Somatostatin Analogs (for Ohio Only)

Policy Number: CSOH2024D0036.B
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Instructions for Use

Table of Contents **Page**

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;[49] **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:[53]
  - 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:[22,26]
  - 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:

- 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
B20	Human immunodeficiency virus [HIV] disease
C7A.010	Malignant carcinoid tumor of the duodenum
C7A.011	Malignant carcinoid tumor of the jejunum
C7A.012	Malignant carcinoid tumor of the ileum
C7A.019	Malignant carcinoid tumor of the small intestine, unspecified portion
C7A.020	Malignant carcinoid tumor of the appendix
C7A.021	Malignant carcinoid tumor of the cecum
C7A.022	Malignant carcinoid tumor of the ascending colon
C7A.024	Malignant carcinoid tumor of the descending colon
C7A.025	Malignant carcinoid tumor of the sigmoid colon
C7A.026	Malignant carcinoid tumor of the rectum
C7A.029	Malignant carcinoid tumor of the large intestine, unspecified portion
C7A.092	Malignant carcinoid tumor of the stomach
C7A.094	Malignant carcinoid tumor of the foregut, unspecified
C7A.095	Malignant carcinoid tumor of the midgut, unspecified
C7A.096	Malignant carcinoid tumor of the hindgut, unspecified
C17.0	Malignant neoplasm of duodenum
C17.1	Malignant neoplasm of jejunum
C17.2	Malignant neoplasm of ileum
C17.3	Meckel's diverticulum, malignant
C17.8	Malignant neoplasm of overlapping sites of small intestine
C17.9	Malignant neoplasm of small intestine, unspecified
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.0	Malignant neoplasm of anus, unspecified
C21.1	Malignant neoplasm of anal canal
C21.2	Malignant neoplasm of cloacogenic zone
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C25.0	Malignant neoplasm of head of pancreas
C25.1	Malignant neoplasm of body of pancreas
C25.2	Malignant neoplasm of tail of pancreas
C25.4	Malignant neoplasm of endocrine pancreas

Diagnosis Code	Description
C25.7	Malignant neoplasm of other parts of pancreas
C25.8	Malignant neoplasm of overlapping sites of pancreas
C25.9	Malignant neoplasm of pancreas, unspecified
E22.0	Acromegaly and pituitary gigantism
E24.0	Pituitary-dependent Cushing's disease
E34.0	Carcinoid syndrome
E34.4	Constitutional tall stature
I85.01	Esophageal varices with bleeding
I85.11	Secondary esophageal varices with bleeding
K52.0	Gastroenteritis and colitis due to radiation
K52.89	Other specified noninfective gastroenteritis and colitis
K52.9	Noninfective gastroenteritis and colitis, unspecified
R19.7	Diarrhea, unspecified

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.[36]

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.[37]

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.[49]

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.[49, 53]

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.[47, 57]

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.[50] 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. [51] 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.[56] 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.[55] 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.[54] 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 (2014)[46]

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).

American Association of Clinical Endocrinologists

The recently updated guidelines of the American Association of Clinical Endocrinologists for the diagnosis and treatment of acromegaly list the somatostatin analogues (SSAs) octreotide and lanreotide with a Grade A recommendation. (Grade A = one or more conclusive level 1 publications exist demonstrating benefit > risk; recommendation is based upon strong evidence; recommendation is considered first-line therapy.)[22]

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.[49]

Signifor LAR is indicated for the treatment of:[53]

- 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
04/01/2024	**Applicable Codes** • Added ICD-10 diagnosis codes C17.0, C17.1, C17.2, C17.3, C17.8, C17.9, C18.0, C18.1, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8, C18.9, C19, C20, C21.0, C21.1, C21.2, C21.8, C25.0, C25.1, C25.2, C25.7, C25.8, and C25.9 • Removed ICD-10 diagnosis codes K56.1, K56.2, K56.50, K56.51, K56.52, K56.600, K56.601, K56.609, K56.690, K56.691, K56.699, and K59.9 **Supporting Information** • Archived previous policy version CSOH2024D0036.A

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.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.