

SANDOSTATIN LAR® DEPOT (OCTREOTIDE ACETATE)

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Related Policies
<ul style="list-style-type: none"> • Acquired Rare Disease Drug Therapy Exception Process • Drug Coverage Guidelines • Injectable Chemotherapy Drugs: Application of NCCN Clinical Practice Guidelines

INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting Oxford benefit plans. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members. Oxford reserves the right, in its sole discretion, to modify its policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Clinical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Clinical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Clinical Policy. Other Policies may apply.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines 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.

CONDITIONS OF COVERAGE

Applicable Lines of Business/Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	General benefits package ³
Referral Required (Does not apply to non-gatekeeper products)	No
Authorization Required (Precertification always required for inpatient admission)	Yes ^{1,2,3,4}
Precertification with Medical Director Review Required	Yes ^{2,3}
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	Office ³ , Outpatient
Special Considerations	<p>¹New Jersey Commercial Members should refer to their certificate of coverage for precertification and quantity limit guidelines.</p> <p>²Precertification with review by a Medical Director or their designee through Oxford's Medical Management is required for Sandostatin LAR® Depot.</p>

Special Considerations
(continued)

³Participating Providers in the Office Setting:

Precertification is required for services performed in the office of a participating provider. **Non-Participating/Out-of-Network Providers in the Office Setting:** Precertification is not required, but is encouraged for out-of-network services performed in the office. If precertification is not obtained, Oxford will review for out-of-network benefits and medical necessity after the service is rendered.

⁴Sandostatin LAR Depot used for oncology indications requires precertification through eviCore. Refer to: [Injectable Chemotherapy Drugs: Application of NCCN Clinical Practice Guidelines](#).

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Sandostatin[®] subcutaneous formulation is covered under the Member's pharmacy benefit. For information regarding coverage, refer to the policy titled [Drug Coverage Guidelines](#).

Sandostatin LAR[®] Depot is covered under the Member's general benefits package (medical benefit).

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The specific benefit 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. Consult regulations for your individual state to determine whether and under what circumstances such coverage is mandated for a particular state. 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 titled [Acquired Rare Disease Drug Therapy Exception Process](#).

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE RATIONALE

Please refer to the policy titled [Injectable Chemotherapy Drugs: Application of NCCN Clinical Practice Guidelines](#) for updated information based on the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium for oncology indications.

Note: For information regarding coverage for **Sandostatin[®] subcutaneous formulation**, refer to the policy titled [Drug Coverage Guidelines](#).

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

- **Bleeding gastroesophageal varices associated with liver disease**
Octreotide acetate is medically necessary for the treatment of bleeding esophageal varices when both of the following criteria are met:
 - Diagnosis of bleeding esophageal varices associated with liver disease; **and**
 - Octreotide acetate will be used as an adjunct to endoscopic therapy
- **Diarrhea, chemotherapy and/or radiation-induced**
- **Diarrhea, refractory HIV/AIDS-related**

Octreotide acetate is medically necessary for the treatment of refractory HIV/AIDS-related diarrhea when both of the following criteria are met:

- Diagnosis of HIV/AIDS-related diarrhea; **and**
- History of failure, contraindication, or intolerance to standard therapy (e.g., loperamide, diphenoxylate/atropine)

- **Malignant bowel disease**

Sandostatin LAR is proven for the treatment of acromegaly.

Sandostatin LAR is medically necessary for the treatment of acromegaly when all of the following criteria are met:

- Diagnosis of acromegaly by **one** of the following:³²
 - Serum GH level > 1 ng/mL after a 2 hour oral glucose tolerance test (OGTT) at time of diagnosis
 - Elevated serum IGF-1 levels (above the age and gender adjusted normal range as provided by the physician's lab) at time of diagnosis

and

- **One** of the following:^{22,26}
 - Inadequate response to one of the following:
 - Surgery
 - Radiotherapy
 - Dopamine agonist (e.g., bromocriptine, cabergoline) therapy
 - Not a candidate for **any** of the following:
 - Surgery
 - Radiotherapy
 - Dopamine agonist (e.g., bromocriptine, cabergoline) therapy

and

- Initial treatment with octreotide immediate release (IR) has been shown to be effective and tolerated³⁷

Sandostatin LAR is unproven and not medically necessary for treating the following conditions:

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

Sandostatin LAR is unproven and not medically necessary for treating other conditions not listed above as proven and medically necessary due to the lack of published clinical evidence of safety and/or efficacy in published peer reviewed medical literature.

Documentation required for Medical Director Review: Letter of medical necessity and/or office notes.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Sandostatin is indicated for the following:³⁶

- 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 symptomatic treatment of patients with metastatic carcinoid tumors where it suppresses or inhibits the severe diarrhea and flushing episodes associated with the disease.
- In the treatment of the profuse watery diarrhea associated with VIP-secreting tumors.

Sandostatin LAR[®] Depot is indicated in patients in whom initial treatment with Sandostatin subcutaneous injection has been shown to be effective and tolerated for:³⁷

- **Acromegaly**
 - 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.
- **Carcinoid Tumors**
 - Long-term treatment of the severe diarrhea and flushing episodes associated with metastatic carcinoid tumors.
- **Vasoactive Intestinal Peptide Tumors (VIPomas)**
 - Long-term treatment of the profuse watery diarrhea associated with VIP-secreting tumors.

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.³⁷ The principal effects of octreotide includes inhibition of growth hormone (GH), glucagon, and insulin. Other effects include diminution of luteinizing hormone response to gonadotropin-releasing hormone, reduction of splanchnic blood flow, and inhibition of release of several gastrointestinal hormones, including serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.³⁶

Sandostatin LAR is a long-acting dosage form that maintains all of the clinical and pharmacological characteristics of the immediate-release dosage form with the added feature of slow release of octreotide from the site of injection, reducing the need for frequent administration. It is indicated in patients in whom initial treatment with Sandostatin® injection has been shown to be effective and tolerated. Sandostatin LAR Depot® is designed to be injected intramuscularly and must be administered under the supervision of a physician.³⁷

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 may apply.

HCPCS Code	Description
J2353	Injection, octreotide, depot form for intramuscular injection, 1 mg [Sandostatin LAR®]

ICD-10 Diagnosis Code	Description
B20	Human immunodeficiency virus [HIV] disease
C25.4	Malignant neoplasm of endocrine pancreas
C7A.010	Malignant carcinoid tumor of the duodenum
C7A.011	Malignant carcinoid tumor of the jejunum
C7A.012	Malignant carcinoid tumor of the ileum
C7A.019	Malignant carcinoid tumor of the small intestine, unspecified portion
C7A.020	Malignant carcinoid tumor of the appendix
C7A.021	Malignant carcinoid tumor of the cecum
C7A.022	Malignant carcinoid tumor of the ascending colon
C7A.024	Malignant carcinoid tumor of the descending colon
C7A.025	Malignant carcinoid tumor of the sigmoid colon
C7A.026	Malignant carcinoid tumor of the rectum
C7A.029	Malignant carcinoid tumor of the large intestine, unspecified portion
C7A.092	Malignant carcinoid tumor of the stomach
C7A.094	Malignant carcinoid tumor of the foregut, unspecified
C7A.095	Malignant carcinoid tumor of the midgut, unspecified
C7A.096	Malignant carcinoid tumor of the hindgut, unspecified
E22.0	Acromegaly and pituitary gigantism
E34.0	Carcinoid syndrome
E34.4	Constitutional tall stature
I85.01	Esophageal varices with bleeding
I85.11	Secondary esophageal varices with bleeding
K52.0	Gastroenteritis and colitis due to radiation
K52.89	Other specified noninfective gastroenteritis and colitis
K52.9	Noninfective gastroenteritis and colitis, unspecified
K56.1	Intussusception

ICD-10 Diagnosis Code	Description
K56.2	Volvulus
K56.50	Intestinal adhesions [bands], unspecified as to partial versus complete obstruction
K56.51	Intestinal adhesions [bands], with partial obstruction
K56.52	Intestinal adhesions [bands] with complete obstruction
K56.600	Partial intestinal obstruction, unspecified as to cause
K56.601	Complete intestinal obstruction, unspecified as to cause
K56.609	Unspecified intestinal obstruction, unspecified as to partial versus complete obstruction
K56.690	Other partial intestinal obstruction
K56.691	Other complete intestinal obstruction
K56.699	Other intestinal obstruction unspecified as to partial versus complete obstruction
K59.9	Functional intestinal disorder, unspecified
R19.7	Diarrhea, unspecified

CLINICAL EVIDENCE

Octreotide: Proven/Medically Necessary

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.¹⁷

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).³⁸

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.⁴²

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.⁴

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/terlipressin (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.⁷

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.⁵

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.⁴¹

Malignant Bowel Obstruction

Octreotide administration is recommended early in the diagnosis of malignant bowel obstruction due to high efficacy and tolerability.²⁹

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.⁴⁴

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.²⁷

Refractory HIV/AIDS-Related Diarrhea

Agents utilized for symptomatic treatment include loperamide, diphenoxylate/atropine, paregoric, deodorized tincture of opium.³¹

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. (Cello, 1991) Limitations of this study include small sample size and lack of randomization.⁶

Although a 3 week study (Simon, 1995) 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 1000-2000 g/day did show improvement with octreotide (p=0.06).³⁹

Several small reports also support octreotide's use in refractory AIDS-related diarrhea.^{13,15,24,28,35}

Unproven/Not Medically Necessary

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.⁹

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.²³

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.³⁴

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.²¹

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.¹⁰

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.²⁵

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.⁴⁰

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=3818) employing a variety of 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.³³

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=2784) 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.⁴³

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).²⁰

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.²

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.³

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.¹⁸

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.¹⁹

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.⁴²

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 ($n=1359$), 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.¹

Short Bowel Syndrome

Nehra et al. assessed the effects of octreotide acetate depot in patients with short bowel syndrome by conducting a 15-wk, 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 wk 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.³⁰

Professional Societies

Acromegaly

Endocrine Society & European Society of Endocrinology (2014)⁴⁶

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

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

American Association of Clinical Endocrinologists

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

Bleeding Gastroesophageal Varices

American College of Gastroenterology

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.)¹⁶

Refractory HIV/AIDS-Related Diarrhea

American College of Gastroenterology

The American College of Gastroenterology's Practice Guidelines on Acute Infectious Diarrhea in Adults consider octreotide an effective alternative for otherwise refractory cases of AIDS-induced diarrhea. Whereas the drug is best used in pathogen-negative diarrhea, it may be useful in some patients with microsporidiosis and possibly other otherwise nontreatable conditions. Because octreotide must be administered by injection and it is quite expensive, it should be considered a last resort to symptomatic management.¹²

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.¹⁴

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
12/01/2018	<ul style="list-style-type: none"> • Updated conditions of coverage/special considerations; modified notation to clarify: <ul style="list-style-type: none"> ○ For participating providers in the office setting: Precertification is required for services performed in the office of a participating provider ○ For non-participating/out-of-network providers in the office setting: Precertification is not required, but is encouraged for out-of-network services performed in the office; if precertification is not obtained, Oxford will review for out-of-network benefits and medical necessity after the service is rendered • Archived previous policy version PHARMACY 176.20 T2