter, randomized, double-blind, placebo-controlled	Phase 3, multicenter, randomized, double-blind, placebo-controlled
Population	111 adults with biochemically uncontrolled acromegaly (IGF-1 ≥1.3× ULN if medically naive/off meds or ≥1.1× ULN after washout)	58 adults with acromegaly biochemically controlled on injected octreotide or lanreotide (IGF-1 ≤1.0× ULN)
Intervention	Paltusotine (n=54) titrated from 20 mg to 40 mg or 60 mg QD for 24 weeks	paltusotine (n=30) 40 mg or 60 mg QD for 36 weeks
Comparator	Placebo (n=57)	Placebo (n=28)
Results	**Primary Endpoint:** Proportion of patients with IGF-1 normalization (≤1.0× ULN) at Week 24 55.6% (30/54) vs. 5.3% (3/57) (p<0.0001) **Secondary Endpoints:** GH <1.0 ng/mL at Week 22; Change in ASD score from baseline to EOR; Mean change in IGF-1 • **GH <1.0 ng/mL:** 57.4% (31/54) vs. 17.5% (10/57) (p<0.0001). • **ASD Score Change (LSM):** -2.7 (SE 1.4) vs. 2.8 (SE 1.4) (p=0.0039 • **IGF-1 Change (LSM):** -0.819 (SE 0.079) vs. 0.087 (SE 0.075) (p<0.0001)	**Primary Endpoint:** Proportion of patients maintaining IGF-1 ≤1.0× ULN at Week 36 83.3% (25/30) vs. 3.6% (1/28) (p<0.0001) **Secondary Endpoints:** Change in IGF-1; GH maintained <1.0 ng/mL; Change in ASD score from baseline to EOR • **GH maintained <1.0 ng/mL:** 87.0% (20/23) vs. 27.8% (5/18) (p=0.0003) • **ASD Score Change (LSM):** -0.6 (SE 1.5) vs. 4.6 (SE 1.6) (p=0.02) • **IGF-1 Change (LSM):** 0.04 (SE 0.09) vs. 0.83 (SE 0.10) (p<0.0001)

SAFETY CONSIDERATIONS

Boxed Warnings	none
Contraindications	none
Other Warnings	Cholelithiasis: May inhibit gallbladder contractility; monitor for stones or sludge Hyperglycemia/Hypoglycemia: May alter the balance of insulin, glucagon, and GH; monitor blood glucose Cardiac Abnormalities: May cause sinus bradycardia or PR interval prolongation Vitamin B12 Deficiency: Long-term use may decrease B12 levels Ocular Toxicity: Signal of retinal degeneration in animal studies; significance in humans is uncertain
Top 5 AEs	Diarrhea (33.3%), arthralgia (30.0%), headache (20.4%), abdominal pain (16.7%), nausea (13.3%), bradycardia (7.4%)
Drug Interactions	Strong/Moderate CYP3A4 Inducers: May decrease paltusotine exposure; increase dose as needed PPIs: May decrease paltusotine exposure; increase dose as needed Cyclosporine: paltusotine may decrease cyclosporine bioavailability; monitor levels

PLACE IN THERAPY			
DRUG	**VANF**	**CFU**	**FDA**
Paltusotine (PALSONIFY)	TBD	TBD	Acromegaly in adults with inadequate response/contraindication to surgery
Octreotide INJ, SUSP, SA	Yes	No	Acromegaly after inadequate surgical response First line pharmacologic agent
Lanreotide INJ, SUSP, SA	Yes	No	Acromegaly after inadequate surgical response
Pegvisomant INJ, PWDR	No	No	Acromegaly after inadequate surgical/radiation response. Not typically used first line
Octreotide CAP, EC	No	No	Long-term maintenance in patients already controlled on injectable SRLs (octreotide LAR or lanreotide)
Pasireotide INJ, SUSP, SA	No	No	Off label; second-line use
Cabergoline TAB	Yes	No	Off label; most effective with mild IGF-1 elevation or GH/PRL co-secreting tumors

CONSIDERATIONS FOR PLACE IN THERAPY

1. Significant cost impact compared to first line agents, octreotide and lanreotide.
2. Clinical trial data demonstrates biochemical control rates similar to first-generation injectable SRLs, with 56% achieving IGF-1 normalization in treatment-naïve patients and 83% maintaining control when switched from injectables. No head-to-head trials directly compare paltusotine to injectable SRLs or pegvisomant. Network meta-analysis suggests comparable or superior efficacy to some comparators, but real-world comparative effectiveness data are lacking.
3. Long-term efficacy and safety: Clinical trial data extend to 36 weeks; longer-term real-world effectiveness and safety data are needed, particularly regarding tumor size control and durability of response.
4. Improved convenience and adherence: Once-daily oral dosing eliminates the need for monthly clinic visits for injections, which may be challenging for Veterans in rural areas or those with transportation barriers.
5. Adherence in practice: While oral administration may theoretically improve adherence, real-world adherence data are needed. The requirement for fasting administration (≥6 hours after meal, ≥1 hour before next meal) may pose adherence challenges for some patients.
6. The adverse event profile is consistent with other SRLs (primarily mild, transient GI effects), with lower discontinuation rates compared to oral octreotide.
7. Guideline integration: Current acromegaly treatment guidelines do not yet incorporate paltusotine. Future guideline updates will be needed to establish its place in treatment algorithms relative to established therapies.

Original: July 2026.
Contact: A. McGehee, Acting National Program Manager, VA Pharmacy Benefits Management Services–Formulary Management (12PBM)

References

1. PALSONIFY (paltusotine) Prescribing Information. Crinetics Pharmaceuticals, Inc. September 2025. Available at: https://crinetics.com/PALSONIFY_pi/. Accessed Date April 4, 2026
2. Biller BMK, et al. PATHFNDR-2: Rapid and Sustained Response of Biochemically Uncontrolled Acromegaly to Once-daily Oral Paltusotine Treatment. J Clin Endocrinol Metab. 2025.
3. Gadelha MR, et al. PATHFNDR-1: Acromegaly disease control maintained after switching from injected somatostatin receptor ligands to oral paltusotine. J Clin Endocrinol Metab. 2024.
4. Gadelha MR, et al. ACROBAT Edge: Safety and efficacy of switching injected SRLs to oral paltusotine in patients with acromegaly. J Clin Endocrinol Metab. 2023.
5. FDA Integrated Review. NDA 219070. PALSONIFY (paltusotine). 2025.