BlueCross BlueShield of Alabama

Signifor® (pasireotide) and Signifor LAR (pasireotide) Prior Authorization with Quantity Limit Program Summary

Signifor is the only target in this prior authorization program. Signifor LAR is not targeted in this pharmacy prior authorization program.

This program applies to Commercial, NetResults A series, SourceRx, and Health Insurance Marketplace formularies.

OBJECTIVE

The intent of the Signifor (pasireotide) and Signifor LAR Prior Authorization (PA) program is to appropriately select patients for treatment according to product labeling and/or clinical studies and/or clinical practice guidelines. The program will approve for doses within the set limit. Doses above the set limit will be approved if the requested quantity is below the FDA limit and cannot be dose optimized or when the quantity is above the FDA limit and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis.

TARGET DRUGS

Signifor (pasireotide)

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Initial Evaluation

Signifor will be approved for INITIAL USE when ALL of the following are met:

1. If Signifor, ONE of the following:
    - A. The patient has a diagnosis of Cushing's disease and ONE of the following:
        - I. The patient has had recurrence or persistence after pituitary surgical resection
        - **OR**
        - II. The patient is not a candidate for pituitary surgical resection
    - **OR**
    - B. The patient has another FDA approved diagnosis

    AND
2. If Signifor LAR, ONE of the following:
    - A. The patient has a diagnosis of acromegaly and ONE of the following:
        - I. The use of requested agent is for adjunctive therapy with irradiation to alleviate acromegaly symptoms
        - **OR**
        - II. The patient had an inadequate response to surgery or pituitary irradiation defined by ONE of the following:
            - a. Growth hormone level > 5 ng/mL
            - **OR**
            - b. IGF-1 level > 1.9 U/mL for males or > 2.2 U/mL for females
        - **OR**
        - III. The patient is not a candidate for both surgical resection AND pituitary irradiation
    - **OR**
    - B. The patient has another FDA approved diagnosis

    AND

3. The patient does not have severe hepatic impairment (i.e. Child Pugh C)
   AND
4. The patient does not have an FDA labeled contraindication(s) to therapy with the requested agent
   AND
5. ONE of the following:
   A. The quantity requested (dose) is less than or equal to the program quantity limit
      OR
   B. ALL of the following:
      I. The requested quantity (dose) is greater than the program quantity limit
         AND
      II. The requested quantity (dose) is less than or equal to the FDA labeled dose
         AND
      III. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit
      OR
   C. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit
         AND
      ii. The requested quantity (dose) is greater than the FDA labeled dose
         AND
      iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis and is pharmacist reviewed and approved

Length of Approval: Signifor: 3 months for Cushing's Disease and 12 months for all other FDA approved diagnosis.

Renewal Evaluation
Signifor will be approved for RENEWAL when ALL of the following are met:
1. The patient has been previously approved through the Prime Therapeutics PA approval process
   AND
2. If Signifor, ALL of the following:
   A. The patient has had a 15% or greater decrease in urinary free cortisol levels
      AND
   B. The patient has shown improvement in at least ONE of the following clinical signs and symptoms
      I. Fasting plasma glucose
      II. Hemoglobin A1c
      III. Hypertension
      IV. Weight
   AND
3. If Signifor LAR, ONE of the following:
   A. Growth hormone level <5 ng/mL
      OR
   B. IGF-1 level <1.9 U/mL for males or <2.2 U/mL for females
      OR
   C. Clinical improvement (e.g. reduction in tumor size, decreased headaches, improved cardiovascular or respiratory symptoms)
   AND
4. The patient does not have severe hepatic impairment (i.e. Child Pugh C)

AND

5. The patient does not have any FDA labeled contraindications to therapy with the requested agent
   AND
6. ONE of the following:
   A. The quantity requested (dose) is less than or equal to the program quantity limit
      OR
   B. ALL of the following:
      I. The requested quantity (dose) is greater than the program quantity limit
         AND
      II. The requested quantity (dose) is less than or equal to the FDA labeled dose
         AND
      III. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit

   OR

   C. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit
         AND
      ii. The requested quantity (dose) is greater than the FDA labeled dose
         AND
      iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis and is pharmacist reviewed and approved

Length of Approval: 12 months

FDA APPROVED INDICATIONS AND DOSAGE[1,6]

Signifor:
FDA Indication: For the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.

Dosing: The recommended initial dose is either 0.6 mg or 0.9 mg subcutaneously twice a day. Titrate based on treatment response (clinically meaningful reduction in 24-hour urinary free cortisol (UFC) and/or improvements in signs or symptoms) and tolerability.
Maximum dose for patients with Child Pugh B score (moderate hepatic impairment) is 0.6 mg twice daily. Avoid use in patients with Child Pugh C score (severe hepatic impairment).

Signifor LAR:
FDA Indication: For the treatment of patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option.

Dosing: The recommended initial dose is 40 mg administered by intramuscular injection 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 at 40 mg and who tolerate this dose. Management of Signifor LAR-related adverse reactions or over-response to treatment (age and sex adjusted IGF-1 less than the lower limit of normal) may require dose reduction. The dose may be decreased, either temporarily or permanently, by 20 mg decrements.

CLINICAL RATIONALE[2-5,11-13]

Cushing's Syndrome

Cushing's syndrome is a relatively rare hormonal disorder caused by increased levels of cortisol (hypercortisolism). Cushing's disease (CD) is when excess adrenocorticotropic hormone (ACTH) comes from the pituitary gland causing the adrenal glands to make cortisol. The increased cortisol is caused mostly by benign pituitary tumors that secrete ACTH. Symptoms such as sudden weight gain, hypertension, hyperlipidemia, acne, hirsutism, osteopenia, easy bruising, etc. can vary but most people present with upper body obesity, a rounded face, and increased fat around the neck. Children tend to be obese with slowed growth rates. Clinical findings include weight gain, truncal obesity, striae, hypertension, and glucose intolerance. Surgery to remove the tumor has the potential to cure the disease but recurrence rates are anywhere from 5% to 45%. Treatment options for patients whose hypercortisolemia persists despite surgery or for those with recurrence, other therapeutic options include additional pituitary surgery (lower success rates), radiotherapy, medical management or bilateral adrenalectomy as a last resort. Medical therapy can be used initially for certain circumstances (e.g. surgery is contraindicated or a tumor is unresectable) but typically medical therapy is second line or add on therapy to surgery or radiotherapy.

The Endocrine Society Guidelines for Cushing's syndrome states that the treatment of Cushing's syndrome is essential to reduce mortality and associated comorbidities. Effective treatment includes the normalization of cortisol levels or action. It also includes the normalization of comorbidities via directly treating the cause of Cushing's syndrome and by adjunctive treatments (eg, antihypertensives). Surgical resection of the causal lesion(s) is generally the first-line approach. The choice of second-line treatments, including medication, bilateral adrenalectomy, and radiation therapy (for corticotrope tumors), must be individualized to each patient. In the listing of medical treatment options, pasireotide and cabergoline are included as the pituitary directed agents. Pasireotide is approved for treatment of patients with CD who are not surgical candidates or have failed surgery. An additional review echoes the guidelines and suggests first-line treatment for CD is pituitary surgery. Patients with persistent or recurrent CD require additional treatments (e.g., pituitary

radiotherapy, adrenal surgery and/or medical therapy). Pituitary radiotherapy is effective in controlling cortisol excess in a large percentage of patients, but is associated with risk of hypopituitarism. Adrenal surgery is followed by a rapid control of cortisol excess in nearly all patients, but induces adrenal insufficiency. Medical therapy is used as a presurgical treatment, particularly for severe disease, or as post-surgical treatment (failure or incomplete surgical tumor resection), or as bridging therapy before, during and after radiotherapy while waiting for disease control or, in selected cases, as primary therapy, mainly when surgery is not an option.

Pasireotide binds to somatostatin receptors but exhibits a different pattern of receptor binding and different affinities compared to lanreotide and octreotide. Pasireotide binds to a broader range of receptors (SSTR1, STTR2, STTR3 and SSTR5) compared to lanreotide and octreotide which bind primarily to SSTR2.

Efficacy was evaluated in a phase 3, uncontrolled study with two doses of pasireotide (600 mcg [0.6 mg] twice daily or 900 mcg [0.9 mg] twice daily). The study was not powered to detect a difference between doses. Based on consultation with clinical endocrinologists the manufacturer determined that ≥15% improvement in urinary free cortisol (UFC) would be a clinically meaningful improvement. The totality of data showed that both doses are effective.

Acromegaly

Endocrine Society Guidelines (2014) continue to recommend either octreotide or lanreotide as primary medical therapy for acromegaly patients who are not surgical candidates or in those patients that require pre- or post-surgical medical treatment. They state that pasireotide is a novel somatostatin receptor ligand (SRL) shown to normalize IGF-1 in 35% of patients in a phase 3 trial. In addition to side effects similar with octreotide and lanreotide, pasireotide is associated with hyperglycemia in 57% of patients.[9]

The Acromegaly Consensus Group (U.S., Europe, 2014) also recommends either octreotide or lantreotide as primary medical treatment for nonsurgical candidates, or for those patients that require additional therapy along with surgery.[10]

The approval for pasireotide long acting release (LAR) was approved based on two studies. One involved drug naïve patients and the other involved patient not adequately controlled on other somatostatin analogs.

Drug Naïve Patients[6,7]:

Patients with medically naive acromegaly (GH >5 µg/L or GH nadir >1 µg/L after an oral glucose tolerance test and IGF-1 above the upper limit of normal) were enrolled (N=358). Patients either had previous pituitary surgery but no medical treatment or were de novo with a visible pituitary adenoma on magnetic resonance imaging. Patients received pasireotide LAR 40 mg/28 days (n = 176) or octreotide LAR 20 mg/28 days (n = 182) for 12 months. At months 3 and 7, titration to pasireotide LAR 60 mg or octreotide LAR 30 mg was permitted, but not mandatory, if GH >2.5 µg/L and/or IGF-1 was above the upper limit of normal (ULN).

The primary endpoint was the proportion of patients in each treatment arm with biochemical control (GH <2.5 µg/L and normal IGF-1) at month 12. Biochemical control was achieved by more pasireotide LAR patients than octreotide LAR patients (31.3% vs 19.2%; p = 0.007; 35.8% vs 20.9% when including patients with IGF-1 below the lower normal limit). In pasireotide LAR and octreotide LAR patients, respectively, 38.6% and 23.6% (p= 0.002) achieved normal IGF-1, and 48.3% and 51.6% achieved GH <2.5 µg/L. Thirty-one percent of pasireotide LAR and 22.2% of octreotide LAR patients who did not achieve biochemical control did not receive the recommended dose increase. Hyperglycemia-related adverse events were more common with pasireotide LAR (57.3°/o vs 21.7%).

Patients Inadequately Controlled on other Somatostatin Analogs[6,8]:
Patients were randomized to double-blind pasireotide LAR 40 mg (n=65) or 60 mg (n=65) or to continued open-label pre-trial SRLs at maximal or near maximal doses (n=68). Inadequate control was defined as GH >2.5 µg/L and a sex-and age-adjusted IGF-1 level >1.3 times the ULN. Patients were required to have been treated with other SRLs for >6 months prior to randomization. The efficacy endpoint was the proportion of patients with a mean GH level < 2.5 µg/L and normal IGF-1 levels at week 24. The primary analysis compared pasireotide LAR 60 mg and 40 mg to continued pretrial therapy (i.e., no change in treatment. At 6 months, the primary endpoint was reached for 15.4% and 20% of patients on pasireotide LAR 40 mg and 60 mg, respectively, and for zero patients in the control arm.

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