Somatostatin Analogs

Policy Number: 2025D0036V
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➲ Instructions for Use

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Coverage Rationale

➲ See Benefit Considerations

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

Sandostatin (octreotide acetate) and Sandostatin LAR (octreotide acetate LAR) are proven for the treatment of:
- 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
- Severe diarrhea and flushing episodes associated with metastatic carcinoid tumors
- Profuse watery diarrhea associated with vasoactive intestinal peptide tumors (VIPomas)-secreting tumors
- Bleeding gastroesphoageal varices associated with liver disease
- Chemotherapy and/or radiation-induced diarrhea
- Malignant bowel disease

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

Signifor and Signifor LAR (pasireotide diaspartate) are proven for the treatment of patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.

Signifor LAR (pasireotide) is proven for the treatment of patients with acromegaly who have had an inadequate response to surgery or for whom surgery is not an option.

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.

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 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.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
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

Diagnosis Code	Description	J1930	J1932	J2502	J2353 J2354
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
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.

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. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. Refer to the Policy and Procedure addressing the treatment of serious rare diseases.

Clinical Evidence

Octreotide

Proven

Bleeding Gastroesophageal Varices

Octreotide alone may not be useful for acute variceal bleeding due to the risk for tachyphylaxis, and results of meta-analyses of trials of octreotide are controversial. A Cochrane review of trials comparing somatostatin or its analogues with placebo in general showed that the drugs did not significantly reduce mortality. Overall, units of blood transfused were reduced, and the number of patients failing initial hemostasis was reduced in the studies.

A randomized, controlled clinical trial (n = 105) compared the efficacy of octreotide (50 g/hr. for 48 hours) combined with sclerotherapy versus sclerotherapy alone in patients with acute bleeding from gastroesophageal varices. Initial control of bleeding was achieved in 46/51 (90.2%) patients who received combined treatment compared to 41/54 (75.9%) patients (p = 0.05) in the sclerotherapy alone group. Rebleeding after the first 48 hours was less in the octreotide treated patients 2/46 vs. 8/41 patients (p = 0.003). The octreotide treated patients had a better short term (5 days) survival without rebleeding 44/51 vs. 33/54 (p = 0.003) and shorter hospital stay, 5.31 ±3.87 days vs. 6.63 ±3.86 (p = 0.008) as compared to sclerotherapy alone group. The blood transfusion requirement was also less in the combined treatment group 3.88 ±2.80 vs. 5.37 ±3.15 units (p = 0.002).

The efficacy of subcutaneous octreotide, administered after emergency sclerotherapy, was investigated to prevent rebleeding of esophageal varices. After a bolus injection of octreotide 50 mcg, the standard therapy (ST) group (n = 34) received octreotide infusion at a rate of 50 mcg/hr. until endoscopic sclerotherapy was performed within 36 hours. The same procedure was applied to another 27 patients in the maintenance therapy (MT) group in which octreotide was given at 100 mcg/8hr via the subcutaneous route after sclerotherapy for five days. In both groups, sclerotherapy was repeated on the 5th-7th day. Patients were followed for three weeks for rebleeding. Nine patients rebled in the ST group but only

one patient bled in the MT group (3.7% vs. 26.5% vs. 3.7%; $p < 0.05$). Transfusion requirement and duration of hospitalization period were similar in both groups.

Another meta-analysis showed that use of agents such as octreotide in combination with endoscopic therapy improved initial control of bleeding and 5-day hemostasis, without differences in mortality or severe adverse events, compared to endoscopic therapy alone.

Corley et al. present a meta-analysis on the safety and efficacy of octreotide for esophageal variceal hemorrhage. Octreotide improved control of esophageal variceal hemorrhage compared with all alternative therapies combined [relative risk (RR), 0.63; 95% confidence interval (CI), 0.51-0.77]; vasopressin/terlipressin (RR, 0.58; 95% CI, 0.42-0.81); or no additional intervention/placebo (among patients that received initial sclerotherapy/banding before randomization) (RR, 0.46; 95% CI, 0.32-0.67). Octreotide had comparable efficacy to immediate sclerotherapy for control of bleeding (RR, 0.94; 95% CI, 0.55-1.62), fewer major complications than vasopressin/terlipessin (RR, 0.31; 95% CI, 0.11-0.87), and a complication profile comparable to no intervention/placebo (RR, 1.06; 95% CI, 0.72-1.55). The results favor octreotide over vasopressin/terlipressin in the control of esophageal variceal bleeding and suggest it is a safe and effective adjunctive therapy after variceal obliteration techniques. Trials are needed to determine the optimal dose, route, and duration of octreotide treatment.

In a randomized trial (n = 124), there was no significant difference in early rebleeding rates with octreotide continuous infusion for 2 days or 5 days (4.8% vs 8.6%) in patients with cirrhosis and acute variceal bleeding who were also undergoing endoscopic therapy. One patient from the 2-day group died 3 weeks following rebleeding. The study concluded that 2 days of octreotide infusion following endoscopic therapy is as effective as 5 days in preventing early rebleed.

Chemotherapy and/or Radiation-Induced Diarrhea

A panel of oncology experts recommends that if mild to moderate chemotherapy-induced diarrhea persists for more than 48 hours despite treatment with loperamide, it should be discontinued and the patient started on a second-line antidiarrheal agent such as octreotide. However, in the majority of mild to moderate cases of radiation-induced diarrhea, octreotide may not be sufficiently effective. Aggressive management of complicated cases of chemotherapy-induced diarrhea should involve intravenous fluids, octreotide, and antibiotics. For patients presenting with a complicated case of radiation-induced diarrhea, hospitalization may be required, and octreotide therapy may or may not be appropriate.

Although the somatostatin analog octreotide is currently used in the treatment of chemotherapy-induced diarrhea and secretory diarrhea associated with various disorders, its role in the management of radiation enteritis is not well defined. Yavuz, et al. performed a randomized study (n = 61) that compared octreotide acetate with diphenoxylate hydrochloride plus atropine sulfate, the drug commonly used as therapy for acute radiation-induced diarrhea (ARID). Within 3 days, ARID completely resolved in 20 patients in the octreotide arm vs. only 4 in the diphenoxylate/atropine arm ($p = 0.002$). On the diphenoxylate/atropine arm, 15/28 patients were required to discontinue pelvic radiotherapy; on the octreotide arm, 6/33 patients were required to discontinue pelvic radiotherapy for an average of 1.89 ±0.5 and 0.45 ±0.2 days, respectively ($p = 0.003$). Octreotide seems to be more effective than conventional therapy with diphenoxylate and atropine in controlling ARID and eliminating the need for radiotherapy interruptions.

Malignant Bowel Obstruction

Octreotide administration is recommended early in the diagnosis of malignant bowel obstruction due to high efficacy and tolerability.

Researchers investigated improvements in symptoms caused by gastrointestinal obstruction following administration of octreotide acetate (Sandostatin®) injection through steroid administration. Patients (n = 37) hospitalized with malignant gastrointestinal obstructions were enrolled in the present study and 27 of them were investigated for gastrointestinal symptoms. Octreotide acetate was administered intravenously (IV) to all 27 patients. Out of them, 17 showed a marked response, 4 a good response, and 6 no response. The overall response rate was 77.8%. Octreotide acetate with a steroid was administered to 19 patients; 13 showed a marked response, 4 a good response, and 2 no response at all. Multiple logistic regression analysis showed that that steroid administration improved the efficacy of octreotide acetate after adjusting for infusion dose ($p = 0.03$). Researchers concluded that IV administration of octreotide acetate with steroid can effectively improve gastrointestinal symptoms due to malignant gastrointestinal obstruction without adverse events.

A systematic review was conducted that included fifteen randomized controlled trials or observational reports with a significant number of patients (total n = 281) treated with octreotide for malignant bowel obstruction. The authors reported a therapeutic success ranging between 60% and 90%. Despite the limited number of controlled studies, the large

experience acquired through 20 years suggests that octreotide is the first-choice antisecretory agent for malignant bowel obstruction.

In a randomized, double-blind, non-comparative pilot study involving 64 adults with inoperable symptomatic bowel obstruction due to peritoneal carcinomatosis, an intention-to-treat analysis showed that IM long-acting repeatable (LAR) octreotide administered with immediate-release (IR) octreotide for the first 6 days of therapy was successful in 38% of patients (12/32) compared to 28% (9/32) in the placebo group. Patients received corticosteroids (methylprednisolone 3 to 4 mg/kg/day IV for 6 days) and best supportive care, and were randomized to either IM octreotide LAR 30 mg every 28 days with octreotide IR 600 mcg/day (subQ in 2 to 3 divided doses or by continuous infusion) for 6 days (n = 32), or placebo (n = 32). The primary endpoint at day 14, a composite of the absence of a nasogastric tube, vomiting less than twice per day, and no need for anticholinergic agents, was not met due to the study's exploratory nature and limited enrollment (64 of 102 planned patients). Baseline data showed a higher proportion of patients with a Karnofsky score below 50 in the octreotide group (46.4%) compared to the placebo group (21.9%). In patients with Karnofsky scores of 50 or greater, the response rate was higher in the octreotide group (60% vs 28%). Octreotide was well tolerated, with only 3 drug-related events (severe hyperglycemia, mild injection erythema, and mild local inflammation). However, 28 patients withdrew after randomization (11 in the octreotide group and 17 in the placebo group), with insufficient clinical response being the most common reason for discontinuation in the placebo group and death in the octreotide group, likely due to the poor condition of these patients.

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 hyperglycaemia, 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.

Somatuline Depot

Salvatori et al. evaluated the 2-year effectiveness and safety of lanreotide depot/autogel (LAN), as well as treatment convenience and acromegaly symptom relief, from the Somatuline® Depot for Acromegaly (SODA) registry, in a post-marketing, open-label, observational, multicenter, registry study. Patients with acromegaly treated with LAN were eligible for enrollment. The following items were collected as part of the registry: demographics, LAN dose, extended dosing interval (EDI), insulin-like growth factor 1 (IGF-1), growth hormone (GH), glycated hemoglobin, adverse events (AEs), injection convenience, as well as symptom data. IGF-1 levels below age- and gender-adjusted upper normal limit (ULN) were achieved in 71.2% at month (M) 12 and 74.4% at M24; GH ≤ 2.5 µg/L in 83.3% at M12 and 80.0% at M24; GH < 1.0 µg/L in 61.7% at M12 and 61.4% at M24. Both IGF-1 < ULN and GH ≤ 2.5 µg/L were achieved in 65.0% at M12 and 54.8% at M24; both IGF-1 < ULN and GH < 1.0 µg/L were achieved in 51.7 and 42.9% at M12 and M24, respectively. EDI regimen was 5.0% at baseline and 12.0% at M24. Acromegaly symptoms appeared stable or improved at 24 months.

Arthralgia was the most common adverse event at 25.7%. At M24, 73.1% of patients rated LAN as convenient. The authors conclude that SODA indicates 2-year biochemical control with majority of patients achieving both IGF-1 < ULN and GH ≤ 2.5 µg/L. In addition, LAN was generally well tolerated during the 24-month observation period with no new or unexpected safety signals reported.

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 most common adverse events were gastrointestinal in nature. The authors concluded that at 48 weeks lanreotide treatment, titrated for optimal hormonal control, controlled IGF-I and GH levels effectively, reduced acromegaly symptoms and was well tolerated.

Lanreotide Injection

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

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. 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.

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 dopamine agonist (e.g., bromocriptine, cabergoline) therapy.
- 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.
- 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 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.

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 gastroenteropancreatc neuroendocrine tumors (GEP-NETs) to improve progression-free survival.

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Policy History/Revision Information

Date	Summary of Changes

04/01/2025	**Coverage Rationale**
	• Added language to indicate Somatostatin analogs are unproven and not medically necessary for treating HIV-AIDS-related diarrhea
	Sandostatin and Sandostatin LAR
	• Added language to indicate:
	  ○ Sandostatin (octreotide acetate) and Sandostatin LAR (octreotide acetate LAR) are proven for the treatment of:
	  ▪ Severe diarrhea and flushing episodes associated with metastatic carcinoid tumors.

Date	Summary of Changes
	▪ Profuse watery diarrhea associated with vasoactive intestinal peptide tumors (VIPomas)-secreting tumors ○ In patients with carcinoid syndrome and VIPomas, the effect of Sandostatin and Sandostatin LAR on tumor size, rate of growth, and development of metastases has not been determined • Removed language indicating Sandostatin and Sandostatin LAR are proven for the treatment of refractory HIV/AIDS-related diarrhea • Replaced language indicating "Sandostatin (octreotide acetate) and Sandostatin LAR (octreotide acetate LAR) are proven for the treatment of acromegaly" with "Sandostatin (octreotide acetate) and Sandostatin LAR (octreotide acetate LAR) are proven for the treatment of acromegaly *patients who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation, ordopamine agonist (e.g., bromocriptine, cabergoline) therapy*" • Removed medical necessity criteria for the treatment of: ○ Acromegaly ○ Bleeding gastroesophageal varices associated with liver disease ○ Refractory HIV/AIDS-related diarrhea ***Signifor and Signifor LAR*** • Replaced language indicating: ○ "Signifor and Signifor LAR (pasireotide diaspartate) are proven for the treatment of Cushing's disease *when [the listed] criteria are met*" with "Signifor and Signifor LAR (pasireotide diaspartate) are proven for the treatment *of patients* with Cushing's disease *for whom pituitary surgery is not an option or has not been curative*" ○ "Signifor LAR (pasireotide) is proven for the treatment of acromegaly" with "Signifor LAR (pasireotide) is proven for the treatment of *patients with* acromegaly *who have had an inadequate response to surgery or for whom surgery is not an option*" • Removed medical necessity criteria for the treatment of: ○ Acromegaly ○ Cushing's disease ***Somatuline Depot and Lanreotide Injection*** • Replaced language indicating "Somatuline Depot (lanreotide) and lanreotide injection are proven for the treatment of acromegaly" with "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*" • Removed medical necessity criteria for the treatment of acromegaly **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*, *FDA*, and *References* sections to reflect the most current information • Archived previous policy version 2024D0036U

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, please 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.