



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

**DATE REVIEWED:** 07/31/2019

### OVERVIEW

Signifor LAR is indicated for the treatment of patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option.<sup>1</sup> It is also indicated for the treatment of patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.

The recommended initial dose of Signifor LAR for the treatment of acromegaly is 40 mg administered intramuscularly (IM) once every 4 weeks (every 28 days). The dose may be increased to a maximum of 60 mg for patients who have not normalized growth hormone (GH) and/or age and sex adjusted insulin-like growth factor-1 (IGF-1) levels after 3 months of treatment with Signifor LAR at 40 mg and who tolerate this dose. Dose reduction by 20 mg decrements may be required for the management of adverse events or over response to treatment (age and sex adjusted IGF-1 less than the lower limit of normal). For patients with moderately impaired hepatic function, the recommended initial dose for acromegaly is 20 mg once every 4 weeks to a maximum dose of 40 mg once every 4 weeks.

The recommended initial dose for the treatment of Cushing's disease is 10 mg administered by IM once every 4 weeks (every 28 days). After 4 months of treatment with the initial dose of 10 mg once every 28 days, the dose may be increased for patients who have not normalized 24-hour urinary free cortisol levels, for up to a maximum dose of 40 mg once every 28 days. For management of adverse events, the dose may be lowered to the previous tolerated dose or the therapy can be interrupted or discontinued. For patients with moderately impaired hepatic function, the recommended initial dose for Cushing's disease is 10 mg once every 4 weeks to a maximum of 20 mg once every 4 weeks.

Baseline fasting plasma glucose and hemoglobin A1c levels, liver tests, electrocardiogram, serum potassium, and serum magnesium levels need to be evaluated prior to initiating Signifor LAR. Signifor LAR must be reconstituted by a trained health care professional immediately before use. It must be administered by a trained healthcare professional only by IM injection in the right or left gluteus immediately after reconstitution. Signifor LAR must never be administered intravenously.

Signifor LAR is available as a 10 mg, 20 mg, 30 mg, 40 mg, or 60 mg powder that needs to be reconstituted immediately before use with a 2 mL diluent.

### 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.<sup>2</sup> 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.

The Endocrine Society Clinical Practice Guidelines for the treatment of Cushing’s Syndrome (2015) recommends surgery as the first-line treatment option, unless surgery is not possible or is unlikely to reduce glucocorticoid excess.<sup>3</sup> Medical therapy maybe an initial therapy for patients with adrenocorticotrophic hormone (ACTH)- dependent disease who have failed surgery, has persistent metastatic disease, or who has occult tumor. Signifor/Signifor LAR is listed as one of several medical therapy options available for Cushing’s Syndrome. Some of the other medical therapy options include ketoconazole, metyrapone, mitotane, Korlym® (mifepristone tablets), etomidate, and cabergoline. 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.<sup>4-6</sup>

### **POLICY STATEMENT**

Prior authorization is recommended for medical 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 and long-term efficacy, initial 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.

### **RECOMMENDED AUTHORIZATION 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.

**Dosing.** Approve if the dose meets the following (A and B):

- A) Each dose is ≤ 60 mg; **AND**
- B) Each dose is given no more frequently than every 4 weeks.

- 
- 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 prescriber, 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.

**Dosing.** Approve if the dose meets the following (A and B):

- A) Each dose is  $\leq 40$  mg; AND
- B) Each dose is given no more frequently than once every 28 days.

---

### Other Uses with Supportive Evidence

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

**Dosing.** Approve if the dose meets the following (A and B):

- A) Each dose is  $\leq 40$  mg; AND
- B) Each dose is given no more frequently than once every 28 days.

---

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

**Dosing.** Approve if the dose meets the following (A and B):

- A) Each dose is  $\leq 40$  mg; AND
- B) Each dose is given no more frequently than once every 28 days.

---

### 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.

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. 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.
  3. Nieman LK, Biller BM, Findling JW, et al. Treatment of Cushing’s Syndrome: An Endocrine Society Clinical Practice Guidelines. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4525003/?report=reader>. Accessed on August 7, 2018.
-

4. Tritos NA, Biller BM. Advances in medical therapies for Cushing's syndrome. *Discov Med.* 2012;13(69):171-179.
5. Mazziotti G, Gazzaruso C and Giustina A. Diabetes in Cushing syndrome: basic and clinical aspects. *Trends Endocrinol Metab.* 2011;22(12):499-506.
6. Rizk A, Honegger J, Milian M and Psaras T. Treatment options in Cushing's disease. *Clin Med Insights Oncol.* 2012(6):75-84.

**HISTORY**

Type of Revision	Summary of Changes	Approval Date
New Policy	--	08/22/2018
Annual revision	<p>The following sections were removed throughout the policy; Initial Approval/Extended Approval, Duration of Therapy, Labs/Diagnostics, and Waste Management. In addition, the following was changed:</p> <ol style="list-style-type: none"> <li>1. <b>Acromegaly.</b> In criteria A., "Initial therapy" was removed and all of criteria B. was removed to match PA policy. Dosing was changed from specific regimens to a range utilizing criteria verbage of "each dose is ≤" and "each dose is given no more frequently than". The route of administration was removed.</li> <li>2. <b>Cushing's Disease.</b> Dosing was changed from specific regimens to a range utilizing criteria verbage of "each dose is ≤" and "each dose is given no more frequently than". The route of administration was removed.</li> <li>3. <b>Cushing's Disease/Syndrome – Patients Awaiting Surgery.</b> Dosing was changed from specific regimens to a range utilizing criteria verbage of "each dose is ≤" and "each dose is given no more frequently than". The route of administration was removed.</li> <li>4. <b>Cushing's Disease/Syndrome – Patients Awaiting Therapeutic Response After Radiotherapy.</b> Dosing was changed from specific regimens to a range utilizing criteria verbage of "each dose is ≤" and "each dose is given no more frequently than". The route of administration was removed.</li> </ol>	07/31/2019