Pharmacy Policy Bulletin: J-0178 Signifor (pasireotide) – Commercial and Healthcare Reform	
Number: J-0178	**Category:** Prior Authorization
Line(s) of Business: ☒ Commercial ☒ Healthcare Reform ☐ Medicare	**Benefit(s):** **Commercial:** **Prior Authorization (1.):** **1.** Miscellaneous Specialty Drugs Injectable = Yes w/ Prior Authorization **Healthcare Reform:** Not Applicable
Region(s): ☒ All ☐ Delaware ☐ New York ☐ Pennsylvania ☐ West Virginia	**Additional Restriction(s):** None
Version: J-0178-016	**Original Date:** 03/06/2013
Effective Date: 12/20/2024	**Review Date:** 12/04/2024

Drugs Product(s):	• Signifor (pasireotide)
FDA-Approved Indication(s):	• Treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.

Background:	• Signifor is an injectable cyclohexapeptide somatostatin analogue that binds and activates the somatostatin receptors resulting in inhibition of adrenocorticotropic hormone (ACTH) secretion, which leads to decreased cortisol secretion. • Cushing's syndrome refers to the condition caused by excess cortisol in the body, regardless of the cause. When Cushing's syndrome is caused by a pituitary gland tumor that over-secretes ACTH, thus overstimulating the adrenal glands' cortisol production, it is called Cushing's disease. • Signs and symptoms of Cushing's disease result from excess cortisol in the body and may include weight gain; fatty tissue deposits; hypertension; abnormal glucose tolerance; lethargy and depression; striae on the skin of the abdomen, thighs, and arms; thinning, fragile skin; reduced wound healing; hirsutism and irregular menses in women; and decreased libido and erectile dysfunction in men. • The Endocrine Society guidelines for the treatment of Cushing's syndrome recommend complete surgical resection of the primary lesion(s) underlying Cushing's disease, unless surgery is not possible or unlikely to significantly reduce glucocorticoid excess. For patients who underwent a non-curative surgery or for whom surgery was not possible, second-line treatment options include additional surgeries, radiotherapy, and pharmacological therapy. The choice of medication therapy should be guided by efficacy, individual patient factors, and cost. The goal is clinical normalization using reduction of cortisol levels as a proxy endpoint. • The Pituitary Society guideline update adds in mild disease, if residual tumor is present and there is a potential for tumor shrinkage, consider pasireotide or

	cabergoline. They may be used in combination if there is a visible tumor present. When there is no visible tumor on MRI, ketoconazole, osilodrostat or metyrapone are preferred.
	• Cabergoline and pasireotide are recommended pharmacological treatment options for patients with Cushing's disease who are not surgical candidates for or who have persistent disease following surgery. Ketoconazole, metyrapone, mitotane, and etomidate are recommended as second-line treatment options following surgery with or without radiotherapy in patients with Cushing's disease. Mifepristone is recommended in patients with diabetes or glucose intolerance who are not surgical candidates or who have persistent disease after surgery.
	• Urinary free cortisol (UFC) measurements are used primarily in the diagnosis of hypercortisolism caused by Cushing's syndrome. In normal circumstances, less than 5% of circulating cortisol is free (unbound). Free cortisol is the physiologically active form of cortisol and is filterable by renal glomeruli. With increased levels of plasma cortisol, free cortisol levels increase, which is then filtered through the glomeruli. The concentration of plasma free cortisol correlates well with UFC.
	• Patients should be evaluated for a treatment response (clinically meaningful reduction in 24-hour 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 two months of treatment.
	• Prescribing considerations:
	  ○ Signifor should be avoided in patients with Child-Pugh C hepatic impairment.
	  ○ Signifor has a high rate of hyperglycemia and should be considered when selecting therapies.

Approval Criteria

I. Initial Authorization

When a benefit, coverage of Signifor may be approved when all of the following criteria are met **(A. through D.)**:

A. The member is 18 years of age or older.

B. The member has a diagnosis of Cushing's disease. (ICD-10: E24.0)

C. Signifor is being prescribed by or in consultation with an endocrinologist.

D. The member meets one (1) of the following criteria **(1. or 2.)**:

1. The member is not a candidate for pituitary surgery.

2. Pituitary surgery has not been curative.

II. Reauthorization

When a benefit, reauthorization of Signifor may be approved when all of the following criteria are met **(A. and B.)**:

A. The member has experienced a reduction in 24-hour urinary free cortisol (UFC) levels from baseline.

B. The prescriber attests that the member has experienced an improvement in signs and symptoms of Cushing's disease from baseline.

III. An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations.

Limitations of Coverage

I. Coverage of drug(s) addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support effectiveness and safety in other conditions unless otherwise noted in the approval criteria.

II. For Commercial and HCR members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy.

Authorization Duration

Initial Authorization

- Commercial and HCR plans: If approved, up to a 6 month authorization may be granted.
  - For Delaware Commercial fully-insured and ACA members, a 12 month authorization must be granted pursuant to 18 *Del. C.* §§3376(a) and 3586(a) and market conduct examination docket #5467 (Exam Authority #53287-22-701).

Reauthorization

- Commercial and HCR plans: If approved, up to a 12 month authorization may be granted.

Automatic Approval Criteria

None

References:

1. Signifor subcutaneous injection [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; July 2024.
2. Biller BMK, Grossman AB, Stewart PM, et al. Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab*. 2008. 93(7):2454–62.
3. Arnaldi G, Boscaro M. New treatment guidelines on Cushing's disease. *Medicine Reports.* 2009. 1:64.
4. Lynnette K. et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2015;100(8)2807-2831.
5. Medscape. Serum Cortisol. Available at: https://emedicine.medscape.com/article/2088826-overview. Accessed October 07, 2023.
6. Cuevas-Ramos D, Lim DST, Fleseriu M. Update on medical treatment for Cushing's disease. Clin Diabetes Endocrinol. 2016;2:16. Published 2016 Sep 13.
7. Fleseriu M, Auchus R, Bancos I, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet Diabetes Endocrinol. 2021;9(12):847-875.