



PRIOR AUTHORIZATION POLICY

POLICY: Cushing's – Signifor™ (pasireotide injection – Novartis)

TAC APPROVAL DATE: 05/08/2019

OVERVIEW

Signifor is an injectable cyclohexapeptide somatostatin analogue indicated for the treatment of adults with Cushing's disease for whom pituitary surgery is not an option or has not been curative.¹ Signifor exerts its pharmacological activity via binding to somatostatin receptors (sst). Five human somatostatin receptor (hsst) subtypes are known: hsst 1, 2, 3, 4, and 5; these receptor subtypes are expressed in different tissues under normal physiological conditions. Corticotroph tumor cells from patients with Cushing's disease frequently over-express hsst 5 whereas the other receptor subtypes are often not expressed or are expressed at lower levels. Signifor binds and activates the hsst receptors resulting in inhibition of adrenocorticotropic hormone (ACTH) secretion, which leads to decreased cortisol secretion.

Signifor is administered by subcutaneous (SC) injection twice a day (BID) and the dose is titrated based on response and tolerability.¹ Patients should be evaluated for a treatment response (clinically meaningful reduction in 24-hour urinary free cortisol [UFC] levels and/or improvement in signs or symptoms of the disease) and should continue receiving therapy with Signifor as long as benefit is derived. Maximum UFC reduction is typically seen by 2 months of treatment. Management of suspected adverse events (AEs) may require temporary dose reduction of Signifor.

Prior to the start of Signifor, patients should have baseline levels of the following: fasting plasma glucose (FPG), glycosylated hemoglobin (HbA_{1c}), liver tests and serum potassium and magnesium levels.¹ Patients should also have a baseline electrocardiogram (ECG) and gallbladder ultrasound. Treatment of patients with poorly controlled diabetes mellitus should be intensively optimized with anti-diabetic therapy prior to starting Signifor.

Cushing's Disease

Causes of endogenous Cushing's syndrome can be divided into ACTH-dependent and ACTH-independent.² 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.³ 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.⁴ Immediate remission rates range from 65% to 90%, with recurrence rates reaching about 25% after 10 years.

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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.^{2,5,6} Drug therapies act at the hypothalamic-pituitary level and decrease ACTH secretion (e.g., Signifor, bromocriptine), at the adrenal level and inhibit cortisol synthesis (steroidogenesis inhibitors [e.g., ketoconazole, Metopirone[®] {metyrapone capsules}, Lysodren[®] {mitotane tablets}, etomidate]), or at the peripheral level by competing with cortisol (Korlym[®] [mifepristone tablets]).^{2,4} Pituitary-directed medical treatments are suggested in patients with Cushing's disease who are not surgical candidates or have persistent disease after surgery.⁷

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Signifor. Because of the specialized skills required for evaluation and diagnosis of patients treated with Signifor as well as the monitoring required for AEs and long-term efficacy, approval requires Signifor to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration specified below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

Food and Drug Administration (FDA)-Approved Indications

1. Cushing's Disease.

- A) **Initial Therapy.** Approve for 4 months of initial therapy if the patient meets the following criteria (i, ii, and iii):
 - i. Patient is ≥ 18 years of age; AND
 - ii. Signifor is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's syndrome; AND
 - iii. 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 awaiting surgery, see *Other Uses with Supportive Evidence*.
- B) **Patients Currently Receiving Signifor/Signifor LAR.** Approve for 1 year of continuation therapy if the patient has already been started on Signifor/Signifor LAR; patient has had a response, as determined by the prescribing physician; and patient is continuing therapy to maintain response.

Other Uses with Supportive Evidence

- 2. **Cushing's Disease/Syndrome – Patients Awaiting Surgery.** Approve for 4 months if the patient meets the following criteria (A and B):
 - A) Patient is ≥ 18 years of age; AND
 - B) Signifor is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's syndrome.
- 3. **Cushing's Disease/Syndrome – Patients Awaiting Therapeutic Response After Radiotherapy.** Approve for 4 months if the patient meets the following criteria (A and B):

- A) Patient is \geq 18 years of age; AND
- B) Signifor is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's syndrome.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Signifor 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 are 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

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3. 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.
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6. Rizk A, Honegger J, Milian M and Psaras T. Treatment options in Cushing's disease. *Clin Med Insights Oncol*. 2012(6):75-84.
7. Nieman LK, Biller BM, Findling JW. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2015;100(8):2807-2831.

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- Petersenn S, Salgado LR, Schopohl J, et al. Long-term treatment of Cushing's disease with pasireotide: 5-year results from an open-label extension study of a Phase III trial. *Endocrine*. 2017;57(1):156-165.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Annual revision	No criteria changes	04/16/2016
Annual revision	No criteria changes	04/12/2017
Annual revision	Updated policy title to include Cushing's. The requirement that Signifor be prescribed by an endocrinologist was modified to add "a physician who specializes in the treatment of Cushing' syndrome".	05/23/2018
Selected revision	Added Signifor LAR to the policy under patient currently receiving therapy. 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.	09/12/2018
Annual revision	Removal of the following Conditions Not Recommended for Approval: Acromegaly and Neuroendocrine Tumors	05/08/2019

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