Somatostatin Analogs (for Ohio Only)

Policy Number: CSOH2025D0036.E
Effective Date: May 1, 2025

➲ Instructions for Use

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Related Policy

- Oncology Medication Clinical Coverage (for Ohio Only)

Application

This Medical Benefit Drug Policy only applies to the state of Ohio. Any requests for services that are stated as unproven or services for which there is a coverage or quantity limit will be evaluated for medical necessity using Ohio Administrative Code 5160-1-01.

Coverage Rationale

This policy refers only to the following drug products, somatostatin analogs for non-oncology conditions:

- Lanreotide acetate
- Sandostatin® (octreotide acetate)
- Sandostatin® LAR (octreotide acetate LAR)
- Somatuline® Depot (lanreotide)
- Signifor® (pasireotide diaspartate)
- Signifor® LAR (pasireotide)

For oncology indications, refer to the Medical Benefit Drug Policy titled Oncology Medication Clinical Coverage (for Ohio Only) for updated information based on the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium.

Lanreotide acetate, Sandostatin (octreotide acetate), Sandostatin LAR (octreotide acetate LAR), and Somatuline Depot (lanreotide) are proven and medically necessary for the treatment of certain conditions outlined within the InterQual® criteria. For medical necessity clinical coverage criteria for non-oncology indications, refer to the current release of the InterQual® guideline:

- **Lanreotide acetate and Somatuline Depot**: CP: Specialty Rx Non-Oncology Lanreotide (Somatuline Depot)
- **Sandostatin**: CP: Specialty Rx Non-Oncology Octreotide acetate (Sandostatin)
- **Sandostatin LAR**: CP: Specialty Rx Non-Oncology Octreotide acetate (Sandostatin LAR Depot)

Click here to view the InterQual® criteria.

Signifor and Signifor LAR (pasireotide diaspartate) are proven and medically necessary for the treatment of Cushing's disease when both of the following criteria are met:

- Diagnosis of Cushing's disease; **and**
- **One** of the following:
  - Inadequate response to pituitary surgery; **or**

- Not a candidate for pituitary surgery

Signifor LAR (pasireotide) is proven and medically necessary for the treatment of acromegaly when both of the following criteria are met:

- Diagnosis of acromegaly; **and**
- Diagnosis has been confirmed by **one** of the following:
  - Serum GH level > 1 ng/mL after a 2 hour oral glucose tolerance test (OGTT) at time of diagnosis; **or**
  - Elevated serum IGF- 1 levels (above the age and gender adjusted normal range as provided by the physician's lab) at time of diagnosis

  and
- **One** of the following:
  - Inadequate response to **one** of the following:
    - Surgery
    - Radiotherapy
    - Dopamine agonist (e.g., bromocriptine, cabergoline) therapy

    or
  - Not a candidate for **any** of the following:
    - Surgery
    - Radiotherapy
    - Dopamine agonist (e.g., bromocriptine, cabergoline) therapy

Somatostatin analogs are unproven and not medically necessary for treating the following conditions:

- HIV-AIDS-related diarrhea
- Chylothorax
- Dumping syndrome
- Pancreatitis
- Persistent hyperinsulinemic hypoglycemia of infancy
- Prevention of postoperative complications following pancreatic surgery
- Short bowel syndrome

Somatostatin analogs are unproven for treating other conditions not listed above as proven due to the lack of published clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J1930	Injection, lanreotide, 1 mg
J1932	Injection, lanreotide, (cipla), 1 mg
J2353	Injection, octreotide, depot form for intramuscular injection, 1 mg
J2354	Injection, octreotide, non-depot form for subcutaneous or intravenous injection, 25 mcg
J2502	Injection, pasireotide long acting, 1 mg

Diagnosis Code	Description	J1930	J1932	J2502	J2353 J2354
C17.0	Malignant neoplasm of duodenum	x	x		x
C17.1	Malignant neoplasm of jejunum	x	x		x
C17.2	Malignant neoplasm of ileum	x	x		x
C17.3	Meckel's diverticulum, malignant	x	x		x
C17.8	Malignant neoplasm of overlapping sites of small intestine	x	x		x

Diagnosis Code	Description	J1930	J1932	J2502	J2353 J2354
C17.9	Malignant neoplasm of small intestine, unspecified	x	x		x
C18.0	Malignant neoplasm of cecum	x	x		x
C18.1	Malignant neoplasm of appendix	x	x		x
C18.2	Malignant neoplasm of ascending colon	x	x		x
C18.3	Malignant neoplasm of hepatic flexure	x	x		x
C18.4	Malignant neoplasm of transverse colon	x	x		x
C18.5	Malignant neoplasm of splenic flexure	x	x		x
C18.6	Malignant neoplasm of descending colon	x	x		x
C18.7	Malignant neoplasm of sigmoid colon	x	x		x
C18.8	Malignant neoplasm of overlapping sites of colon	x	x		x
C18.9	Malignant neoplasm of colon, unspecified	x	x		x
C19	Malignant neoplasm of rectosigmoid junction	x	x		x
C20	Malignant neoplasm of rectum	x	x		x
C21.0	Malignant neoplasm of anus, unspecified	x	x		x
C21.1	Malignant neoplasm of anal canal	x	x		x
C21.2	Malignant neoplasm of cloacogenic zone	x	x		x
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal	x	x		x
C25.0	Malignant neoplasm of head of pancreas	x	x		x
C25.1	Malignant neoplasm of body of pancreas	x	x		x
C25.2	Malignant neoplasm of tail of pancreas	x	x		x
C25.4	Malignant neoplasm of endocrine pancreas	x	x		x
C25.7	Malignant neoplasm of other parts of pancreas	x	x		x
C25.8	Malignant neoplasm of overlapping sites of pancreas	x	x		x
C25.9	Malignant neoplasm of pancreas, unspecified	x	x		x
C7A.010	Malignant carcinoid tumor of the duodenum	x	x		x
C7A.011	Malignant carcinoid tumor of the jejunum	x	x		x
C7A.012	Malignant carcinoid tumor of the ileum	x	x		x
C7A.019	Malignant carcinoid tumor of the small intestine, unspecified portion	x	x		x
C7A.020	Malignant carcinoid tumor of the appendix	x	x		x
C7A.021	Malignant carcinoid tumor of the cecum	x	x		x
C7A.022	Malignant carcinoid tumor of the ascending colon	x	x		x
C7A.024	Malignant carcinoid tumor of the descending colon	x	x		x
C7A.025	Malignant carcinoid tumor of the sigmoid colon	x	x		x
C7A.026	Malignant carcinoid tumor of the rectum	x	x		x
C7A.029	Malignant carcinoid tumor of the large intestine, unspecified portion	x	x		x
C7A.092	Malignant carcinoid tumor of the stomach	x	x		x
C7A.094	Malignant carcinoid tumor of the foregut, unspecified	x	x		x
C7A.095	Malignant carcinoid tumor of the midgut, unspecified	x	x		x
C7A.096	Malignant carcinoid tumor of the hindgut, unspecified	x	x		x

Diagnosis Code	Description	J1930	J1932	J2502	J2353 J2354
E22.0	Acromegaly and pituitary gigantism	x	x	x	x
E24.0	Pituitary-dependent Cushing's disease			x	
E34.00	Carcinoid syndrome, unspecified	x			
E34.01	Carcinoid heart syndrome	x			
E34.09	Other carcinoid syndrome	x			
E34.4	Constitutional tall stature	x	x	x	x
I85.01	Esophageal varices with bleeding				x
I85.11	Secondary esophageal varices with bleeding				x
K52.0	Gastroenteritis and colitis due to radiation				x
K52.89	Other specified noninfective gastroenteritis and colitis				x
K52.9	Noninfective gastroenteritis and colitis, unspecified				x

Background

Sandostatin is a cyclic octapeptide prepared as a clear sterile solution of octreotide acetate salt, in a buffered lactic acid solution for administration by deep subcutaneous (SC) or intravenous (IV) injection. It is a long-acting octapeptide with pharmacologic actions mimicking those of the natural hormone somatostatin. The principal effects of octreotide include inhibition of growth hormone (GH), glucagon, and insulin. Other effects include diminution of luteinizing hormone response to gonadotropin-releasing hormone, reduction of splanchnic blood flow, and inhibition of release of several gastrointestinal hormones, including serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.

Sandostatin LAR is a long-acting dosage form that maintains all of the clinical and pharmacological characteristics of the immediate-release dosage form with the added feature of slow release of octreotide from the site of injection, reducing the need for frequent administration. It is indicated in patients in whom initial treatment with Sandostatin injection has been shown to be effective and tolerated. Sandostatin LAR is designed to be injected intramuscularly (intragluteally) once every 4 weeks and must be administered under the supervision of a physician.

Signifor is an injectable cyclohexapeptide somatostatin analogue. Pasireotide exerts its pharmacological activity via binding to somatostatin receptors (SSTRs). Five human somatostatin receptor subtypes are known: SSTR 1, 2, 3, 4, and 5. These receptor subtypes are expressed in different tissues under normal physiological conditions. Corticotroph tumor cells from Cushing’s disease patients frequently over-express SSTR5 whereas the other receptor subtypes are often not expressed or are expressed at lower levels. Pasireotide binds and activates the SSTRs resulting in inhibition of ACTH secretion, which leads to decreased cortisol secretion.

Signifor LAR is a long-acting release form of pasireotide, a somatostatin analogue. Pasireotide exerts its pharmacological activity via binding to somatostatin receptors (SSTRs). Five human somatostatin receptor subtypes are known: SSTR 1, 2, 3, 4, and 5. These receptor subtypes are expressed in different tissues under normal physiological conditions. Corticotroph tumor cells from Cushing’s disease patients frequently over-express SSTR5 whereas the other receptor subtypes are often not expressed or are expressed at lower levels. Pasireotide binds and activates the SSTRs resulting in inhibition of ACTH secretion, which leads to decreased cortisol secretion.

Somatuline Depot and Lanreotide Injection are prolonged-release formulations for deep subcutaneous injection. They are synthetic octapeptide analogs with a biological activity similar to naturally occurring somatostatin. Like somatostatin, lanreotide is an inhibitor of various endocrine, neuroendocrine, exocrine, and paracrine functions. In acromegalic patients, lanreotide reduces growth hormone and IGF-1 levels.

Clinical Evidence

Unproven

Refractory HIV/AIDS-Related Diarrhea

Agents utilized for symptomatic treatment include loperamide, diphenoxylate/atropine, paregoric, deodorized tincture of opium.

Fifty-one patients with refractory uncontrolled AIDS related diarrhea were treated with octreotide in a prospective, open-label study. All fifty-one patients completed the 28 day protocol. Stool frequency and volume decreased significantly ($p < 0.001$). 41.2% (21) were considered to be partial or complete responders (decrease in daily stool volume by > 50% of initial collections or reduction to 250 mL/d). Of the responders, 67% (14 of 21) were negative for pathogens at initial screening compared to 30% (9 of 30) of nonresponders ($p < 0.01$). The study concluded that patients with refractory AIDS related diarrhea, especially those without pathogens, may respond favorably to octreotide. Limitations of this study include small sample size and lack of randomization.

Although a 3 week study of 129 patients with refractory AIDS-associated diarrhea and a baseline stool weight of > 500 g/day did not show octreotide to be more effective than placebo (48% vs. 39% response, respectively), those with a baseline stool weight of 1,000-2,000 g/day did show improvement with octreotide ($p = 0.06$).

A panel from the National Institutes of Health, HIV Medicine Association, and Infectious Diseases Society of America, which also contributes to the Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV, has indicated that octreotide is no more effective than other oral antidiarrheal agents and is generally not recommended in HIV/AIDs-related diarrhea.

Chylothorax

A Cochrane review of octreotide in the treatment of congenital or acquired chylothorax in neonates concluded that no practice recommendation can be made based on the evidence identified. Search included randomized or quasi-randomized controlled trials of octreotide in the treatment of congenital or acquired chylothorax in term or preterm neonates, with any dose, duration or route of administration. The authors reported that no randomized controlled trials were identified. Nineteen case reports of 20 neonates with chylothorax in whom octreotide was used either subcutaneously or intravenously were identified. Fourteen case reports described successful use (resolution of chylothorax), four reported failure (no resolution), and one reported equivocal results following use of octreotide. The timing of initiation, dose, duration and frequency of doses varied markedly. A prospective registry of chylothorax patients and a subsequent multicenter randomized controlled trial are needed to assess the safety and efficacy of octreotide in the treatment of chylothorax in neonates.

In a retrospective review, Landvoigt examined the efficacy of octreotide in resolving chylothoraces in infants and children following cardiac surgery. Eight courses of octreotide treatment were identified in seven patients who met the inclusion criteria. The median duration of therapy was 5 days, and dosing ranged from 1 to 4 mcg/kg/hr. Treatment did not result in an overall decrease in average chest tube output after 3 days of therapy. However, in two patients (29%) the chylothoraces ultimately resolved during the octreotide infusion. Treatment was well tolerated, and no serious side effects were noted. In contrast to previously published reports, the author found that octreotide therapy for postoperative chylothoraces was successful in only a minority of cases.

Roehr et al. systematically reviewed the evidence on the efficacy and safety of somatostatin and octreotide in treating young children with chylothorax. Thirty-five children treated for primary or secondary chylothorax were identified. Ten of the 35 children had been given somatostatin, as an IV infusion at a median dose of 204 mcg/kg/day, for a median duration of 9.5 days. The remaining 25 children had received octreotide, either as an IV infusion at a median dose of 68 mcg/kg/day over a median 7 days, or SC at a median dose of 40 mcg/kg/day and a median duration of 17 days. A positive treatment effect was evident for both somatostatin and octreotide in the majority of reports. Minor side effects have been reported; however, caution should be exercised in patients with an increased risk of vascular compromise as to avoid serious side effects. Systematic clinical research is needed to establish treatment efficacy and to develop a safe treatment protocol.

Kalomenidis performed a literature review to examine the role of somatostatin and its synthetic analog, octreotide, in the treatment of chylothorax. Several case reports and series have shown that octreotide is safe and probably effective in both children and adults with chylothorax of different origins. The property of somatostatin and octreotide to induce leak closure is attributed to a decelerating effect on lymph flow, although their exact mechanism of action is not well defined. In successful cases, a substantial reduction of lymph drainage through the chest tube is evident within the first few days of commencing the drug, and treatment lasts for 1-2 weeks. Treatment failure has been also reported, however. Although accumulating evidence suggests that octreotide is a putative novel therapeutic intervention for chylothorax, it is imperative that randomized controlled studies are conducted in order to fully elucidate the efficacy and safety of this treatment.

A retrospective review of pediatric patients less than 18 years of age who experienced chylothorax after cardiac surgery (N = 46; 29 of which were included in efficacy and safety analyses), showed resolution occurring in 62% of patients (28% complete and 34% partial) after treatment with octreotide IV infusion. Those who did not respond to octreotide therapy required thoracic duct ligation. Octreotide was initiated in all patients after failure of first-line nutritional interventions. The

mean initial and maximum doses of octreotide were 4 mcg/kg/hr and 6 mcg/kg/hr, with a mean duration of treatment of 10 days. The time from chylothorax diagnosis to treatment with octreotide was 12 days. Minor adverse events were reported but no patients were required to discontinue treatment.

Dumping Syndrome

Octreotide therapy is effective in controlling severe dumping symptoms during short-term follow-up but little is known about long-term results. Didden et al. report on the long-term results of 34 patients with severe dumping syndrome treated with subcutaneous or depot intramuscular (long-acting release) octreotide. All patients had excellent initial relief of symptoms during octreotide subcutaneous therapy. However, during follow-up, 16 patients stopped therapy because of side effects (n = 9) or loss of efficacy (n = 7). Four patients died. Fourteen patients (41%) remained using octreotide (follow-up 93 ±15 months), seven on octreotide subcutaneous and seven on octreotide long-acting release. The authors concluded that long-term efficacy of octreotide is much less favorable compared with short-term treatment.

In a systematic review of seven randomized, controlled trials, Li-Ling found that although sample sizes were small in all the studies, compared with the control cases, octreotide pre-treatment resulted in significant improvement in symptoms in nearly all patients. However, long term use of octreotide for dumping syndrome was limited by severe side effects.

Vecht et al. reported the results of an open-label study including 20 patients with severe dumping symptoms after gastric surgery treated with octreotide. Mean follow-up was 37 ±9 months (range 1-107 months). Doses of octreotide ranged from 25 to 200 mcg/day. Initial relief of symptoms was achieved in all subjects, but after three months of therapy symptom relief persisted in 80% of patients. Mean body weight increased by 2.4 ±1.2 kg despite a significant increase in faecal fat excretion from 10 ±2 g/24 h to 24 ±3 g/24 h. Reasons for discontinuation of therapy were diminished efficacy in the longer term in 4 patients and side-effects in 7 patients. Biliary complications were encountered in 3 patients. Self-administration of octreotide provides an effective symptomatic treatment of severe dumping, even on the long-term. However, its use is frequently limited by the occurrence of side-effects.

Pancreatitis

Omata et al. performed a recent meta-analysis of double-blinded randomized controlled trials that analyzed the efficacy of somatostatin or octreotide for the prevention of post-ERCP pancreatitis and had a primary outcome measure of acute pancreatitis following ERCP. A comprehensive literature review revealed seventeen studies (n = 3,818) employing a variety methods of administration in various populations with different risks of developing post-ERCP pancreatitis. The investigators concluded that somatostatin may have significant preventive efficacy against post-ERCP pancreatitis, especially when used in appropriate diagnostic or therapeutic procedures or with high-dose administration as a 12-h infusion or a bolus. High-dose octreotide may also prevent post- ERCP pancreatitis. The efficacy of both somatostatin and octreotide in these contexts is expected to be confirmed by large high-quality randomized controlled trials in the future.

Zhang et al. conducted a comprehensive literature search to examine the effects of octreotide on post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP). Seventeen randomized controlled trials (n = 2,784) were analyzed and divided into two groups according to the total dosage of octreotide: < 0.5 mg (OCT1) and ≥ 0.5 mg (OCT2). The investigators concluded that octreotide is effective in preventing post-ERCP pancreatitis and hyperamylasemia, but must be given at dosages ≥ 0.5 mg. However, there are insufficient data to determine the optimal route of administration for octreotide or its optimal timing.

Heinrich et al. performed an evidence-based analysis to assess the best available treatment for acute pancreatitis (AP), looking at the value of aprotinin, lexipafant, gabexate mesylate and octreotide treatment. Recommendations were based on the available level of evidence (A = large randomized; B = small randomized; C = prospective trial). None of the evaluated medical treatments is recommended (level A).

Uncertainties still exist about the clinical benefit of pharmacological prevention of post- endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis by either antisecretory drugs such as somatostatin and its long-acting analogue octreotide, or protease inhibitors such as gabexate mesilate. Recent, large-scale prospective studies have reported a fourfold reduction in acute pancreatitis as compared to a placebo with the prophylactic administration of either gabexate mesilate or somatostatin, whereas octreotide was found to be ineffective. An initial meta-analysis of all available controlled trials on this topic has confirmed these findings. Current literature does not support the prophylactic use of either somatostatin or gabexate mesilate for the prevention of ERCP-related pancreatic damage, even in patients deemed to be at high risk for complications.

In a systematic review and meta-analysis of randomized trials, the impact of octreotide on patients with acute pancreatitis was evaluated. Short-term mortality (up to 3 months) showed no significant difference between the octreotide and control

groups (OR, 0.76; 95% CI, 0.47 to 1.23; n = 927; 6 studies). Octreotide significantly reduced the number of serious adverse events (RR, 0.74; 95% CI, 0.6 to 0.89; n = 770; 5 studies) and the likelihood of organ failure (OR, 0.51; 95% CI, 0.27 to 0.97; n = 430; 3 studies), but did not significantly affect the proportion of patients experiencing adverse events, infected pancreatic necrosis (OR, 0.52; 95% CI, 0.04 to 6.06; n = 58; 1 study), or sepsis (OR, 0.4; 95% CI, 0.05 to 3.53; n = 340; 2 studies). Control groups received placebo, standard of care, ulinastatin, or octreotide combined with another medication. Octreotide was administered subcutaneously or as a continuous IV infusion for 3 to 14 days, or until hospital discharge, with dosages ranging from 100 to 300 mcg subcutaneously once to thrice daily, or 25 to 50 mcg/hr IV infusions. The mean age ranged from 37 to 69 years, with 22.8% to 55.2% female participants. Patients with varying severities of pancreatitis were included, though most studies did not specify the percentages for each severity.

Persistent Hyperinsulinemic Hypoglycemia of Infancy

Long-term experience with octreotide in patients with persistent hyperinsulinemic hypoglycemia of infancy is limited, including information about possible side effects such as growth suppression. Appropriate dose and place in therapy in combination with other agents also need to be established.

Postoperative Complications Following Pancreatic Surgery

Graham et al. conducted a prospective study of prophylactic long-acting octreotide to prevent postoperative pancreatic fistula (POPF) in high-risk patients undergoing pancreaticoduodenectomy. Sixty-eight patients evaluated for the study were divided into two groups: pancreatic ducts ≤ 3 mm (high risk, n = 36) and those with ducts > 3 mm (low risk, n = 32). High-risk patients were treated preoperatively with depot octreotide and begun on an intravenous drip for 24 hours. Low-risk patients underwent pancreaticoduodenectomy without pharmacologic intervention. In contrast, the control cohort represented 106 retrospectively analyzed patients who underwent a pancreaticoduodenectomy without depot octreotide injection without regard to low- or high-risk status. Overall, POPF was 11 of 68 (16%). Nine of 36 high risk patients treated with depot octreotide developed POPF (25%), and 2 of 32 low risk patients developed POPF (6%). In the control cohort of high-risk patients, 9 of 44 (20%) and 3 of 62 (5%) low-risk patients developed POPF (p = 0.628 when comparing the development of POPF in high-risk patients with or without pharmacologic intervention). The authors concluded that prophylactic use of depot octreotide in high-risk patients does not result in reduced incidence of POPF. However, duct size has a significant impact on the occurrence of POPF.

A recent Cochrane review of somatostatin analogues (SSAs) for pancreatic surgery concluded that SSAs reduce perioperative complications but do not reduce perioperative mortality. In those undergoing pancreatic surgery for malignancy, they shorten hospital stay. Further adequately powered trials with low risk of bias are necessary. Based on the current available evidence, somatostatin and its analogues are recommended for routine use in patients undergoing pancreatic resection for malignancy. There is currently no evidence to support their routine use in pancreatic surgeries performed for other indications.

In a meta-analysis by Zeng et al., eight studies were reviewed to evaluate the efficacy of somatostatin and its analogues in the prevention of postoperative complications after pancreaticoduodenectomy. The use of somatostatin or its analogues did not significantly benefit for reducing the incidence of pancreatic fistula (odds ratio [OR] 95% confidence interval [CI], 0.64-1.37; p = 0.73), total pancreas-specific postoperative complications (OR 95% CI, 0.63-1.42; p = 0.79), delayed gastric emptying (OR 95% CI, 0.50-1.78; p = 0.86), total complication (OR 95% CI, 0.73-1.70; p = 0.61), mortality (OR 95% CI, 0.59-7.72; p = 0.97) and length of postoperative hospital stay (weighted mean difference 95% CI, -7.74 to 4.47; p = 0.60). The use of somatostatin and its analogues does not significantly reduce postoperative complications after pancreaticoduodenectomy.

Several clinical trials have evaluated the use of octreotide to prevent the development of pancreatic fistula after pancreatic surgery with conflicting recommendations. Alghamdi et al. conducted a meta-analysis of seven randomized controlled trials (n = 1,359), reporting comparisons between octreotide and a control. The primary outcome was the incidence of postoperative pancreatic fistula, and the secondary outcome was the postoperative mortality. In these studies, sample sizes ranged from 75 to 252 patients. In total, 679 patients were given octreotide and 680 patients formed the control group. Perioperative octreotide is associated with a significant reduction in the incidence of pancreatic fistula after elective pancreatic surgery, with a relative risk of 0.59 (95% confidence interval 0.41-0.85, p = 0.004). However, this risk reduction was not associated with a significant difference in postoperative mortality (p > 0.05). Further studies are warranted to confirm the results of this meta-analysis and to define which patient subgroups might benefit the most from prophylactic octreotide administration.

Short Bowel Syndrome

Nehra et al. assessed the effects of octreotide acetate depot in patients with short bowel syndrome by conducting a 15-week, prospective, open-label study of eight patients (five women and three men; mean age 52 yr., range 37-72 yr.).

Treatment with octreotide acetate depot significantly increased small bowel transit time (p = 0.03). Changes in body weight, urine volume, stool weight, fecal fat excretion, stool sodium and potassium excretion, or gastric emptying rate were highly variable, and no overall significance was observed. Octreotide acetate depot for 15 weeks significantly prolonged small bowel transit time. However, octreotide acetate treatment needs to be assessed further in multicenter studies assessing dose, frequency of administration and a larger sample size.

Signifor

Petersenn et al. conducted a randomized, double-blind study, to investigate the safety and efficacy of pasireotide. in adult patients with persistent/recurrent or de novo Cushing's disease. Patients with mean urinary free cortisol at or below the upper limit of normal or clinical benefit at month 12 could continue receiving pasireotide during this open-ended, open-label phase. For the 16 patients that received 5 years of pasireotide treatment, the median (95% confidence interval) percentage change from baseline in mean urinary free cortisol was −82.6% (−89.0, −41.9) and −81.8% (−89.8, −67.4) at months 12 and 60. Eleven patients had mean urinary free cortisol ≤ upper limit of normal at month 60. Improvements in clinical signs were sustained during long-term treatment. The safety profile of pasireotide at 5 years was similar to that reported after 12 months. Fifteen of 16 patients experienced a hyperglycemia-related adverse event; glycated hemoglobin levels were stable between months 6 and 60. Adverse events related to hyperglycemia, bradycardia, gallbladder/biliary tract, and liver safety were most likely to first occur by month 6, and severity did not tend to worsen over time. The authors conclude that the use of pasireotide is an effective long-term therapy for some patients with Cushing's disease.

In a double-blind, phase 3 study, Colao et al evaluated the efficacy of pasireotide on urinary free cortisol. Adults with Cushing's disease and a urinary free cortisol level of at least 1.5 times the upper limit of the normal were randomly assigned to receive subcutaneous pasireotide at a twice daily dose of 600 μg or 900 μg. At month 3, patients with urinary free cortisol 2 times the upper limit of the normal range or less, and not exceeding their baseline level remained on their randomly assigned dose. All other patients received an increase in dose of 300 μg twice daily. The primary end point was a urinary free cortisol level at or below the upper limit of the normal at 6 months without an increased dose. Open-label treatment continued for a total of 12 months. The primary endpoint was met by 12 of 82 patients in the 600-μg group and 21 of 80 patients in the 900-μg group. The median urinary free cortisol level decreased by approximately 50% by month 2 and remained stable in both groups. Patients with baseline levels not exceeding 5 times the upper limit of the normal more frequently achieved a normal urinary free cortisol level than patients with higher baseline levels. Serum and salivary cortisol and plasma corticotropin levels decreased, as well as clinical signs and symptoms of Cushing's disease. Hyperglycemia-related adverse events occurred in 118 of 162 patients. Additionally, other adverse events were similar to those associated with other somatostatin analogues. Even with declines in cortisol levels, blood glucose and glycated hemoglobin levels increased shortly after the initiation of treatment and then stabilized; glucose- lowering medication was initiated in 74 of 162 patients. The authors concluded that there was a significant decrease in cortisol levels in patients receiving pasireotide with Cushing's disease. This supports its potential use as a targeted treatment for corticotropin secreting pituitary adenomas.

Signifor LAR

In this double-blind extension to a multicenter, 12-month, Phase III core study, Sheppard et al evaluated the efficacy and safety of pasireotide LAR and octreotide LAR after up to 26 months' treatment. Patients with GH < 2.5 μg/L and IGF-1 ≤ 1× ULN at month 12, or patients considered to be experiencing clinical benefit, were eligible to continue receiving their randomized therapy in this extension. Efficacy and safety were evaluated for up to 26 months.

Overall, 120 patients who completed the core study continued receiving pasireotide LAR or octreotide LAR in this extension study. At month 25, biochemical control, defined as GH < 2.5 μg/L and normal IGF-1, was achieved by 48.6% and 45.7% of patients in the pasireotide LAR and octreotide LAR arms respectively. In total, 74.7% of pasireotide LAR and 71.6% of octreotide LAR patients had tumor volume decrease ≥ 20% from baseline to month 26. Most adverse events were mild or moderate. Hyperglycemia-related adverse events were seen in 62.9 and 25.0% of pasireotide LAR and octreotide LAR patients, respectively. The authors conclude that GH and IGF-1 suppression is maintained for up to 25 months during pasireotide LAR treatment. Additionally, they conclude that the safety profile of pasireotide LAR is typical of a somatostatin analogue, except for the frequency and degree of hyperglycemia.

In the PAOLA trial, Gadelha et al evaluated the efficacy and safety of pasireotide long-acting release compared with octreotide or lanreotide in patients with inadequately controlled acromegaly. In this randomized, phase 3 trial, patients 18 years and older with acromegaly who were inadequately controlled, and had received 30 mg octreotide long-acting or 120 mg lanreotide as monotherapy for 6 months or longer were enrolled. Patients were randomly assigned in a 1:1:1 ratio to receive 40 mg pasireotide long-acting release once every 28 days, 60 mg pasireotide long-acting release once every 28 days, or continued treatment with octreotide or lanreotide (active control) for 24 weeks. Patients were stratified according to previous treatment and growth hormone concentrations at screening. The primary endpoint was number of patients

achieving biochemical control, defined as mean growth hormone concentration less than 2.5 μg/L and normalized IGF-1 concentration. Enrolled patients were randomly assigned to pasireotide 40 mg, pasireotide 60 mg, or active control groups. At 24 weeks, ten (15%) patients in the pasireotide 40 mg group and 13 (20%) patients in the pasireotide 60 mg group achieved biochemical control, compared with no patients in the active control group. The most common adverse events were hyperglycemia, diabetes, and diarrhea. The authors concluded that pasireotide provides superior efficacy compared with continued treatment with octreotide or lanreotide.

Coloa et al evaluated the superiority of pasireotide LAR over octreotide LAR in medically naive patients with acromegaly in a multicenter prospective, randomized, double-blind study. Enrollment included 358 patients with medically naive acromegaly. Patients either had previous pituitary surgery but no medical treatment or were de novo with a visible pituitary adenoma on magnetic resonance imaging. In the study, patients receiving pasireotide LAR 40 mg/28 days were compared to patients receiving octreotide LAR 20 mg/28 days for 12 months. At months 3 and 7, patients who had IGF-1 levels above the upper limit of normal had the option of having their doses titrated to pasireotide LAR 60mg or octreotide LAR 30mg. The primary outcome was the proportion of patients in each treatment group achieving biochemical control, defined at GH 2.5 µg/L and normal IGF-1 at month 12. Biochemical control was achieved by significantly more pasireotide LAR patients than octreotide LAR patients. In pasireotide LAR and octreotide LAR patients, respectively, 38.6% and 23.6% (P.002) achieved normal IGF-1, and 48.3% and 51.6% achieved GH 2.5 µg/L. 31.0% of pasireotide LAR and 22.2% of octreotide LAR patients who did not achieve biochemical control did not receive the recommended dose increase. Hyperglycemia-related adverse events were more common with pasireotide LAR (57.3% vs 21.7%). The authors conclude that pasireotide LAR demonstrated superior efficacy over octreotide LAR and is a viable new treatment option for acromegaly.

Professional Societies

Acromegaly

Endocrine Society & European Society of Endocrinology

In 2014, the Task Force of the Endocrine Society Clinical Guidelines Subcommittee published an evidence based guideline regarding the evaluation and management of acromegaly. The guidelines state (Strong recommendations = the number 1, weak recommendations = the number 2; quality of evidence):

- Preoperative use of somatostatin analogues to reduce surgical risk from severe comorbidities (2; very low quality).
- The use of somatostatin analogues (e.g., octreotide) or pegvisomant in a patient with significant disease, as the initial adjuvant medical therapy (2; low quality).
- The addition of pegvisomant or cabergoline in a patient with inadequate response to a somatostatin analogue (2; low quality).
- The use of somatostatin analogue as primary therapy in a patient who cannot be cured by surgery, has extensive cavernous sinus invasion, does not have chiasmal compression, or is a poor surgical candidate (2; moderate quality).
- Discontinue long acting somatostatin analogue formulations and pegvisomant approximately 2 months before conceiving, with use of short acting octreotide as necessary until conception (2; low quality).

Pituitary Society

In 2021, the Pituitary Society published an update to the Endocrine Society guidelines and Acromegaly Consensus Group Statements. This update focused on how recent key advances affect treatment decision-making and outcomes, and also highlights the likely role of recently FDA-approved therapies as well as novel combination therapies within the treatment armamentarium. Key summary points on medical therapy are listed below (DR = Discretionary recommendation based on very low quality or low quality evidence; SR = Strong recommendation based on moderate quality or high quality):

Injectable SRL

- Older age, female sex, lower IGF-I levels, and tumor T2 MRI hypointensity at baseline predict more favorable long-term biochemical responses to primary lanreotide 120 mg therapy every 4 weeks. (SR)
- Recent studies confirm that extended-dosing intervals (> 4 weeks) for 120 mg lanreotide may be effective among selected patients previously controlled with long-acting SRLs. (LDR)
- Several studies confirm efficacy of pasireotide LAR for some patients uncontrolled on lanreotide or octreotide LAR. However, rates of treatment-induced hyperglycemia and DM are high, requiring careful monitoring for glycemic side effects. (SR)

Pegvisomant

- Ten-year follow-up from ACROSTUDY shows a 73% biochemical control rate with very low rates of transient elevated transaminases and 6.8% exhibiting tumor growth visible on MRI. (SR)

- Pegvisomant use in patients with DM improves glucose metabolism independent of IGF-I control, but does not affect glycemic endpoints in patients without DM. (SR)
- Patients with DM and those with a higher BMI require higher doses of pegvisomant and more rapid up-titration to achieve IGF-I normalization. (SR)

Combination Therapy With SRL + Pegvisomant

- Low-dose octreotide LAR or lanreotide plus weekly pegvisomant is a cost-effective and efficacious option for patients requiring combination therapy. (SR)
- Combination of pasireotide plus pegvisomant can yield biochemical control rates exceeding 70% even when pegvisomant doses are kept low. However, the addition of pegvisomant does not ameliorate the high rates of pasireotide-induced hyperglycemia. (SR)
- Patient selection for combination pasireotide plus pegvisomant should be carefully considered. (LDR)

Bleeding Gastroesophageal Varices

American College of Gastroenterology

In 2007, the American Association for the Study of Liver Diseases and the Practice Parameters Committee of the American College of Gastroenterology's Practice Guidelines for the Prevention and Management of Gastroesophageal Varices and Variceal Hemorrhage in Cirrhosis recommend octreotide as a useful adjunct to endoscopic therapy. Pharmacological therapy (somatostatin or its analogues) should be initiated as soon as variceal hemorrhage is suspected and continued for 3-5 days after diagnosis is confirmed (Class I, Level A). (Class I - conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure or treatment is beneficial, useful, and effective. Level A - data derived from multiple randomized clinical trials or meta-analyses.)

Cushing's Syndrome

Endocrine Society

In 2015, the Endocrine Society published the Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline which suggests pituitary-directed medical treatments (i.e., cabergoline, pasireotide) in patients with Cushing's disease who are not surgical candidates or who have persistent disease after transsphenoidal selective adenomectomy TSS (weak recommendation; moderate quality of evidence).

Pancreatitis

American Gastroenterological Association

An American Gastroenterological Association Technical Review on Acute Pancreatitis lists somatostatin and octreotide as pharmacological options to limit pancreatic secretion. However, the review states that the data supporting the use of these agents is not very convincing. Of note, the largest single randomized trial (by far) of octreotide in 302 patients with moderate to severe acute pancreatitis found absolutely no effect on mortality, organ failure, or secondary infections. Somatostatin is not easily available in the United States, and the data on octreotide are controversial, so neither can currently be recommended as routine management for acute pancreatitis.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Signifor is indicated for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.

Signifor LAR is indicated for the treatment of:

- Patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option
- Patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative

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Policy History/Revision Information

Date	Summary of Changes
05/01/2025	**Coverage Rationale** • Added language to indicate Somatostatin analogs are unproven and not medically necessary for treating HIV-AIDS-related diarrhea **Applicable Codes** • Reformatted list of applicable ICD-10 diagnosis codes to reflect/include the corresponding HCPCS codes • Removed ICD-10 diagnosis codes B20 and R19.7 **Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version CSOH2025D0036.D

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state (Ohio Administrative Code [OAC]), or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state (OAC), or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state (OAC), or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state (OAC), or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

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