

Corporate Medical Policy

Somatostatin Analogs

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Description of Procedure or Service

Somatostatin, a hypothalamic peptide, regulates the functions of several endocrine and exocrine glands. It acts on the anterior pituitary to inhibit the release of growth hormone and thyroid-stimulating hormone. It is also secreted by cells in the pancreas and in the intestine where it inhibits the secretion of a variety of other hormones. Its regulatory actions are mediated by way of 5 different receptors, which are expressed in a tissue-specific manner. Somatostatin receptors are also present in neuroendocrine gastro-entero-pancreatic tumors. Gastrointestinal endocrine tumors include carcinoid tumors as well as vasoactive intestinal polypeptide-secreting tumors.

Somatostatin analogs are synthetic compounds that mimic the action of natural somatostatin. Somatostatin binds to its receptor located on the surfaces of neuroendocrine cells. This initiates a cascade of events in the cells that change cellular processes such as:

- slowing down hormone production, including many of the gut hormones
- slowing down the emptying of the stomach and bowel
- controlling release of hormones made by the pancreas, including insulin
- slowing down or stopping release of growth hormones

This policy addresses pasireotide (Signifor® LAR), octreotide acetate (Sandostatin® LAR Depot), and lanreotide (Somatuline® Depot).

Pasireotide (Signifor), self-injected subcutaneously, is used to lower cortisol levels in the treatment of Cushing's disease. It has not been proven to improve long-term consequences of Cushing's disease such as cardiovascular morbidity and mortality or bone loss. Signifor LAR is a different formulation given intramuscularly for the treatment of acromegaly, as well as for the treatment of Cushing's disease.

Octreotide acetate, a cyclic octapeptide agent, inhibits growth hormone, glucagon, and insulin more effectively than natural somatostatin hormone. Its suppression of luteinizing hormone's (LH) response to gonadotropin releasing hormone (GnRH) and inhibition of the release of serotonin, gastrin, vasoactive intestinal peptide (VIP), secretin, motilin, and pancreatic polypeptide are similar to somatostatin's actions. The drug also reduces growth hormone and/or IGF-I (somatomedin C) levels in acromegaly patients, inhibits gallbladder contractions, reduces bile secretion and suppresses the secretion of thyroid stimulating hormone (TSH). Octreotide is available in a short acting form (Sandostatin®) that is administered subcutaneously or intravenously and a long-acting form (Sandostatin LAR® Depot) administered as a deep intramuscular injection.

Lanreotide acetate, an octapeptide analog of natural somatostatin, inhibits secretion of various endocrine, neuroendocrine, exocrine and paracrine functions which normalizes growth hormones and/or insulin-like growth factor-1 (IGF-1) levels in patients with acromegaly. It is administered by deep subcutaneous injection.

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*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for somatostatin analogs when they are determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When somatostatin analogs are covered

Pasireotide (Signifor® LAR) may be medically necessary when the following criteria are met:

1. The patient has acromegaly, and
 - a. The patient has had an inadequate response to surgery and/or surgery is not an option, and
 - b. The patient has had previous failed trial or contraindication to a somatostatin analog (octreotide or lanreotide) and a dopamine agonist (cabergoline), OR
2. The patient has a confirmed diagnosis of Cushing's disease, and
 - a. Pituitary surgery is not an option or has not been curative, and
 - b. The patient has experienced a therapeutic failure or inadequate response to any one of the following oral agents: mitotane, metyrapone, or ketoconazole, or
 - c. The patient had a documented intolerance, hypersensitivity, or FDA labeled contraindication to any one of the following agents: mitotane, metyrapone, or ketoconazole, and
3. The patient does not have severe decompensated liver disease (Child-Pugh C), and
4. Signifor® LAR has been prescribed or recommended in consultation with an endocrinologist, and
5. Initial approval is 90 days, and
 - a. For acromegaly:
 - i. * Continued approval upon documentation of improved GH and/or IGF-1 levels
 - ii. * Renewal occurs every 6 months upon satisfaction of 6a.
 - b. For Cushing's disease:
 - i. * Continued approval upon documentation of pre-treatment 24-hour urinary free cortisol levels (UFC) and post- 24-hour UFC, and/or
 - ii. * Symptomatic improvement of Cushing's disease
 - iii. * Renewal occurs every 12 months upon satisfaction of 7a.

** Medical record documentation is required.*

Octreotide acetate (Sandostatin® LAR Depot) may be medically necessary when the following criteria are met:

1. The patient has a diagnosis of acromegaly, and
 - a. The use of requested agent is for adjunctive therapy with irradiation to alleviate acromegaly symptoms, or
 - b. The patient has had an inadequate response to surgery or pituitary irradiation defined by ONE of the following documented parameters:
 - i. Growth hormone level > 5 ng/mL, or
 - ii. IGF-1 level > 1.9 U/mL for males or > 2.2. U/mL for females, or
 - c. Patient is not a candidate for surgical resection or pituitary irradiation.

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2. The patient has a diagnosis of carcinoid tumor, locally advanced/metastatic gastroenteropancreatic neuroendocrine tumor or poorly differentiated (high-grade)/large or small cell neuroendocrine tumor, pancreas islet cell neuroendocrine tumor, or vasoactive intestinal polypeptidoma and one of the following:
 - a. The patient will be using the medication for symptom control for carcinoid syndrome or hormone hypersecretion, or
 - b. The patient has had an inadequate response to or is not a candidate for surgical resection or radiation therapy.
3. Approval duration: 24 weeks.
4. Continued coverage:
 - a. The patient was approved through the initial coverage criteria and is continuing therapy for one of the indications in the initial coverage criteria, and
 - b. The patient has objective markers for improvement exemplified by:
 - i. Growth hormone (GH) level < 5 ng/mL; or
 - ii. IGF-1 level < 1.9 U/mL for a male or 2.2 U/mL for a female; or
 - iii. Clinical improvement in conditions related to the approved diagnosis:
 - Reduction in tumor size
 - Decreased headaches
 - Improved cardiovascular symptoms
 - Improved respiratory symptoms

Lanreotide (Somatuline® Depot) may be medically necessary when the following criteria are met:

1. The patient has a diagnosis of acromegaly, and one of the following:
 - a. The use of requested agent is for adjunctive therapy with irradiation to alleviate acromegaly symptoms, or
 - b. The patient had an inadequate response to surgery or pituitary irradiation defined by ONE of the following documented parameters:
 - i. Growth hormone level > 5 ng/mL, or
 - ii. IGF-1 level > 1.9 U/mL for males or > 2.2 U/mL for females, or
 - c. Patient is not a candidate for surgical resection or pituitary irradiation, or
2. The patient has a diagnosis of carcinoid tumor, locally advanced/metastatic gastroenteropancreatic neuroendocrine tumor or poorly differentiated (high-grade)/large or small cell neuroendocrine tumor, pancreas islet cell neuroendocrine tumor, or vasoactive intestinal polypeptidoma and one of the following:
 - a. The patient will be using the medication for symptom control for carcinoid syndrome or hormone hypersecretion, or
 - b. The patient has had an inadequate response to or is not a candidate for surgical resection or radiation therapy.
3. Approval duration: 24 weeks.
4. Continued coverage:
 - a. The patient was approved through the initial coverage criteria and is continuing therapy for one of the indications in the initial coverage criteria, and
 - b. The patient has objective markers for improvement exemplified by:
 - iv. Growth hormone (GH) level < 5 ng/mL; or
 - v. IGF-1 level < 1.9 U/mL for a male or 2.2 U/mL for a female; or
 - vi. Clinical improvement in conditions related to the approved diagnosis:
 - Reduction in tumor size
 - Decreased headaches
 - Improved cardiovascular symptoms
 - Improved respiratory symptoms

When somatostatin analogs are not covered

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Somatostatin analogs pasireotide (Signifor® LAR), octreotide acetate (Sandostatin® LAR Depot), and lanreotide (Somatuline® Depot) are considered not medically necessary when criteria listed above are not met.

Policy Guidelines

Pasireotide (Signifor® LAR) is administered by intramuscular injection immediately after reconstitution. It should never be given intravenously. For the treatment of acromegaly, the recommended initial dose is 40 mg once every 4 weeks (every 28 days). For the treatment of Cushing's disease, the recommended initial dose is 10 mg once every 4 weeks (every 28 days). Dosage should be adjusted based on biochemical response and tolerability. Use in patients with severe hepatic impairment (Child-Pugh C) should be avoided.

Sandostatin LAR Depot is indicated in patients in whom initial treatment with Sandostatin Injection has been shown to be effective and tolerated. Patients not currently receiving octreotide acetate should begin therapy with Sandostatin Injection given subcutaneously in an initial dose of 50 mcg three times daily which may be titrated. Most patients require doses of 100 mcg to 200 mcg three times daily for maximum effect but some patients require up to 500 mcg three times daily. Patients should be maintained on Sandostatin Injection subcutaneous for at least 2 weeks to determine tolerance to octreotide. Patients who are considered to be "responders" to the drug, based on GH and IGF-1 levels and who tolerate the drug can then be switched to Sandostatin LAR Depot.

Patients currently receiving Sandostatin Injection can be switched directly to Sandostatin LAR Depot in a dose of 20 mg given IM intragluteally at 4-week intervals for 3 months. After 3 months, dosage may be adjusted as follows:

- GH \leq 2.5 ng/mL, IGF-1 normal, and clinical symptoms controlled: maintain Sandostatin LAR Depot dosage at 20 mg every 4 weeks.
- GH $>$ 2.5 ng/mL, IGF-1 elevated, and/or clinical symptoms uncontrolled, increase Sandostatin LAR Depot dosage to 30 mg every 4 weeks.
- GH \leq 1 ng/mL, IGF-1 normal, and clinical symptoms controlled, reduce Sandostatin LAR Depot dosage to 10 mg every 4 weeks.
- If GH, IGF-1, or symptoms are not adequately controlled at a dose of 30 mg, the dose may be increased to 40 mg every 4 weeks. Doses higher than 40 mg are not recommended.

In patients who have received pituitary irradiation, Sandostatin LAR Depot should be withdrawn yearly for approximately 8 weeks to assess disease activity. If GH or IGF-1 levels increase and signs and symptoms recur, Sandostatin LAR Depot therapy may be resumed.

Lanreotide (Somatuline® Depot) is given via deep subcutaneous route at 4-week intervals for an initial 3 months. After 3 months, dosage may be adjusted according to response of the patient as judged by a reduction in serum GH and/or IGF-1 levels; and/or changes in symptoms of acromegaly.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: J1930, J2353, J2354, J2502

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

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Scientific Background and Reference Sources

SIGNIFOR® LAR (pasireotide) for injectable suspension. Prescribing information December 2014. Available at: http://www.pharma.us.novartis.com/product/pi/pdf/signifor_lar.pdf . Last accessed June 2015.

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Novartis Pharmaceuticals Corporation. Sandostatin LAR Depot (octreotide acetate for injectable suspension). Prescribing Information. East Hanover, NJ:Novartis; Revised 7/2016. Available at: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/sandostatin_lar.pdf. Accessed June 2018.

Ipsen Biopharmaceuticals, Inc. Somatuline Depot (lanreotide) injection for subcutaneous use. Prescribing Information. Basking Ridge, NJ:Ipsen; Revised 2/2018. Available at: https://www.ipseus.com/pdfs/Somatuline_Depot_Full_Prescribing_Information.pdf. Accessed June 2018.

Specialty Matched Consultant Advisory Panel – 6/2018

Novartis Pharmaceuticals Corporation. Signifor LAR (pasireotide) injectable suspension for intramuscular use. Highlights of Prescribing Information. Revised 4/2019. Available at: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/signifor_lar.pdf. Accessed June 2019.

Specialty Matched Consultant Advisory Panel – 6/2019

Medical Director review 6/2019

Medical Director review 8/2019

Policy Implementation/Update Information

For policy titled: Pasireotide (Signifor® LAR)

7/28/15 New medical policy issued. Pasireotide (Signifor® LAR) may be medically necessary when criteria are met. Medical director review 7/2015. Notification given 7/28/2015 for policy effective date 10/1/2015. (sk)

12/30/15 Code J2502 added and codes C9454, J3490, and J3590 removed from Billing/Coding section. (sk)

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For policy titled: Somatostatin Analogs

- 7/26/16 Policy titled “Pasireotide” combined with new medical policy titled “Somatostatin Analogs.” This new policy addresses pasireotide (Signifor® LAR), octeotide acetate (Sandostatin® LAR Depot), and lanreotide (Somatuline® Depot). BCBSNC will provide coverage for somatostatin analogs when they are determined to be medically necessary because the medical criteria and guidelines outlined in the policy are met. **Notification given 7/26/2016 for effective date 9/30/2016.** (an)
- 8/11/17 Description Section updated. Specialty Matched Consultant Advisory Panel review 7/26/2017. No change to policy statement. (an)
- 7/13/18 Corrected minor typographical errors. References added. Specialty Matched Consultant Advisory Panel review 6/27/2018. No change to policy statement. (krc)
- 7/16/19 Added the following indication as medically necessary for Signifor LAR: The treatment of patients with Cushing’s disease for whom pituitary surgery is not an option or has not been curative. Updated Description and Policy Guideline sections to reflect addition of new indication. References added. Specialty Matched Consultant Advisory Panel review 6/19/2019. Medical Director review 6/2019. (krc)
- 8/27/19 Updated “When Covered” section to change “AND” to “OR” within the following statements: “patient is not a candidate for surgical resection or pituitary irradiation” and “patient has had an inadequate response to or is not a candidate for surgical resection or radiation therapy”. Medical Director review 8/2019. (krc)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.