Somatostatin Analogs

Policy Number: 2026D0036W
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➲ Instructions for Use

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Related Commercial Policy

- Oncology Medication Clinical Coverage (for Commercial Only)
- Oncology Medication Clinical Coverage (for Individual Exchange Only)

Community Plan Policy

- Somatostatin Analogs

Application

UnitedHealthcare Commercial

This Medical Drug Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Drug Policy applies to Individual Exchange benefit plans.

Coverage Rationale

➲ See Benefit Considerations

This policy refers to the following somatostatin analogs for non-oncology indications:

- Lanreotide® Injection
- Sandostatin® (octreotide acetate)
- Sandostatin LAR® (octreotide acetate)
- Signifor LAR® (pasireotide)
- Somatostatin Depot® (lanreotide)

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

Sandostatin (octreotide acetate) is proven for the following conditions:

- Acromegaly patients who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation, or bromocriptine mesylate at maximally tolerated doses
- Severe diarrhea and flushing episodes associated with metastatic carcinoid tumors
- Profuse watery diarrhea associated with vasoactive intestinal peptide (VIP) secreting tumors

Sandostatin LAR (octreotide acetate LAR) is proven for the treatment of the following conditions:

- Acromegaly patients who have had inadequate response to or cannot be treated with surgery and/or radiotherapy
- Severe diarrhea and flushing episodes associated with metastatic carcinoid tumors
- Profuse watery diarrhea associated with vasoactive intestinal peptide (VIP) secreting tumors

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- Chemotherapy and/or radiation-induced diarrhea
- Malignant bowel disease

Signifor LAR (pasireotide) is proven for the treatment of the following conditions:
- Acromegaly patients who have had an inadequate response to surgery or for whom surgery is not an option
- Cushing's disease in patients for whom pituitary surgery is not an option or has not been curative

Somatuline Depot (lanreotide) and Lanreotide Injection are proven for the treatment of acromegaly in patients who have had an inadequate response to surgery and/or radiotherapy, or for who, surgery and/or radiotherapy is not an option.

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 the member specific benefit plan document 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
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.023	Malignant carcinoid tumor of the transverse 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
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

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Diagnosis Code	Description	J1930	J1932	J2502	J2353 J2354
C17.3	Meckel's diverticulum, malignant	x	x		x
C17.8	Malignant neoplasm of overlapping sites of small intestine	x	x		x
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
C25.3	Malignant neoplasm of pancreatic duct	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
E22.0	Acromegaly and pituitary gigantism	x	x	x	x
E24.0	Pituitary-dependent Cushing's disease			x	
E24.8	Other Cushing’s syndrome			x	
E24.9	Cushing’s syndrome, unspecified			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
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

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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 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.

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

Clinical Evidence

Sandostatin and Sandostatin LAR

Acromegaly

The efficacy and safety of octreotide LAR for the treatment of acromegaly was studied in three clinical trials performed in patients who achieved GH levels of < 10 ng/mL while on subcutaneous octreotide injection. In 2 of the clinical trials, a total of 101 patients were entered who had, in most cases, achieved a GH level < 5 ng/mL on subcutaneous octreotide injection given in doses of 100 mcg or 200 mcg three times daily. Most patients were switched to 20 mg or 30 mg doses of octreotide LAR given once every 4 weeks for up to 27 to 28 injections. A few patients received doses of 10 mg and a few required doses of 40 mg. Growth hormone and IGF-1 levels were at least as well controlled with octreotide LAR as they had been on subcutaneous octreotide injection and this level of control remained for the entire duration of the trials. A third trial was a 12-month study that enrolled 151 patients who had a GH level < 10 ng/mL after treatment with subcutaneous octreotide injection. The starting dose of octreotide LAR was 20 mg every 4 weeks for 3 doses. Thereafter, patients received 10 mg, 20 mg, or 30 mg every 4 weeks, depending upon the degree of GH suppression. Growth hormone and IGF-1 were at least as well controlled on octreotide LAR as they had been on subcutaneous octreotide injection. For the 88 patients in the first two clinical trials who received all 27 to 28 injections, a mean GH level of < 2.5 ng/mL was observed in 47% receiving octreotide LAR. Over the course of the trials, 42% of patients maintained mean growth hormone levels of < 2.5 ng/mL and mean normal IGF-1 levels. For the 122 patients who received all 12 injections in the third trial, a mean GH level of < 2.5 ng/mL was observed in 66% receiving octreotide LAR. Over the course of the trial, 57% of patients maintained mean growth hormone levels of < 2.5 ng/mL and mean normal IGF-1 levels. In comparing the hormonal response in these trials, note that a higher percentage of patients in the third trial suppressed their mean GH to < 5 ng/mL on octreotide injection, 95%, compared to 78% across the 2 previous trials. In all 3 trials, GH, IGF-1, and clinical symptoms were similarly controlled on octreotide LAR as they had been on octreotide injection. Of the

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25 patients who completed the trials and were partial responders to octreotide injection (GH > 5.0 ng/mL but reduced by > 50% relative to untreated levels), 1 patient (4%) responded to octreotide LAR with a reduction of GH to < 2.5 ng/mL and 8 patients (32%) responded with a reduction of GH to < 5.0 ng/mL.

Signifor LAR

Acromegaly

In a 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.

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.

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%).

Cushing's Disease

Colao et al evaluated the efficacy and safety of pasireotide in Cushing's disease in a 12-month double-blind, phase 3 study. One hundred and sixty two adults with Cushing's disease and a urinary free cortisol level of at least 1.5 times the upper limit of the normal range were randomized to receive subcutaneous pasireotide at a dose of 600 µg (82 patients) or 900 µg (80 patients) twice daily. Patients with urinary free cortisol not exceeding 2 times the upper limit of the normal range and not exceeding the baseline level at month 3 continued to receive their randomly assigned dose; all others received an additional 300 µg twice daily. The primary end point was a urinary free cortisol level at or below the upper limit of the normal range at month 6 without an increased dose. At month 6, 15% [95% confidence interval (CI), 7 to 22] of patients in the 600-µg group and 26% (95% CI, 17 to 36) of those in the 900-µg group had urinary free cortisol levels at or below the upper limit of the normal range without a prior dose increase. Most drug-related adverse events were grade 1 or 2 and resolved without dose modification. The most frequently reported grade 3 or 4 adverse events were hyperglycemia and diabetes mellitus, occurring in 13% and 7% of patients, respectively. Overall, 118 of 162 patients (73%) had a hyperglycemia-related adverse event; 6% of patients discontinued treatment because of a hyperglycemia-related adverse event. Preexisting diabetes or impaired glucose tolerance increased the risk of hyperglycemia-related adverse events.

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Somatuline Depot

Acromegaly

Chanson et al. conducted an open-label, multicenter, phase III, 48-week trial to assess the efficacy and safety of 48 weeks titrated dosing of lanreotide. Patients with active acromegaly (IGF-I levels > 1-3 times upper limit of age-adjusted normal range) were recruited and received 12 injections of lanreotide Autogel at 28-day intervals. Dosing during the 16-week fixed-dose phase was 90 mg; in the 32-week dose-titration phase, patients received 60, 90 or 120 mg based on GH and IGF-I levels. At the end of the study, an intention-to-treat analysis was performed to determine the proportion of patients with normalized age-adjusted IGF-I levels. GH levels, clinical acromegaly signs, and safety were secondary measures. Fifty-seven of 63 patients completed the study. Lanreotide resulted in normalized age-adjusted IGF-I levels in 27 patients (43%, 95% CI 31–55). Mean GH levels decreased from 6·2 to 1·5 μ g/l at study end, with 53 of 62 patients (85%) having GH levels ≤ 2·5 μ g/l (95% CI 76·7–94·3) and 28 of 62 patients (45%) with levels < 1 μg/l (95% CI 32·8–57·6). Twenty-four (38%) had both normal IGF-I levels and GH levels ≤ 2·5μ g/l. Symptoms of acromegaly reduced significantly in most patients during the study. The majority of adverse events were mild (111 events in 18 patients, 29%) or moderate (78 events in 25 patients, 40%) in severity. The most common adverse events were gastrointestinal in nature, with 36 (57%) and 17 (27%) patients reporting at least one episode of diarrhea or abdominal pain, respectively, over the 48-week study.

Lanreotide Injection

Acromegaly

The effect of lanreotide on reducing GH and IGF-levels and control of symptoms in patients with acromegaly was studied in 2 long-term, multiple-dose, randomized, multicenter studies. Study 1 included a 4-week, double-blind, placebo-controlled phase; a 16-week single-blind, fixed-dose phase; and a 32-week, open-label, dose-titration phase. Patients with active acromegaly, based on biochemical tests and medical history, entered a 12-week washout period if there was previous treatment with a somatostatin analog or a dopaminergic agonist. Upon entry, patients were randomly allocated to receive a single, deep subcutaneous injection of lanreotide 60, 90, or 120 mg or placebo. Four weeks later, patients entered a fixed-dose phase where they received 4 injections of lanreotide followed by a dose-titration phase of 8 injections for a total of 13 injections over 52 weeks (including the placebo phase). Injections were given at 4-week intervals. During the dose-titration phase of the study, the dose was titrated twice (every fourth injection), as needed, according to individual GH and IGF-1 levels. A total of 108 patients (51 males, 57 females) were enrolled in the initial placebo-controlled phase of the study. Half (54/108) of the patients had never been treated with a somatostatin analog or dopamine agonist or had stopped treatment for at least 3 months prior to their participation in the study and were required to have a mean GH level greater than 5 ng/mL at their first visit. The other half of the patients had received prior treatment with a somatostatin analog or a dopamine agonist before study entry and at study entry were required to have a mean GH concentration greater than 3 ng/mL and at least a 100% increase in mean GH concentration after washout of medication. One hundred and seven (107) patients completed the placebo-controlled phase, 105 patients completed the fixed-dose phase, and 99 patients completed the dose-titration phase. Patients not completing withdrew due to adverse events (5) or lack of efficacy (4). In the double-blind phase of Study 1, a total of 52 (63%) of the 83 lanreotide-treated patients had a greater than 50% decrease in mean GH from baseline to Week 4, including 52%, 44%, and 90% of patients in the 60, 90, and 120 mg groups, respectively, compared to placebo (0%, 0/25). In the fixed-dose phase at Week 16, 72% of all 107 lanreotide-treated patients had a decrease from baseline in mean GH of greater than 50%, including 68% (23/34), 64% (23/36), and 84% (31/37) of patients in the 60, 90, and 120 mg lanreotide treatment groups, respectively. Efficacy achieved in the first 16 weeks was maintained for the duration of the study.

Study 2 was a 48-week, open-label, uncontrolled, multicenter study that enrolled patients who had an IGF-1 concentration 1.3 times or greater than the upper limit of the normal age adjusted range. Patients receiving treatment with a somatostatin analog (other than lanreotide) or a dopaminergic agonist had to attain this IGF-1 concentration after a washout period of up to 3 months. Patients were initially enrolled in a 4-month, fixed-dose phase where they received 4 deep subcutaneous injections of lanreotide 90 mg, at 4-week intervals. Patients then entered a dose-titration phase where the dose of lanreotide was adjusted based on GH and IGF-1 levels at the beginning of the dose-titration phase and, if necessary, again after another 4 injections. Patients titrated up to the maximum dose (120 mg) were not allowed to titrate down again. A total of 63 patients (38 males, 25 females) entered the fixed-dose phase of the trial and 57 patients completed 48 weeks of treatment. Six patients withdrew due to adverse reactions (3), other reasons (2), or lack of efficacy (1). After 48 weeks of treatment with lanreotide at 4-week intervals, 43% (27/63) of the acromegalic patients in this study achieved normal age-adjusted IGF-1 concentrations. Mean IGF-1 concentrations after treatment completion were 1.3 ±0.7 times the upper limit of normal compared to 2.5 ±1.1 times the upper limit of normal at baseline. The reduction in IGF-1 concentrations over time correlated with a corresponding marked decrease in mean GH concentrations. The proportion of patients with mean GH concentrations less than 2.5 ng/mL increased significantly from 35% to 77% after the fixed dose phase and 85% at the end of the study. At the end of treatment, 24/63 (38%) of patients had both normal IGF-1

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concentrations and a GH concentration of less than or equal to 2.5 ng/mL (see Table 5) and 17/63 patients (27%) had both normal IGF-1 concentrations and a GH concentration of less than 1 ng/mL.

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. Key recommendations regarding use of medical therapy with somatostatin receptor ligands (SRL) are listed below (strong recommendation = 1, weak recommendation = 2; ⊕○○○ very low quality evidence; ⊕⊕○○, low quality of evidence; ⊕⊕⊕○, moderate quality of evidence; and ⊕⊕⊕⊕, high quality of evidence):

- Medical therapy with SRL in a patient with persistent disease following surgery. (1|⊕⊕⊕⊕)
- SRL or pegvisomant as the initial adjuvant medical therapy in patients with significant disease (i.e., with moderate-to-severe signs and symptoms of growth hormone excess and without local mass effects), (2|⊕⊕○○)
- Trial of a dopamine agonist, usually cabergoline, as the initial adjuvant medical therapy in patients with only modest elevations of serum IGF-1 and mild signs and symptoms of GH excess. (2|⊕⊕○○)
- Addition of pegvisomant or cabergoline in a patient with inadequate response to an SRL. (2|⊕⊕○○)
- SRL 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|⊕⊕⊕○)

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 (VLQ) or low-quality evidence (LQ); SR = Strong recommendation based on moderate quality (MQ) or high quality (HQ)]:

- **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. (MQ, 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. (LQ, DR)
  - 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. (HQ, 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. (HQ, 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. (MQ, 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. (MQ, 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. (HQ, 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. (MQ, SR)
  - Patient selection for combination pasireotide plus pegvisomant should be carefully considered. (LQ, DR)

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).

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Cancer-Related Diarrhea and Malignant Bowel Syndrome

National Comprehensive Cancer Network (NCCN)

The 2026 NCCN Palliative Care guidelines note somatostatin analogs can be considered in patients with grade 3 or 4 (severe) diarrhea and management of malignant bowel obstruction.

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.

Sandostatin is indicated for the following:

- To reduce blood levels of growth hormone and IGF-I (somatomedin C) in acromegaly patients who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation, and bromocriptine mesylate at maximally tolerated doses.
- For the symptomatic treatment of patients with metastatic carcinoid tumors where it suppresses or inhibits the severe diarrhea and flushing episodes associated with the disease.
- For the treatment of the profuse watery diarrhea associated with VIP-secreting tumors.

Limitation of Use*:* Improvement in clinical signs and symptoms, or reduction in tumor size or rate of growth, were not shown in clinical trials performed with Sandostatin Injection; these trials were not optimally designed to detect such effects.

Sandostatin LAR Depot is indicated in patients in whom initial treatment with Sandostatin subcutaneous injection has been shown to be effective and tolerated for:

- Long-term maintenance therapy in acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option. The goal of treatment in acromegaly is to reduce GH and IGF-1 levels to normal.
- Long-term treatment of the severe diarrhea and flushing episodes associated with metastatic carcinoid tumors.
- Long-term treatment of the profuse watery diarrhea associated with VIP-secreting tumors.

Limitation of Use*:* In patients with carcinoid syndrome and VIPomas, the effect of Sandostatin and Sandostatin LAR Depot on tumor size, rate of growth and development of metastases, has not been determined.

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.

Somatuline Depot is indicated for:

- The long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy.
- The treatment of adult patients with unresectable, well-, or moderately differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival.
- The treatment of adults with carcinoid syndrome; when used, it reduces the frequency of short-acting somatostatin analogue rescue therapy.

Lanreotide Injection is indicated for:

- The long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy.
- The treatment of adult patients with unresectable, well, or moderately differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival.
- The treatment of adults with carcinoid syndrome; when used, it reduces the frequency of short-acting somatostatin analogue rescue therapy.

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Policy History/Revision Information

Date	Summary of Changes

04/01/2026	**Template Update**
	• Transferred content to shared policy template that applies to both UnitedHealthcare Commercial and Individual Exchange benefit plans
	• Added *Application* section to indicate this policy applies to:
	  ○ UnitedHealthcare Commercial benefit plans
	  ○ Individual Exchange benefit plans
	Coverage Rationale
	• Added language to indicate this policy refers to the following somatostatin analogs for non-oncology indications:
	  ○ Lanreotide® injection
	  ○ Sandostatin® (octreotide acetate)
	  ○ Sandostatin LAR® (octreotide acetate)
	  ○ Signifor LAR® (pasireotide)
	  ○ Somatostatin Depot® (lanreotide)
	• Removed language indicating:
	  ○ Signifor is proven for the treatment of patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative
	  ○ 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

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Date	Summary of Changes
	▪ Prevention of postoperative complications following pancreatic surgery ▪ Short bowel syndrome ○ Somatostatin analogs are unproven for treating other conditions not listed [in the policy] as proven due to the lack of published clinical evidence of safety and/or efficacy in published peer-reviewed medical literature ○ In patients with carcinoid syndrome and vasoactive intestinal peptide tumors (VIPomas), the effect of Sandostatin and Sandostatin LAR on tumor size, rate of growth, and development of metastases has not been determined ● Revised coverage criteria for: ***Sandostatin (octreotide acetate)*** ○ Removed criterion requiring: ▪ Bleeding gastroesphoageal varices associated with liver disease ▪ Chemotherapy and/or radiation-induced diarrhea ▪ Malignant bowel disease ○ Replaced criterion requiring "acromegaly patients who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation, or *dopamine agonist (e.g., bromocriptine, cabergoline) therapy*" with "acromegaly patients who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation, or *bromocriptine mesylate at maximally tolerated doses*" ***Sandostatin LAR (octreotide acetate LAR)*** ○ Removed criterion requiring bleeding gastroesphoageal varices associated with liver disease ○ Replaced criterion requiring "acromegaly patients who have had inadequate response to or cannot be treated with *surgical resection, pituitary irradiation, or dopamine agonist (e.g., bromocriptine, cabergoline) therapy*" with "acromegaly patients who have had inadequate response to or cannot be treated with *surgery and/or radiotherapy*" **Applicable Codes** ● Added ICD-10 diagnosis codes C7A.023, C25.3, E24.8, and E24.9 ● Removed ICD-10 diagnosis codes I85.01 and I85.11 **Supporting Information** ● Updated *Background*, *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information ● Archived previous policy version 2025D0036V

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicable federal or state mandates. 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.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. 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.

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