PASIREOTIDE

Generic	Brand	HICL	GCN	Exception/Other
PASIREOTIDE	SIGNIFOR	39866		

This drug requires a written request for prior authorization.

GUIDELINES FOR USE

1. Does the patient have a diagnosis of Cushing's disease?

   If yes, continue to #2.
   If no, do not approve.
   DENIAL TEXT: See the denial text at the end of the guideline.

2. Has the patient undergone pituitary surgery or is pituitary surgery not an option for this patient?

   If yes, continue to #3.
   If no, do not approve.
   DENIAL TEXT: See the denial text at the end of the guideline.

3. Has the patient tried ketoconazole, metyrapone, or cabergoline?

   If yes, **approve for 12 months by HICL with a quantity limit of #2 ampules per day.**
   If no, do not approve.
   DENIAL TEXT: See the denial text at the end of the guideline.

DENIAL TEXT: Approval requires a diagnosis of Cushing's disease for which the patient has undergone pituitary surgery or pituitary surgery is not an option, and a trial of ketoconazole, metyrapone, or cabergoline.

RATIONALE

To ensure appropriate use of Signifor consistent with FDA approved indication and dose.

Signifor's recommended dosage range is 0.3 mg to 0.9 mg twice a day. The recommended initial dose is either 0.6 mg or 0.9 mg injected subcutaneously twice a day. For patients with moderate hepatic impairment (Child Pugh B), the recommended initial dosage is 0.3 mg twice a day and the maximum dosage is 0.6 mg twice a day. Avoid the use of SIGNIFOR in patients with severe hepatic impairment (Child Pugh C).

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RATIONALE (CONTINUED)
Cushing's disease is caused by a pituitary gland tumor that produces adrenocorticotropic hormone (ACTH). This additional ACTH acts as a signal to the adrenal glands to make excess cortisol. Signifor binds and activates the human somatostatin receptor subtype 5 resulting in inhibition of ACTH secretion by the pituitary tumor cells, which leads to decreased cortisol secretion. First line treatment for Cushing's disease is transsphenoidal surgery and resection of the pituitary tumor. If surgery is delayed, contraindicated, or unsuccessful, adjunct medical therapy is usually required. Adrenal enzyme inhibitors, ketoconazole, and metyrapone (not FDA approved for this indication) are most commonly prescribed, followed by cabergoline (also not FDA approved for this indication) which targets the corticotrophin tumor. Combination therapy, such as Signifor, cabergoline, and/or ketoconazole, may be necessary to achieve an acceptable response.

A total of 162 patients were enrolled in a Phase III, multicenter, randomized study over a 6-month treatment period to evaluate the safety and efficacy of Signifor in patients with Cushing's disease. The majority of clinical trial subjects (83%) had persistent or recurrent disease despite pituitary surgery whereas surgery was not indicated or surgery was refused in the remaining subjects. Patients with a baseline 24-hour urine free cortisol (UFC) >1.5 x upper limit of normal (ULN) were randomized to receive a twice-daily, subcutaneous injection of either Signifor 0.6 mg or 0.9 mg. The primary efficacy endpoint was the proportion of patients who achieved normalization of mean 24-hour UFC levels after six months of treatment and did not dose increase during this period. At Month 6, the percentages of responders for the primary endpoint were 15% and 26% in the 0.6 mg twice daily and 0.9 mg twice daily groups, respectively. Signifor resulted in a decrease in the mean 24-hour UFC after 1 month of treatment. For patients (n=78) who stayed in the trial, similar UFC lowering was observed at Month 12.

Most common adverse reactions occurring in ≥20% of patients are diarrhea, nausea, hyperglycemia, cholelithiasis, headache, abdominal pain, fatigue, and diabetes mellitus.

Other clinically significant adverse reactions include hypocortisolism, bradycardia and QT prolongation, liver test elevations, and pituitary hormone deficiency.

Treatment with Signifor leads to suppression of adrenocorticotropic hormone (ACTH) secretion in Cushing's disease. Suppression of ACTH may lead to a decrease in circulating levels of cortisol and potentially hypocortisolism. Pituitary hormones other than ACTH may also be inhibited since Signifor mimics the acts of somatostatin. Monitoring of pituitary function (e.g., TSH/free T4, GH/IGF-1) should occur prior to initiation of therapy with Signifor and periodically during treatment. Patients who have undergone transsphenoidal surgery and pituitary irradiation are particularly at increased risk for deficiency of pituitary hormones.

Drug interactions include cyclosporine (decreased cyclosporine levels), bromocriptine (increased bromocriptine levels), and anti-arrhythmic drugs or other medications that prolong QT interval (additive effects on QT interval prolongation).

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PASIREOTIDE

RATIONALE (CONTINUED)
Signifor is Pregnancy Category C.

FDA APPROVED INDICATIONS
Signifor is a somatostatin analog indicated for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.

REFERENCES

- Signifor [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; December 2012.
- UpToDate, Inc. Overview of the treatment of Cushing's syndrome. UpToDate [database online]. Waltham, MA. Available at http://www.uptodate.com/home/index.html. Updated January 17, 2013.
- UpToDate, Inc. Medical therapy of hypercortisolism (Cushing's syndrome). UpToDate [database online]. Waltham, MA. Available at http://www.uptodate.com/home/index.html. Updated January 18, 2013.

Library	Commercial	NSA
Yes	Yes	No

Part D Effective: N/A
Commercial Effective: 07/01/13
Created: 05/13
Client Approval: 05/13
P&T Approval: 05/13