SANDOSTATIN, SANDOSTATIN LAR DEPOT (OCTREOTIDE ACETATE)

Policy Number: PHARMACY 176.8 T2
Effective Date: January 1, 2012

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The services described in Oxford policies are subject to the terms, conditions and limitations of the Member's contract or certificate. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage enrollees. Oxford reserves the right, in its sole discretion, to modify policies as necessary without prior written notice unless otherwise required by Oxford's administrative procedures or applicable state law. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

Certain policies may not be applicable to Self-Funded Members and certain insured products. Refer to the Member's plan of benefits or Certificate of Coverage to determine whether coverage is provided or if there are any exclusions or benefit limitations applicable to any of these policies. If there is a difference between any policy and the Member's plan of benefits or Certificate of Coverage, the plan of benefits or Certificate of Coverage will govern.

**CONDITIONS OF COVERAGE**

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<th>Applicable Lines of Business/Products</th>
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<td>Benefit Type</td>
<td>General benefits package (^{2,3,4}) Pharmacy (^{1,2})</td>
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<td>Referral Required (does not apply to non-gatekeeper products)</td>
<td>No</td>
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<tr>
<td>Authorization Required (Precertification always required for inpatient admission)</td>
<td>Yes (^{1,2,3,4})</td>
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<tr>
<td>Precertification with Medical Director Review Required</td>
<td>No (^3)</td>
</tr>
<tr>
<td>Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)</td>
<td>Home, Office (^{4}), Outpatient, Pharmacy</td>
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<td>Special Considerations</td>
<td>1. Precertification through Pharmacy Benefit Manager (PBM) is required for Sandostatin(^8). 2. New Jersey Commercial Members should refer to their certificate of coverage for precertification and quantity limit</td>
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<td>3Precertification with Medical Director review through Oxford's Medical Management is required for Sandostatin LAR® Depot.</td>
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<td>4Precertification is required for services covered under the Member's general benefits package when performed in the office of a participating provider. For Commercial, precertification is not required, but encouraged for out of network services performed in the office that are covered under the Member's general benefits package. If precertification is not obtained, Oxford may review for medical necessity after the service is rendered.</td>
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**Note:**
- For coverage of outpatient prescription drugs and specific exclusions, exceptions, and dispensing limitations, refer to the Member's pharmacy plan, if applicable.
- Not all Oxford Members have a pharmacy benefit.
- Oxford's Pharmacy Benefit Manager (PBM) provides a nationwide network of participating pharmacies that dispense prescription medications on a retail level. Commercial groups with outpatient prescription drug coverage will have their pharmacy benefit administered by the PBM.
- For information regarding any quantity level limitations, refer to Prescription Drug Quantity Duration (QD) and Quantity Level Limitations (QLL).

**DESCRIPTION OF SERVICE/BACKGROUND INFORMATION**

Octreotide acetate (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 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.

Octreotide acetate is FDA approved 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. It is also approved 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, and for the treatment of profuse watery diarrhea associated with VIP-secreting tumors.\(^{37}\)

The NCCN (National Comprehensive Cancer Network) approves of the use of octreotide acetate for the treatment of functioning (i.e. symptomatic) neuroendocrine tumors of the gastroenteropancreatic system, such as insulinomas, glucagonomas and gastrinomas (Zollinger-Ellison syndrome).\(^{29,32}\) The NCCN also recommends octreotide acetate for perioperative use in patients with neuroendocrine tumors including carcinoid; islet cell; neuroendocrine tumor of unknown primary origin (before biopsy); and insulinomas, glucagonomas, or VIPomas associated with multiple endocrine neoplasia, type 1.\(^{29,32}\) Octreotide acetate is also NCCN recommended for hormone-secreting poorly differentiated (high grade or anaplastic) or small cell neuroendocrine tumors, 29,32 thymomas or thymic carcinomas, 37 and thyroid stimulating hormone (TSH)-producing pituitary adenomas associated with multiple endocrine neoplasia (MEN), type 1.\(^{32}\)

Sandostatin LAR Depot\(^{®}\) (octreotide acetate for injectable suspension) 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.

**CLINICAL EVIDENCE**

**Medically Necessary Uses:**

**Neuroendocrine tumors of the gastroenteropancreatic system**
Patients benefiting from treatment with octreotide include those with functional neuroendocrine tumors of fore- and mid-gut origin. Glucagonomas, VIPomas and to a lesser extent gastrinomas and metastatic insulinomas are examples of functioning pancreatic endocrine tumors amenable to treatment with octreotide. A more controversial area concerns the treatment of patients with non-functioning endocrine tumors of the gastroenteropancreatic system. The accepted indications for the use of a somatostatin analog include: patients with peptide/amine-induced syndromes with clinical symptoms, and patients with progression of metastatic disease even without a syndrome. (Oberg, 2004; NCCN, 2011)

**Perioperative use in patients with neuroendocrine tumors**
Octreotide should be used pre-operatively for and during resection of neuroendocrine tumors (NCCN, 2011). The perioperative use of somatostatin analogs is critical in the prevention of 'carcinoid crisis'. (Oberg, 2004) The product labeling (Sandostatin [package insert], 2010) contains information regarding administration by rapid bolus for emergency situations (e.g., carcinoid crisis).

**Poorly differentiated (high grade or anaplastic) or small cell neuroendocrine tumors**
Octreotide is recommended for primary treatment of hormone-secreting poorly differentiated (high grade or anaplastic) or small cell neuroendocrine tumors whether resectable, locoregional unresectable, or metastatic. (NCCN, 2011)

**Thymomas and thymic carcinomas**
Octreotide is recommended as second-line therapy with or without prednisone following radiation therapy for locally advanced unresectable thymic malignancies. (NCCN, 2011)

**TSH-producing pituitary adenomas associated with MEN, type 1**
Octreotide may be utilized short-term (2 weeks or less) prior to surgery for large (>1 cm) TSH-producing adenomas. It is also indicated when these tumors are associated with visual changes or symptoms, or after incomplete resection. (NCCN, 2011)

Valdes Socin et al. describe the surgical and/or pharmacological treatment with of somatostatin analogs (octreotide) of 43 patients with TSH-secreting pituitary adenomas, including two women with MEN, type 1 (Valdes Socin, 2003).

**Gastroesophageal varices**
Octreotide alone may not be useful for acute variceal bleeding due to 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 a negligible beneficial effect (Gotzsche, 2008). Another meta-analysis (Banares, 2002) 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/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. (Corley, 2001)

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. (Benson, 2004)

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. (Yavuz, 2002)

Refractory acquired immunodeficiency syndrome (AIDS)-related diarrhea
Agents utilized for symptomatic treatment include loperamide, diphenoxylate/atropine, paregoric, deodorized tincture of opium. (New York State Department of Health, 2006)

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.

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).

Several small reports also support octreotide's use in refractory AIDS-related diarrhea (Fanning, 1991; Romeu, 1991; Liberti, 1992; Moroni, 1993; Garcia Compean, 1994).

Not Medically Necessary Uses:

Chylothorax
A recent 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. (Das, 2010)

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. (Landvoigt, 2006)

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. (Roehr, 2006)

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. (Kalomenidis, 2006)

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. (Didden, 2006)
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. (Li-Ling, 2001)

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. (Vecht, 1999)

**Metastatic bowel obstruction**

The use of symptomatic agents has greatly improved the medical treatment of advanced cancer patients with inoperable bowel obstruction. A systematic review of studies of the most popular drugs used in the medical management of inoperable malignant bowel obstruction was performed to assess the effectiveness of these treatments. Randomized trials that involved patients with a clinical diagnosis of intestinal obstruction due to advanced cancer treated with these drugs were reviewed. Three studies compared octreotide (OC) and hyoscine butylbromide (HB), and two studies compared corticosteroids (CS) and placebo. Globally, 52 patients received OC, 51 patients received HB, 37 patients received CS, 15 patients received placebo and 37 patients received both placebo and CS. The superiority of OC over HB in relieving gastrointestinal symptoms was evidenced in a total of 103 patients. Data on CS are less convincing, due to the methodological weakness of existing studies. This review confirms the difficulties in conducting randomized controlled trials in this population. (Mercadante, 2007)

**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 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. (Omata, 2010)

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. (Zhang, 2009)

Heinrich et al. performed an evidence-based analysis to assess the best available treatment for acute pancreatitis (AP), looking at the value of aprotinin, leupafant, 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). (Heinrich, 2006)
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. (Andriulli, 2003)

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. (Graham, 2011)

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. (Gurusamy, 2010)

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. (Zeng, 2008)

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. (Alghamdi, 2007)

**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. (Nehra, 2001)

**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. (Aynsley-Green, 2000)

**Professional Societies**

**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) (Katznelson, 2011)

**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.) (Garcia-Tsao, 2007)

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. (DuPont, 1997)

**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. (Forsmark, 2007)

**U.S. Food and Drug Administration**
Sandostatin (octreotide acetate) is indicated for the following:

- 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.
- 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.

Sandostatin LAR® Depot is indicated for treatment in patients who have responded to and tolerated Sandostatin subcutaneous injection for:

- acromegaly
- severe diarrhea/flushing episodes associated with metastatic carcinoid tumors
- profuse watery diarrhea associated with VIP-secreting tumors

**POLICY AND RATIONALE**

Coverage for Sandostatin® or Sandostatin LAR® Depot will be provided for Members who meet the criteria outlined in the Treatment/Application Guidelines section of this policy.

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

**TREATMENT/APPLICATION GUIDELINES**

Oxford considers Sandostatin medically necessary for the indications listed below. Coverage for Sandostatin® will be provided for Members who meet **ONE** of the following criteria:

1. Member has Acromegaly AND
   - Member had an inadequate response to OR is ineligible for surgery, radiation therapy, or bromocriptine therapy.
2. Member has chemotherapy and/or radiation-induced diarrhea
3. Member has severe flushing and diarrhea associated with metastatic carcinoid tumors
4. Member has diarrhea associated with vasoactive intestinal peptide secreting tumors
5. Member has symptomatic tumors of the gastroenteropancreatic system (i.e., insulinomas, glucagonomas and gastrinomas [Zollinger-Ellison syndrome])
6. Member has hormone-secreting poorly differentiated (high grade or anaplastic) or small cell neuroendocrine tumor.
7. Member has thymoma orthymic carcinoma
8. Member has thyroid stimulating hormone-producing pituitary adenoma associated with multiple endocrine neoplasia (MEN), type 1.
9. Member is HIV-positive status AND
   - has a history of failure, contraindication or intolerance to multiple prescription first line diarrheal therapies (e.g., loperamide, diphenoxylate/atropine, paregoric, deodorized tincture of (opium)).

**Note:** If a member has an antiretroviral drug and first line antidiarrheal therapy, or certain oncology drugs, or a drug for acromegaly in their claims history, the prescription for octreotide acetate will automatically process

**Requirement does not apply to New Jersey plans and products**

Supply limitations may also apply.
Oxford considers Sandostatin LAR Depot medically necessary for the indications listed below. Coverage for Sandostatin LAR Depot® will be provided for Members who meet ONE of the following criteria:

1. Member has acromegaly** and has had an inadequate response to or is ineligible for surgery, pituitary radiation or bromocriptine mesylate
2. Member has severe flushing and diarrhea associated with metastatic carcinoid tumors
3. Member has diarrhea associated with vasoactive intestinal peptide-secreting tumors (VIPomas)
4. Member has functioning (i.e. symptomatic) neuroendocrine tumors of the gastroenteropancreatic system, such as insulinomas, glucagonomas and gastrinomas (Zollinger-Ellison syndrome)
5. For perioperative use in patients with neuroendocrine tumors including carcinoid; islet cell; neuroendocrine tumor of unknown primary origin (before biopsy); and insulinomas, glucagonomas, or VIPomas associated with multiple endocrine neoplasia, type
6. Member has hormone-secreting poorly differentiated (high grade or anaplastic) or small cell neuroendocrine tumors
7. Member has thymomas or thymic carcinomas
8. Member has thyroid stimulating hormone (TSH)-producing pituitary adenomas associated with multiple endocrine neoplasia (MEN), type 1
9. Member has bleeding gastroesophageal varices associated with liver disease when used as an adjunct to endoscopic therapy
10. Member has chemotherapy and/or radiation-induced diarrhea
11. Member has refractory HIV/AIDS-related diarrhea that does not respond to first-line anti-diarrheal therapy

Octreotide acetate (Sandostatin and Sandostatin LAR) are considered not medically necessary for treating the following conditions:
1. chylothorax
2. dumping syndrome
3. metastatic bowel obstruction in patients with advanced abdominal or pelvic cancer
4. pancreatitis
5. prevention of postoperative complications following pancreatic surgery
6. short bowel syndrome
7. persistent hyperinsulinemic hypoglycemia of infancy

Octreotide acetate is 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

**Requirement does not apply to New Jersey plans and products

Supply limitations may also apply

Documentation Required for Medical Director Review:

- Letter of medical necessity and/or office notes.

PAYMENT GUIDELINES

The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the Member’s plan of benefits or Certificate of Coverage. This list of codes may not be all inclusive.

Applicable HCPCS Codes

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<tr>
<th>HCPCS Code</th>
<th>Description</th>
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<td>Injection, octreotide, depot form for intramuscular injection, 1 mg</td>
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<tr>
<td>ICD-9 Code</td>
<td>Description</td>
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<td>------------</td>
<td>-------------</td>
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<td>042</td>
<td>Human immunodeficiency virus [HIV]</td>
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<td>157.4</td>
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<tr>
<td>196.2</td>
<td>Secondary and unspecified malignant neoplasm of intra-abdominal lymph nodes</td>
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<tr>
<td>209.12</td>
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<tr>
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### REFERENCES

The foregoing Oxford policy has been adapted from an existing United Healthcare national policy that was researched, developed and approved by the United Healthcare Medical Technology Assessment Committee. [2012D0036D]


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Sandostatin, Sandostatin Lar Depot (Octreotide Acetate): Clinical Policy (Effective 01/01/2012)


POLICY HISTORY/REVISION INFORMATION

<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
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<tbody>
<tr>
<td>09/14/2012</td>
<td>• Added list of applicable ICD-10 codes (preview draft) in preparation for the transition from ICD-9 to ICD-10 medical coding on 10/01/14</td>
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| 01/01/2012 | • Updated description of services to reflect the most current clinical evidence and references; added applicable FDA information  
• Reformatted list of medically necessary indications for Sandostatin; no change to coverage criteria  
  o Added language to indicate a prescription will automatically process if the member has an antiretroviral drug and first line antidiarrheal therapy, certain oncology drugs, or a drug for acromegaly in his/her claim history  
• Reformatted list of medically necessary indications for Sandostatin LAR Depot; no change to coverage criteria  
  o Added language to indicate Sandostatin and Sandostatin LAR are not medically necessary for treating the following conditions:  
    o Chylothorax  
    o Dumping syndrome  
    o Metastatic bowel obstruction in patients with advanced abdominal or pelvic cancer  
    o Pancreatitis  
    o Prevention of postoperative complications following pancreatic surgery  
    o Short bowel syndrome  
    o Persistent hyperinsulinemic hypoglycemia of infancy  
• Added list of applicable ICD-9 codes  
• Archived previous policy version PHARMACY 176.7 T2 |