New Drug Overview

Palsonify (paltusotine)

PDL Category: Somatostatic Agents

Introduction

Disease Background:

- Acromegaly is a disease that progressives slowly and generally produced by a functional sporadic pituitary adenoma (typically a macroadenoma when diagnosed) that secretes growth hormone (GH) which occurs after closure of growth plates (*Leung et al 2025*).
  - It results from continual hypersecretion of GH, and this surplus of GH stimulates extreme secretion of insulin-like growth factor-1 (IGF-1) from the liver. It is IGF-1 that results in most of the clinical symptoms of acromegaly (*Melmed and Katznelson 2025*).
  - It is thought to be a rare disease (*Melmed and Katznelson 2025*), with acromegaly having an estimated worldwide prevalence of 13-14 cases per 100,000 people between the years of 2012 and 2014 and a mean yearly incidence of 4.6 cases per 100,000 people from 1992 to 2021 (*Leung et al 2025*).
- Acromegaly signs and symptoms typically occur in the fifth decade of life (*Leung et al 2025*).
  - Clinical features of excess GH includes enlargement of the jaw, nose and frontal bones, hands, and feet. Soft tissue hypertrophy may occur. Other features includes cardiovascular disease, hypertension, type 2 diabetes, arthropathies, carpal tunnel syndrome, among others (*Leung et al 2025, Melmed and Katznelson 2025*).
- Palsonify was FDA approved in 2025.

Pharmacology/Usage

- Palsonify (paltusotine) is a somatostatin receptor agonist.
  - Similar to the natural hormone somatostatin, paltusotine suppresses growth hormone (GH) and insulin-like growth factor-1 (IGF-1) secretion.
  - Paltusotine exerts its pharmacological activity via selective agonism at somatostatin receptor 2 (SSTR2) and exhibits little or no affinity for other SST receptor subtypes.

Indications

Table 1. Food and Drug Administration Approved Indications

Indication	Palsonify (paltusotine)
• For the treatment of adults with acromegaly who had an inadequate response to surgery and/or for whom surgery is not an option	✔

(Prescribing information: Palsonify 2025)

- Information on indications, mechanism of action, pharmacokinetics, dosing, safety, and clinical efficacy summary has been obtained from the prescribing information for the individual products, except where noted otherwise.

Dosing and administration

Table 2. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Palsonify (paltusotine)	Tablets	PO	Once daily, with water on an empty stomach, at least 6 hours after a	• During initiation period, Palsonify may

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			meal (eg, after overnight fasting) and at least 1 hour before the next meal.	be temporarily reduced to 20mg QD if needed, based on tolerability. Once adverse reactions have resolved, resume Palsonify 40mg QD. • After 2 to weeks on Palsonify 40mg QD, based on IGF-1 levels, titrate to a Palsonify dosage of 60mg QD.

See the current prescribing information for full details.

Clinical efficacy summary

- The efficacy of Palsonify for treatment of adults with acromegaly was assessed in two randomized, double-blind, parallel group, placebo-controlled clinical studies.
- *Study 1* included adults (N=111) with biochemically uncontrolled acromegaly.
  - Patients were either treatment naïve (N=46/111) or had no treatment within the previous 4 months prior to screening (N=36/111) ("Not medically treated' group) or were previously treated on a somatostatin receptor analog and then washed out of treatment during screening (N=29/111) ('Washout' group).
  - The mean age at enrollment was 47 years (range 18 to 80), while 53% were female, 52% were White, and the mean duration since diagnosis of acromegaly was 87 months. In addition, prior to study participation, 95% of participants had received pituitary surgery (mean duration 78 months prior to study participation). In the 'not medically treated' group, IGF-1 levels were required to be ≥1.3 X upper limit of normal (ULN) at screening. In the 'washout' group, IGF-1 levels were required to be ≤1 X ULN at screening and ≥1.1 X ULN with at least a 30% rise in IGF-1 after washout.
  - Participants were randomized to receive Palsonify (N=54) or placebo (N=57) for the 24-week treatment period.
    - Rescue therapy with standard of care treatment was initiated if a participant had evidence of uncontrolled acromegaly based on IGF-1 levels and symptoms.
      - Fourteen participants (13%) received rescue therapy during the study, including one participant (2%) in the Palsonify arm and 13 participants (23%) in the placebo arm.
  - The primary endpoint was the proportion of participants in the Palsonify arm achieving biochemical control (defined as IGF-1 level ≤1.0 X ULN) compared to placebo-treated participants.
    - Results suggested that at week 24, 56% of participants in the Palsonify group achieved biochemical control compared to 5% of participants in the placebo group, which was significantly different ($p<0.0001$).
    - Results are presented in the table below, which was adapted from the prescribing information.

Table 3. Efficacy results

IGF-1 Normalization	Palsonify (N=54)	Placebo (N=57)	p-value
Proportion of participants who achieved response in IGF-1 at week 24	56%	5%	<0.0001
NNT *calculated by Optum Rx*	2		

- IGF-1 at week 24 is based on the average of the last 2 measurements of IGF-1 collected at weeks 22 and 24. When one of the two last IGF-1 measurements was missing a single value was used. Week 24 is the end of the randomized controlled portion of the study; if a participant received rescue therapy, the last assessment prior to rescue is used.
- The majority of participants who achieved IGF-1 normalization during this study did so within the first 2 to 4 weeks following initiation of treatment, with sustained response through the end of the treatment period.
- A post hoc subgroup analysis for the primary efficacy endpoint assessing the response rate in participants who were naïve to medical treatment, who had not achieved biochemical control on prior medical therapy, or for whom prior biochemical control status was unknown (Group A) and participants who demonstrated prior response to medical therapy who were either washed out from the previous therapy prior to baseline or had documented biochemical control on prior medical therapy (Group B) was done. Results are presented in the table below, which was adapted from the prescribing information.

Table 4. Efficacy results

IGF-1 Normalization	Palsonify (N=54)	Placebo (N=57)	Treatment difference
Group A: treatment naïve, uncontrolled on prior therapy, or with unknown biochemical control on prior therapy(s)	34%	3%	32%
Treatment naïve	23%	4%	18%
Absence of biochemical control on prior treatment	57%	0%	57%
Unknown biochemical control on prior treatment	67%	0%	67%
Group B: responders to prior treatment	86%	9%	77%

- In Study 1, Palsonify-treated participants had numerically lower (versus placebo) severity of symptom scores associated with acromegaly as measured by the patient-reported symptom severity instrument, which assessed headaches, joint pain, sweating, fatigue, weakness, swelling, and/or numbness/tingling.

- *Study 2* enrolled adults (N=58) who were previously biochemically controlled (defined as IGF-1 levels ≤1.0 X ULN during screening and at randomization) on injectable depot octreotide or lanreotide somatostatin analog formulations.
  - The mean age at enrollment was 55 years (range 29 to 84 years), while 55% were female, 72% were White, and the mean duration since diagnosis of acromegaly was 155 months. In addition, prior to study participation, 86% of participants had received pituitary surgery (mean duration 138 months prior to study participation).
  - Patients were randomized to receive either Palsonify (N=30) or placebo (N=28) for the 36-week treatment period.
    - Rescue therapy with standard of care treatment was initiated if a participant had evidence of uncontrolled acromegaly based on IGF-1 levels and symptoms.
      - Eighteen participants (31%) received rescue therapy during the study, including one participant (3%) in the Palsonify arm and 17 participants (61%) in the placebo arm.
  - The primary endpoint was the proportion of Palsonify participants with biochemical response maintenance (ie, IGF-1 ≤1.0 X ULN) compared to placebo-treated participants.
    - At week 36, 83% of Palsonify participants maintained biochemical control compared to 4% of placebo participants, which was statistically different ($p<0.0001$).
    - Results are presented in the table below, which was adapted from the prescribing information.

Table 5. Efficacy results

IGF-1 Normalization	Palsonify (N=30)	Placebo (N=28)	p-value
Proportion of participants who maintained response in IGF-1 at week 36	83%	4%	<0.0001
NNT *calculated by Optum Rx*	2		

- Week 36 is the end of the randomized controlled portion of the study; if a participant received rescue therapy, the last assessment prior to rescue is used.
- In this study, Palsonify-treated participants had numerically lower (vs placebo) severity of symptom scores associated with acromegaly as measured by the patient-reported symptom severity instrument, which assessed headaches, joint pain, sweating, fatigue, weakness, swelling, and/or numbness/tingling.

Clinical guidelines

- Note that guidelines do not include recommendations on Palsonify as they were published prior to Palsonify becoming FDA approved.
  - **Consensus on acromegaly therapeutic outcomes: an update** (*Melmed et al 2025*).
    - The guidelines note that specific criteria for clinical remission of acromegaly is not available. A comprehensive method for management of the patient is recommended to improve long-term outcomes.
    - Some recommendations on medical therapy outcomes includes:
      - The best approach should comprise of individualized management per clinical, imaging, and pathological symptoms, done in a shared decision making process.
      - The biochemical goal of medical treatment is to normalize IGF-1 levels.
        - Somatostatin receptor ligand (SRL)-induced biochemical outcomes should be assessed using IGF-1 measurements after the first 3 monthly injections and additional measurements based on IGF-1 reduction. Titrate SRL doses per IGF-1 values.
        - When available, oral octreotide capsules should be thought of as equally effective and having similar adverse effects to injectable SRLs. In addition, they should be recommended per patient preference.
        - Pegvisomant is listed as medical therapy and it is suggested to rotate injection sites and obtain liver function tests before starting treatment. There is often improvement of symptoms, quality of life and comorbidities with pegvisomant, and should be monitored with treatment.
        - Combining pegvisomant with SRLs can be a productive therapeutic approach if acromegaly is partially responsive to SRLs as monotherapy.
        - A useful add-on treatment may include cabergoline if patients with acromegaly are not totally controlled by SRLs.
      - Regarding medical treatment algorithm:
        - SRLs are the first-line option for medical therapy.
        - Only consider cabergoline as first-line treatment in patients with IGF-1 levels<2.0-2.5 times the ULN or in patients with mixed GH-prolactin-secreting adenomas.
        - Pegvisomant monotherapy could be an important first-line medication option.
        - If not controlled with first-line medical options, second-line treatment options should be considered.
        - Adding cabergoline to SRLs could be considered. Pegvisomant monotherapy might be the first choice as a second-line treatment. Combing pegvisomant with SRLs could be considered. When SRLs are not tolerated, combining pegvisomant with cabergoline might be considered.
        - Refer to the guideline for additional information.

Safety summary

- **Contraindications:** None.

- **Box Warning:** None.

- **Warnings and precautions:**
  - Palsonify may inhibit gallbladder contractility and decrease bile secretion, which may lead to gallbladder stones or sludge. Cholelithiasis was reported in patients treated with Palsonify in clinical trials. Complications of cholelithiasis, such as acute cholecystitis and pancreatitis, have also been reported with Palsonify use.
    - Monitor patients periodically. If complications of cholelithiasis occur, discontinue Palsonify and treat appropriately.
  - Palsonify may alter the balance between the counter-regulatory hormones, insulin, glucagon, and growth hormone, which may result in hypoglycemia, hyperglycemia, or diabetes mellitus. Hyperglycemia was reported in participants treated with Palsonify in clinical trials.
    - Monitor blood glucose levels when Palsonify treatment is started or when the dose is altered. Adjust antidiabetic treatment accordingly.
  - Cardiac conduction abnormalities and other ECG changes such as PR interval prolongation have occurred during treatment with Palsonify. Bradycardia, sinus arrest, and atrioventricular block were reported in participants treated with Palsonify in clinical trials. These ECG changes may occur in patients with acromegaly.
    - Dosage adjustments of concomitantly used drugs that have bradycardia effects (eg, beta-blockers) may be necessary.
  - Somatostatin analogs may suppress the secretion of thyroid-stimulating hormone, which may result in hypothyroidism.
    - Periodic assessment of thyroid function (TSH, total, and/or free T4) is recommended during Palsonify treatment.
  - New onset steatorrhea, stool discoloration and loose stools have been reported in patients receiving somatostatin analogs. Somatostatin analogs reversibly inhibit secretion of pancreatic enzymes and bile acids, which may result in malabsorption of dietary fats and subsequent symptoms of steatorrhea, loose stools, abdominal bloating, and weight loss.
    - If new occurrence or worsening of these symptoms are reported in patients receiving Palsonify, assess patients for potential pancreatic exocrine insufficiency, and manage accordingly.
  - Decreased vitamin B12 levels have been observed in patients treated with somatostatin analogs, including Palsonify.
    - Monitor vitamin B12 levels during Palsonify treatment if clinically indicated.

- **Common adverse drug reactions**: Listed % incidence for adverse drug reactions= reported % incidence for drug (Palsonify) minus reported % incidence for placebo in Study 1 (reported in ≥5% of Palsonify-treated patients and 5% greater incidence than placebo-treated participants). 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 diarrhea (19%), abdominal pain (14%), nausea (7%), sinus bradycardia (7%), and hyperglycemia (5%). Note that hyperglycemia also includes impaired fasting glucose and diabetes mellitus.

- **Drug interactions:**
  - Concomitant use of Palsonify with strong CYP3A4 inducers reduced paltusotine exposure and may affect therapeutic response.
    - Concomitant use of Palsonify with strong CYP3A4 inducers may require an increased dosage of Palsonify, not to exceed three-fold the dose prior to concomitant use or 120mg daily, whichever is less.

- Concomitant use of Palsonify with moderate CYP3A4 inducers resulted in a decrease in paltusotine exposure.
  - Concomitant use of Palsonify with moderate CYP3A4 inducers may require an increased dosage of Palsonify, not to exceed two-fold the dose prior to concomitant use or 120mg daily, whichever is less.
- Concomitant use of Palsonify with proton pump inhibitors (PPIs) demonstrated a dose-dependent decrease in paltusotine exposure.
  - Concomitant use of Palsonify with PPIs may require an increased dosage of Palsonify. Patients who are already on Palsonify 60mg should avoid concomitant use with proton pump inhibitors.
- Concomitant use of Palsonify with cyclosporine resulted in a decrease in cyclosporine bioavailability.
  - Adjustment of cyclosporine dose to maintain therapeutic levels may be necessary. Follow recommended therapeutic drug monitoring for cyclosporine.

- **Special populations:**
  - There is no pregnancy category for this medication; however, the risk summary indicates that the available data with use in pregnant women are not sufficient to identify a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.
  - The safety and efficacy of use have not been established in the pediatric population.

Conclusion

- Acromegaly is a disease that progressives slowly and generally produced by a functional sporadic pituitary adenoma (typically a macroadenoma when diagnosed) that secretes growth hormone (GH) which occurs after closure of growth plates (*Leung et al 2025*).
- Palsonify is a somatostatin receptor agonist indicated for the treatment of adults with acromegaly who had an inadequate response to surgery and/or for whom surgery is not an option.
- Drug interactions may require dosage modifications if used concomitantly with strong CYP3A4 inducers, moderate CYP3A4 inducers, or PPIs.
- Its efficacy was assessed in two randomized, double-blind, parallel group, placebo-controlled clinical studies.
  - The primary endpoint of Study 1 was the proportion of Palsonify participants achieving biochemical control (defined as IGF-1 level ≤1 X ULN) compared to placebo-treated participants.
    - Results suggested that at week 24, significantly more Palsonify participants (56%) achieved biochemical control compared to placebo participants (5%; $p<0.0001$).
  - The primary endpoint of Study 2 was the proportion of Palsonify participants with biochemical response maintenance (ie, IGF-1 ≤1 X ULN) compared to placebo participants.
    - Results suggested that at week 36, significantly more in the Palsonify group (83%) maintained biochemical control compared to the placebo group (4%; $p<0.0001$).
- Guidelines have yet to be updated to include Palsonify. Somatostatin receptor ligands (SRLs) are listed as a first-line medical treatment option (*Melmed et al 2025*).

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

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

References

- Leung JH, Correa R, Ehrlich A, et al. Acromegaly. Dynamed Website. Updated November 18, 2025. Accessed February 3, 2026. https://www.dynamed.com.
- Melmed S, Katznelson L. Diagnosis of acromegaly. UpToDate Web site. Updated November 17, 2025. Accessed February 3, 2026. www.uptodate.com.
- Melmed S, di Filippo L, Fleseriu M, et al. Consensus on acromegaly therapeutic options: an update. *Nature Reviews Endocrinol*. 2025; 21:718-737.
- Palsonify. Package insert. Crinetics Pharmaceuticals, Inc.; September 2025.

Publication Date: February 2026.