09-J1000-94

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Subject: Pasireotide (Signifor®, Signifor LAR®) Injection

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Pasireotide is an injectable somatostatin analogue. Pasireotide exerts its pharmacological activity by binding to somatostatin receptors (SSTR). Five human somatostatin receptor subtypes are known: SSTR 1, 2, 3, 4, and 5. These receptor subtypes are expressed in different tissues under normal physiological conditions. Somatostatin analogs bind to SSTRs with different potencies. Pasireotide binds with high affinity to four of the five SSTRs (SSTR1 to 4). Corticotroph tumor cells from Cushing's disease subjects frequently over-express SSTR 5 whereas the other receptor subtypes are often not expressed or are expressed at lower levels. Pasireotide binds and activates the SSTRs resulting in inhibition of adrenocorticotropic hormone (ACTH) secretion, which leads to decreased cortisol secretion. Pasireotide's binding to SSTR2 and SSTR5 subtype receptors is relevant for inhibition of growth hormone (GH) secretion. *In vivo* studies show that long-acting pasireotide lowers GH and insulin-like growth factor-1 (IGF-1) levels in patients with acromegaly. Signifor was FDA-approved for patients with Cushing's disease in December 2012. In December 2014, the FDA approved a long-acting formulation of pasireotide (Signifor LAR) for patients with acromegaly. The FDA has also approved long-acting pasireotide (Signifor LAR) for the treatment of Cushing's disease.

A Phase III, multicenter, randomized study was conducted to evaluate the safety and efficacy of two dose levels of pasireotide over a 6-month treatment period in Cushing's disease subjects with persistent or recurrent disease despite pituitary surgery or de novo subjects for whom surgery was not indicated or who had refused surgery. Individuals with a baseline 24-hour urine free cortisol (UFC) >1.5 x upper limit of normal (ULN) were randomized to receive a pasireotide dosage of either 0.6 mg subcutaneous twice daily or 0.9 mg subcutaneous twice daily. After three months of treatment, individuals with a mean 24-hour UFC ≤ 2.0 x ULN and below or equal to their baseline values continued blinded treatment at the

randomized dose until Month 6. Subjects who did not meet these criteria were unblinded and the dose was increased by 0.3 mg twice daily. After the initial six months in the study, subjects entered an additional 6-month open-label treatment period. The dosage could be reduced by 0.3 mg twice daily at any time during the study for intolerability. A total of 162 individuals were enrolled in this study. The primary efficacy endpoint was the proportion of subjects 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 and 0.9 mg groups, respectively. Dose increases appeared to have minimal effect on 24-hour UFC response.

A Phase III, multicenter, randomized study was conducted to assess the safety and efficacy of long-acting pasireotide in patients with active acromegaly. A total of 358 patients naïve to drugs used to treat acromegaly were randomized in a 1:1 ratio to long-acting pasireotide or another somatostatin analog active comparator. The starting dose of long-acting pasireotide was 40 mg with a max dose of 60 mg. Dose increase was allowed in both arms, at the discretion of investigators, after three and six months of treatment if mean GH was greater than or equal to 2.5 mcg/L and/or IGF-1 was greater than the ULN for age and sex. The efficacy endpoint was the proportion of patients with a mean GH level less than 2.5 mcg/L and a normal IGF-1 levels at month 12 (age- and sex-adjusted). The proportion of patients achieving this level of control was 31.3% and 19.2% for long-acting pasireotide and active comparator, respectively. A Phase III, multicenter, randomized, trial was conducted in patients with acromegaly inadequately controlled on somatostatin analogs. Patients were randomized to double-blind long-acting pasireotide 40 mg (n=65) and 60 mg (n=65) or to continued open-label pre-trial somatostatin analog therapies at maximal or near maximal doses (n=68). The efficacy endpoint was the proportion of patients with a mean GH level less than 2.5 mcg/L and normal IGF-1 levels at week 24. The proportion of patients achieving biochemical control was 15.4% and 20.0% for long-acting pasireotide 40 mg and 60 mg, respectively, at 6 months. Eighty-one percent and 70% of patients treated with long-acting pasireotide 40 mg and 60 mg, respectively, had either a reduction or no change in tumor volume from baseline assessed by MRI at month 6.

POSITION STATEMENT:

Comparative Effectiveness (Signifor ONLY)

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of pasireotide (Signifor®) meets the definition of **medical necessity** when **ALL** of the following criteria met:

1. The member has a diagnosis of Cushing's disease.
2. Pituitary surgery has not been curative or is not an option.
3. **ALL** of the following baseline tests have been ordered or have been completed within the past 6 months:
    a) fasting plasma glucose
    b) hemoglobin A1c
    c) liver tests

d) serum potassium
e) serum magnesium
f) electrocardiogram
g) gallbladder ultrasound

4. The member does not have severe (Child-Pugh C) liver disease.
5. The dosage does not exceed 0.9 mg twice a day.

Approval duration: 90 days

Initiation of long-acting pasireotide (Signifor LAR®) **meets the definition of medical necessity** for the following indications when **ALL** of the following criteria met:

A. Acromegaly
   1. Pituitary surgery has not been curative or is not an option.
   2. The member has an inadequate response to or has a contraindication to at least **ONE** of the following somatostatin analogs:
      - Lanreotide depot injection (Somatuline Depot®)
      - Octreotide acetate depot injection (Sandostatin LAR®)
   3. **ALL** of the following baseline tests have been ordered or have been completed within the past 6 months:
      a) fasting plasma glucose
      b) hemoglobin A1c
      c) liver tests
      d) serum potassium
      e) serum magnesium
      f) electrocardiogram
   4. The member does not have severe (Child-Pugh C) liver disease.
   5. The dosage does not exceed 60 mg every 4 weeks.

B. Cushing's disease
   1. Pituitary surgery has not been curative or is not an option.
   2. **ALL** of the following baseline tests have been ordered or have been completed within the past 6 months:
      a) fasting plasma glucose
      b) hemoglobin A1c
      c) liver tests
      d) serum potassium
      e) serum magnesium
      f) electrocardiogram
   3. The member does not have severe (Child-Pugh C) liver disease.

4. The initial dosage does not exceed 40 mg every 4 weeks.

Approval duration: 90 days

Continuation of pasireotide (Signifor) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member has a history of beneficial response (e.g., decrease in urinary free cortisol) to pasireotide therapy for treatment of Cushing's disease.
2. The member has been previously approved for pasireotide (Signifor) in the treatment of Cushing's disease by Florida Blue or another health plan in the past 2 years, **OR** the member has previously met all indication-specific criteria for coverage
3. The dosage does not exceed 0.9 mg twice daily.

Approval duration: 1 year.

Continuation of long-acting pasireotide (Signifor LAR) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member has a history of beneficial response (e.g., decreased GH and/or IGF-1 for acromegaly or decrease in urinary free cortisol for Cushing's disease) to pasireotide therapy
2. The member has been previously approved for long-acting pasireotide (Signifor LAR) in the treatment of acromegaly or Cushing's disease by Florida Blue or another health plan in the past 2 years, **OR** the member has previously met all indication-specific criteria for coverage
3. The dosage does not exceed the following:
    a. Acromegaly: 60 mg every 4 weeks.
    b. Cushing's disease: 40 mg every 4 weeks.

Approval duration: 1 year.

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved:

Signifor

Cushing's disease: For patients with whom pituitary surgery is not an option or has not been curative. The recommended dose is either 0.6 mg or 0.9 mg and is administered subcutaneously twice daily. The dosage can be titrated based on treatment response and tolerability. Prior to therapy initiation, members should have baseline levels or measurements of the following:

- fasting plasma glucose
- hemoglobin A1c

- liver tests
- electrocardiogram
- gallbladder ultrasound
- serum potassium
- serum magnesium

In members with hepatic impairment, the following is recommended in the product labeling:

- Child-Pugh B: initial dose of 0.3 mg twice daily and max dose of 0.6 mg twice daily
- Child-Pugh C: avoid use

Product Availability: pasireotide is supplied as a 0.3-, 0.6-, and 0.9 mg/mL single-dose ampule. Store at 25° C (77°F); excursions permitted to 15°-30°C (59°-86°F), protect from light.

Signifor LAR

Acromegaly: For patients who have had an inadequate response to surgery and/or for whom surgery is not an option. 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 and who tolerate the 40 mg dose. The dose may be decreased, either temporarily or permanently, by 20 mg decrements.

Cushing's disease: For patients with whom pituitary surgery is not an option or has not been curative. The recommended initial dose is 10 mg administered by intramuscular injection once every 4 weeks (every 28 days). The dose may be increased to a maximum of 40 mg for patients who have not normalized 24-hour urinary free cortisol levels and who tolerate the 40 mg dose. The dose may be titrated, reduced or discontinued based on response.

Prior to therapy initiation, members should have baseline levels or measurements of the following:

- fasting plasma glucose
- hemoglobin A1c
- liver tests
- electrocardiogram
- serum potassium
- serum magnesium

Patients with poorly controlled diabetes mellitus who have inadequate glucose control should have anti-diabetic therapy optimized prior to starting treatment.

In members with hepatic impairment, the following is recommended in the product labeling:

- Child-Pugh B (moderate hepatic impairment):
    - Acromegaly: initial dose 20 mg every 4 weeks and the maximum recommended dose is 40 mg every 4 weeks
    - Cushing's disease: initial dose 10 mg every 4 weeks and the maximum recommended dose is 20 mg every 4 weeks

- Child-Pugh C: avoid use

Product Availability: long-acting pasireotide is supplied as 10, 20, 30, 40, and 60 mg single-use kits. Store at 2°C to 8°C (36°F to 46°F) and do not freeze.

PRECAUTIONS:

CONTRAINDICATIONS

None (both Signifor and Signifor LAR)

WARNINGS

Signifor

- **Hypocortisolism**: Decreases in circulating levels of cortisol may occur resulting in biochemical and/or clinical hypocortisolism. Pasireotide dose reduction or interruption and/or adding a low-dose short-term glucocorticoid may be necessary.
- **Hyperglycemia and Diabetes (occurs with initiation):** Intensive glucose monitoring is recommended and may require initiation or adjustment of anti-diabetic treatment.
- **Bradycardia and QT Prolongation**: Use with caution in at-risk individuals; ECG testing prior to dosing and on treatment.
- **Liver Test Elevations**: Evaluate liver tests prior to and during treatment.
- **Cholelithiasis**: Perform gallbladder ultrasounds before starting treatment and at 6-month intervals. Discontinue if complications of cholelithiasis are suspected.
- **Pituitary Hormone Deficiency(ies):** Monitor for occurrence periodically (e.g., TSH/free T4, GH/IGF-1) and treat if clinically indicated.

Signifor LAR

- **Hyperglycemia and Diabetes:** Sometimes severe. Monitor glucose levels periodically during therapy. Monitor glucose levels more frequently in the months that follow initiation or discontinuation of therapy and following dose adjustment. Use anti-diabetic treatment if indicated per standard of care.
- **Bradycardia and QT Prolongation:** Use with caution in at-risk patients; Evaluate ECG and electrolytes prior to dosing and periodically while on treatment.
- **Liver Test Elevations:** Evaluate liver enzyme tests prior to and during treatment.
- **Cholelithiasis:** Monitor periodically. Discontinue if complications of cholelithiasis are suspected.
- **Pituitary Hormone Deficiency(ies):** Monitor for occurrence periodically (e.g., TSH/free T4, GH/IGF-1) and treat if clinically indicated.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

Signifor

C9399	Unclassified drugs or biologicals (Hospital Outpatient Use ONLY)
J3490	Unclassified drugs

Signifor LAR

J2502	Injection, pasireotide long acting, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity, Signifor

E24.0	Pituitary-dependent Cushing's disease

ICD-10 Diagnosis Codes That Support Medical Necessity, Signifor LAR

E22.0	Acromegaly and pituitary gigantism
E24.0	Pituitary-dependent Cushing's disease

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT.**

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) or Local Coverage Determination (LCD) was found at the time of the last guideline revised date.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

DEFINITIONS:

Acromegaly: is a hormonal disorder that develops when the pituitary gland produces too much growth hormone during adulthood. When this happens, bones increase in size, including those of the hands, feet and face. Acromegaly usually affects middle-aged adults. In children who are still growing, too much growth hormone can cause a condition called gigantism. These children have exaggerated bone growth and an abnormal increase in height.

Cushing's syndrome: is a hormone disorder caused by high levels of cortisol in the blood. This can be caused by taking glucocorticoid drugs, or by tumors that produce cortisol or adrenocorticotropic hormone (ACTH) or CRH.

Cushing's disease: when the pituitary gland makes too much of the hormone ACTH. ACTH then signals the adrenal glands to produce cortisol. Tumor of the pituitary gland may cause this condition.

RELATED GUIDELINES:

Lanreotide (Somatuline® Depot) Injection, 09-J1000-20

Mitotane (Lysodren®) Tablets, 09-J1000-60

Mifepristone (Korlym™) Oral, 09-J1000-69

Octreotide Acetate (Sandostatin LAR® Depot) Injection, 09-J0000-90

OTHER:

Child-Pugh Classification of Severity of Liver Disease: Using the table below, a total score of 5-6 is considered grade A (well-compensated disease); 7-9 is grade B (significant functional compromise); and 10-15 is grade C (decompensated disease).

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin, mg/dL	</= 2	2-3	>3
Albumin, g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time * Seconds over control * INR	 1-3 <1.8	 4-6 1.8 – 2.3	 >6 >2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 06/12/19.

GUIDELINE UPDATE INFORMATION:

06/15/13	New Medical Coverage Guideline.

05/15/14	Review and revision to guideline; consisting of revising and reformatting position statement; revising description section; updating dosage/administration, precautions, and references.
05/15/15	Review and revision to guideline; consisting of adding Signifor LAR, updating the description section, position statement, dosage/administration, precautions, definitions, coding, related guidelines, and references.
07/01/15	Revision to guideline consisting of HCPCS code update.
11/01/15	Revision: ICD-9 Codes deleted.
01/01/16	Annual HCPCS coding update: added code J2502 and deleted code C9454.
05/15/16	Review and revision to guideline; consisting of updating the position statement and references.
05/15/17	Review and revision to guideline; consisting of updating the position statement and references.
05/15/18	Review and revision to guideline; consisting of updating references.
07/15/19	Review and revision to guideline; consisting of updating position statement, coding, dosing and references.