



PRIOR AUTHORIZATION POLICY

POLICY: Somatostatin Analogs – Signifor® LAR (pasireotide for injectable suspension – Novartis)

TAC APPROVAL DATE: 07/31/2019

OVERVIEW

Signifor LAR, a somatostatin analog, is indicated for the treatment of patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option and for patients with Cushing’s disease for whom pituitary surgery is not an option or has not been curative.¹ Signifor LAR is a long-acting release form of pasireotide, which binds to somatostatin receptors (SSTRs) and has pharmacologic properties mimicking those of the natural hormone somatostatin.

Disease Overview

Acromegaly

Acromegaly is a rare disorder (prevalence of 40 to 125 cases per million persons) characterized by growth hormone (GH) hypersecretion most often due to a benign tumor on the pituitary gland, a somatotrophic adenoma ($\geq 95\%$ of cases).²⁻⁶ An increase in insulin-like growth factor-1 (IGF-1) production by the liver accompanies the increase in GH. Clinical manifestations of acromegaly range from subtle signs of enlargement of the extremities, soft tissue swelling, arthralgias, jaw prognathism, fasting hyperglycemia, and hyperhidrosis to “florid” osteoarthritis, frontal bone bossing, diabetes mellitus, hypertension, and respiratory and cardiac failure.⁴ Hypersecretion of GH and IGF-1 over time can have multiple deleterious effects, including cardiovascular complications, impaired glucose tolerance/diabetes, hypertension, respiratory conditions, and colorectal tumors, all of which lead to increased mortality in these patients.⁶ Surgical resection of the tumor is generally the first-line therapy for acromegaly and results in disease control in approximately 60% of patients.⁷ However, radiotherapy and medications, including somatostatin analogs, such as Signifor LAR, are also used to manage this condition. Signifor LAR binds with high affinity to four of the five known human SSTR subtypes, particularly SSTR2 and SSTR5, which may play a role in its inhibition of GH secretion. Through this mechanism, Signifor LAR lowers GH and IGF-1 levels in patients with acromegaly.

Cushing’s Disease

Causes of endogenous Cushing’s syndrome can be divided into ACTH-dependent and ACTH-independent.¹² The majority of cases of endogenous Cushing’s syndrome are ACTH-dependent (80%); most of these cases are caused by pituitary adenoma (also referred to as Cushing’s *disease* [70%]). Other ACTH-dependent causes include ectopic ACTH secretion by a benign or malignant tumor (10%) or rarely ectopic corticotropin-releasing hormone (CRH) secretion by a tumor. ACTH-independent causes of Cushing’s syndrome include adrenal adenoma (10%), adrenal carcinoma (5%), adrenal hyperplasia (1% to 2%), McCune Albright syndrome (1% to 2%) and primary pigmented medullar adrenal disease, including Carney complex (1% to 2%).

The treatment of Cushing’s syndrome requires a multi-modal approach. The goals of treatment are normalization of cortisol excess, long-term disease control, avoidance of recurrence, and reversal of clinical

features.¹³ In general, the initial treatment of choice for Cushing’s *disease* (that is Cushing’s syndrome caused by a pituitary adenoma) is selective pituitary adenectomy by a surgeon with extensive demonstrated experience in pituitary surgery. However, the rate of cure at long-term follow-up is suboptimal and recurrences are high.¹⁴ Immediate remission rates range from 65% to 90%, with recurrence rates reaching about 25% after 10 years. In patients cured by tumor removal, survival rates do not differ from those in the general population.¹³

The role of drug therapy in patients with Cushing’s syndrome is generally adjunctive and may help to improve the medical status of patients in preparation for surgery, and to control severe hypercortisolism in patients who are acutely ill, or in patients awaiting the effects of radiotherapy.^{12,15-16}

Guidelines

The Endocrine Society Clinical Practice Guidelines for Acromegaly (2014) recommend transsphenoidal surgery as the primary therapy in most patients; repeat surgery may be considered in patients with residual intrasellar disease after initial surgery.³ Although routine preoperative medical therapy is not recommended, patients with severe pharyngeal thickness and sleep apnea or high-output heart failure may receive therapy with a somatostatin analog preoperatively to reduce surgical risk from severe comorbidities. A somatostatin analog may be used as primary therapy in patients who cannot be cured by surgery; have extensive cavernous sinus invasion; do not have chiasmal compression; or are poor surgical candidates. The guidelines have not been updated since the FDA-approval of Signifor LAR, but do note the enhanced binding of this agent to somatostatin receptors and the data supporting its ability to normalize IGF-1 levels.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Signifor LAR. Because of the specialized skills required for evaluation and diagnosis of patients treated with Signifor LAR as well as the monitoring required for adverse events (AEs) and long-term efficacy, approval requires Signifor LAR to be prescribed by or in consultation with a physician who specializes in the condition being treated. Refer to criteria below for approval durations. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Signifor LAR is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Acromegaly.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
 - A) The medication is prescribed by or in consultation with an endocrinologist; **AND**
 - B) The patient meets **ONE** of the following (i, ii, or iii):
 - i. The patient has had an inadequate response to surgery and/or radiotherapy; **OR**
 - ii. The patient is **NOT** an appropriate candidate for surgery and/or radiotherapy; **OR**
 - iii. The patient is experiencing negative effects due to tumor size (e.g., optic nerve compression); **AND**
 - C) The patient has (or had) a pre-treatment (baseline) insulin-like growth factor-1 (IGF-1) level above the upper limit of normal (ULN) based on age and gender for the reporting laboratory.

NOTE: Pre-treatment (baseline) refers to the IGF-1 level prior to the initiation of any somatostatin analog (e.g., octreotide acetate injection, Signifor LAR, Sandostatin® LAR Depot [octreotide acetate for injectable suspension], Somatuline® Depot [lanreotide subcutaneous injection]), dopamine agonist (e.g., cabergoline, bromocriptine), or Somavert® (pegvisomant for injection). Reference ranges for IGF-1 vary among laboratories.

2. **Cushing’s Disease.** Approve for the duration noted if the patient meets the following criteria (A or B):
 - A) **Initial Therapy.** Approve for 4 months of initial therapy if the patient meets the following criteria (i and ii):
 - i. Signifor LAR is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing’s disease; **AND**
 - ii. According to the prescribing physician, the patient is not a candidate for surgery, or surgery has not been curative. **Note:** For patients with Cushing’s disease/syndrome awaiting surgery, see *Other Uses with Supportive Evidence*.
 - B) **Patient is Currently Receiving Signifor LAR/Signifor.** Approve for 1 year of continuation therapy if the patient has responded to Signifor/Signifor LAR, as determined by the prescriber.
Note: An example of patient response is decrease in the mean urinary free cortisol level.

Other Uses with Supportive Evidence

3. **Cushing’s Disease/Syndrome – Patients Awaiting Surgery.** Approve for 4 months if Signifor LAR is prescribed by or in consultation with an endocrinologist or a physician who specialized in the treatment of Cushing’s disease/syndrome.
4. **Cushing’s Disease/Syndrome – Patients Awaiting Therapeutic Response After Radiotherapy.** Approve for 4 months if Signifor LAR is prescribed by or in consultation with an endocrinologist or a physician who specialized in the treatment of Cushing’s disease/syndrome.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Signifor LAR has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Signifor® LAR injectable suspension [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; June 2018.
2. Giustina A, Chanson P, Kleinberg D, et al. A consensus on the medical treatment of acromegaly. *Nat Rev Endocrinol.* 2014;10(4):243-248.
3. Katznelson L, Laws ER Jr, Melmed S, et al; Endocrine Society. Acromegaly: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2014;99:3933-3951.
4. Melmed S. Acromegaly. *N Engl J Med.* 2006;355:2558-2573.
5. Christofides EA. Clinical importance of achieving biochemical control with medical therapy in adult patients with acromegaly. *Patient Pref Adherence.* 2016;10:1217-1225.

6. Oberg K, Lamberts SW. Somatostatin analogues in acromegaly and gastroenteropancreatic neuroendocrine tumours: past, present and future. *Endocr Relat Cancer*. 2016;23(12):R551-566.
7. Manjila S, Wu OC, Khan FR, et al. Pharmacological management of acromegaly: a current perspective. *Neurosurg Focus*. 2010;29(4):E14.
8. Colao A, Bronstein MD, Freda P, et al. Pasireotide versus octreotide in acromegaly: a head-to-head superiority study. *J Clin Endocrinol Metab*. 2014;99(3):791-799.
9. Gadelha MR, Bronstein MD, Brue T, et al. Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA): a randomized, phase 3 trial. *Lancet Diabetes Endocrinol*. 2014;2(11):875-884.
10. Sheppard M, Bronstein MD, Freda P, et al. Pasireotide LAR maintains inhibition of GH and IGF-1 in patients with acromegaly for up to 25 months: results from the blinded extension phase of a randomized, double-blind, multicenter, Phase III study. *Pituitary*. 2015;18(3):385-394.
11. Novartis. Efficacy and safety of pasireotide administered monthly in patients with Cushing’s Disease. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2015 Jan 26]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01374906?term=pasireotide+and+cushing%27s&rank=1> NLM Identifier: NCT01374906.
12. Tritos NA, Biller BM. Advances in medical therapies for Cushing’s syndrome. *Discov Med*. 2012;13(69):171-179.
13. Biller BMK, Grossman AB, Stewart PM, et al. Treatment of adrenocorticotropin-dependent Cushing’s syndrome: A consensus statement. *J Clin Endocrinol Metab*. 2008;93:2454-2462.
14. Arnaldi G and Boscaro M. New treatment guidelines on Cushing’s disease. *F1000 Med Rep*. 2009;1.
15. Mazziotti G, Gazzaruso C and Giustina A. Diabetes in Cushing syndrome: basic and clinical aspects. *Trends Endocrinol Metab*. 2011;22(12):499-506.
16. Rizk A, Honegger J, Milian M and Psaras T. Treatment options in Cushing’s disease. *Clin Med Insights Oncol*. 2012(6):75-84.

OTHER REFERENCES UTILIZED

- Katznelson L, Atkinson JL, Cook DM, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly – 2011 update. *Endocr Pract*. 2011;17(4):636-646.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
New Policy	--	08/23/2017
Selected Revision	Criteria created for the following FDA-approved diagnosis: Patients with Cushing’s disease for whom pituitary surgery is not an option or has not been curative. Criteria created for Other Uses with Supportive Evidence: Cushing’s disease, awaiting surgery.	08/01/2018
Annual revision	Specified Cushing’s Disease/”Syndrome” to approval condition and added “Patients” awaiting surgery. Approval duration increased from 2 months to 4 months to align. Created separate approval condition for Cushing’s Disease/Syndrome – Patients Awaiting Therapeutic Response from Radiotherapy with 4 month approval duration. Initial therapy approval criteria for Cushing’s Disease changed to 4 months.	08/22/2018
Annual revision	No criteria changes.	07/31/2019

* For a further summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>; TAC – Therapeutic Assessment Committee.