LOUISIANA BLUE

pasireotide Injection (Signifor®, Signifor LAR®)

Policy # 00384
Original Effective Date: 08/21/2013
Current Effective Date: 05/01/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Signifor®

Based on review of available data, the Company may consider the use of pasireotide diaspartate injection (Signifor®)‡ to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for pasireotide diaspartate injection (Signifor) will be considered when all of the following are met:

- Patient has a diagnosis of Cushing's disease; AND
- Patient is 18 years of age or older; AND
- Pituitary surgery is not an option OR has not been curative for the patient.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of pasireotide diaspartate injection (Signifor) when patient selection criteria are not met to be **investigational.***

Signifor LAR®

Based on review of available data, the Company may consider the use of long acting pasireotide pamoate injection (Signifor LAR®)‡ to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for long acting pasireotide pamoate injection (Signifor LAR) will be considered when the following criteria are met for the patient's diagnosis:

- Patient has a diagnosis of acromegaly and ALL of the following:
    - Patient has had an inadequate response to surgery and/or surgery is not an option; AND
    - Patient has failed therapy with an alternative somatostatin analogue (e.g., octreotide [Sandostatin LAR®]‡, lanreotide [Somatuline Depot®]‡) UNLESS there is clinical evidence or patient history that suggests the alternative somatostatin analogues are ineffective or will cause an adverse reaction to the patient; AND
      *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
    - Dose does not exceed 60 mg every 4 weeks; OR
- Patient has a diagnosis of Cushing's disease; AND
    - Patient meets EITHER of the following:
        - Pituitary surgery is not an option; OR
        - Pituitary surgery has not been curative for the patient; AND
    - Dose does not exceed 40 mg every 4 weeks.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of long acting pasireotide pamoate injection (Signifor LAR) for the treatment of acromegaly when the patient has NOT failed therapy with an alternative somatostatin analogue (e.g., octreotide [Sandostatin LAR], lanreotide [Somatuline Depot]) to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of long acting pasireotide pamoate injection (Signifor LAR) when patient selection criteria are not met to be **investigational*** (with the exception of the criterion denoted above as **not medically necessary****).

Background/Overview

Signifor is an injectable cyclohexapeptide somatostatin analogue approved for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative. Five human somatostatin (hsst) receptors subtypes are known: 1, 2, 3, 4, and 5. These subtypes are expressed in different tissues under normal physiologic conditions. Human somatostatin receptor subtype 5 is frequently over expressed in corticotroph tumor cells in Cushing's disease patients. Signifor binds and activates the hsst receptors resulting in the inhibition of ACTH secretion, which will therefore further lead to decreased cortisol secretion. Signifor is provided as an ampule with 0.3 mg/mL. The recommended initial dose of Signifor is either 0.6 mg or 0.9 mg by subcutaneous

injection twice daily. The recommended dosage range is 0.3 mg to 0.9 mg twice daily. The dosing should be titrated based on treatment response (clinically meaningful reduction in 24-hour urine free cortisol and/or improvements in signs and symptoms of disease) and tolerability.

Signifor LAR contains the same active ingredient as Signifor but is formulated as a long acting product. Signifor LAR is indicated for the treatment of Cushing's disease and acromegaly. Somatostatin receptors are expressed in many tissues including neuroendocrine tumors (e.g., growth hormone secreting pituitary adenomas). Signifor LAR binds to somatostatin receptors 2 and 5 which may be relevant for inhibition of growth hormone secretion (e.g., for those with acromegaly). The dosage for the treatment of acromegaly is 40 mg administered by intramuscular injection once every 4 weeks and can be increased to a maximum of 60 mg monthly. In Cushing's disease, the initial dose is 10 mg administered by intramuscular injection once every 4 weeks and can be increased to a maximum of 40 mg every 28 days. Signifor LAR is available as a powder to be reconstituted as 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg injectable suspensions.

Cushing's Disease
Cushing's disease is a disorder that leads to cortisol excess. Patients with Cushing's exhibit a variety of signs and symptoms such as high blood pressure, loss of libido, diabetes, weight gain, acne, moon face, truncal obesity, and slender extremities. Goals of treatment include normalizing the cortisol excess, avoiding and reversing the clinical features, and controlling the disease long term. Treatment often involves a multi-modal approach. In general, the treatment of choice for Cushing's disease is selective pituitary adenectomy. Medications available that have the ability to inhibit adrenocortical steroidogenesis include ketoconazole, metyrapone, mitotane, and etomidate.

Acromegaly
Acromegaly is a chronic disorder characterized by elevated growth hormone secretion and is associated with multisystem morbidities and increased mortality. Acromegaly is caused by overproduction of growth hormone by the pituitary gland. Growth hormone then induces the creation of insulin like growth factor-1 (IGF-1). IGF-1 is involved in tissue growth and metabolic function. Normally, regulatory mechanisms would slow down the production of growth hormone, however in patients with acromegaly, the growth hormone production is unregulated. Elevated IGF-1 levels increase and lead to bone overgrowth, organ enlargement, and changes in glucose and lipid metabolism. In the majority of cases of acromegaly, the excess hormone production is due to a benign pituitary adenoma. Surgery is typically the treatment of choice, and medications are used as adjuvant treatment when surgery doesn't control the disease. Drug therapies to control acromegaly include somatostatin analogues (Signifor LAR [pasireotide], Sandostatin LAR [octreotide], and Somatuline Depot [lanreotide]), growth hormone receptor antagonists (Somavert®‡ [pegvisomant]), and dopamine agonists (bromocriptime, cabergoline). As mentioned earlier, surgery is typically the first option for treatment. If surgery fails or isn't an option, then somatostatin analogues are typically given. In patients without an adequate response to the somatostatin analogues, the addition of Somavert or cabergoline is an option. The most recent guidelines for the treatment of acromegaly have not incorporated Signifor LAR.

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Signifor was approved by the FDA in December of 2012 for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative. Signifor LAR was approved in late 2014 for the treatment of patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option. In June 2018, Signifor LAR received an additional indication for Cushing's disease in patients for whom pituitary surgery is not an option or has not been curative.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Cushing's Disease

The safety and efficacy of two doses of Signifor was evaluated in a Phase III multicenter randomized study over a 6 month period in patients with Cushing's disease with persistent or recurrent disease despite pituitary surgery or in those patients in which surgery was not indicated or the patient refused surgery. The primary efficacy endpoint was the proportion of patients who achieved normalization of mean 24-hour urine free cortisol (UFC) levels after 6 months of treatment and did not dose increase during this period. Patients included in this study had a baseline 24-hour UFC > 1.5 times the upper limit of normal (ULN) and were randomized to receive either 0.6 mg subcutaneous twice daily or 0.9 mg subcutaneous twice daily of Signifor. After 3 months, patients with a mean 24-hour UFC $\leq$ 2 x ULN and below or equal to their baseline values continued the blinded treatment at the same dose through month 6. Patients who did not meet that criteria were unblinded and the dose was increased by 0.3 mg twice daily. A total of 162 patients were enrolled in the study. 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. The percentages of patients with mean UFC $\leq$ ULN or $\geq$ 50% reduction from baseline, a less stringent endpoint than the primary endpoint, were 34% in the 0.6 mg twice daily and 41% in the 0.9 mg twice daily groups. Dose increases appeared to have minimal effect on 24-hour UFC response.

The safety and efficacy of two dose regimens of Signifor LAR over a 12-month treatment period in patients with Cushing's disease who had persistent or recurrent disease or were not candidates for pituitary surgery was evaluated in a Phase III, randomized, double-blind, multicenter study. The study enrolled 150 patients with a screening mean UFC level $\geq$ 1.5 and $\leq$ 5 x ULN, who were randomized in a 1:1 ratio to receive a Signifor LAR starting dose of either 10 mg or 30 mg IM every 28 days. After 4 months of treatment, patients who had a mean UFC $\leq$ 1.5 x ULN continued on the blinded dose to which they were randomized while those with a mean UFC > 1.5 x ULN had their

doses increased in a blinded manner from 10 mg to 30 mg, or from 30 mg to 40 mg as long as there were no tolerability concerns. Additional dose increases were allowed at month 7 and month 9. Dose reduction for tolerability was also allowed in a blinded fashion for the first 7 months with a minimum dose level of 5 mg. After the first 7 months, blinded down titration of more than one dose level was allowed at any month.

The primary efficacy endpoint was the proportion of patients in each arm who were mean UFC responders (mean UFC < 1.5 x ULN) after 7 months of treatment. The study met the primary efficacy objective for both dose groups. The proportion of patients with mean UFC response at month 7 was 39.2% (95% CI: 28, 51.2) in the 10 mg arm and 40.8% (95% CI: 29.7, 52,7) in the 30 mg arm.

Acromegaly

A multicenter, randomized, double-blind study was conducted to assess the safety and efficacy of Signifor LAR 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 Signifor LAR or another somatostatin analog active comparator (Sandostatin LAR). The starting dose of Signifor LAR was 40 mg. Dose increase was allowed in both arms, at the discretion of investigators, after three and six months of treatment if mean growth hormone was greater than or equal to 2.5 mcg/L and/or IGF-1 was greater than the upper limit of normal for age and sex. The maximum allowed dose for Signifor LAR was 60 mg. The maximum dose of Sandostatin LAR was not used in this trial because the trial was multi-national and the maximum dose approved in the US was not approved in all participating countries. The efficacy endpoint was the proportion of patients with a mean growth hormone level less than 2.5 mcg/L and a normal IGF-1 level at month 12. The proportion of patients achieving this level of control was 31.3% and 19.2% (p = 0.007) for Signifor LAR and the active comparator, respectively.

A multicenter, randomized, 3-arm trial was conducted in patients with acromegaly inadequately controlled on somatostatin analogs (Sandostatin LAR, Somatuline Depot). Patients were randomized to double-blind Signifor LAR 40 mg (n=65) or Signifor LAR 60 mg (n = 65) or to continued open-label pre-trial somatostatin analog therapies at maximal or near maximal doses (n = 68). A total of 181 patients completed the 6 month trial. Inadequate control was defined as a growth hormone concentration of greater than 2.5 mcg/L and a sex- and age-adjusted IGF-1 level greater than 1.3 times the upper limit of normal. Patients were required to have been treated with other somatostatin analogs for at least 6 months prior to randomization. Note that the maximum dose for one of the active comparators approved for use in the United States was not used in this multinational trial; approximately 75% of the population in the comparator group was receiving this active comparator. The efficacy endpoint was the proportion of patients with a mean growth hormone level less than 2.5 mcg/L and normal IGF-1 levels at week 24. The primary analysis compared Signifor LAR 60 mg and 40 mg to continued pre-trial therapy (i.e., no change in treatment). The proportion of patients achieving biochemical control was 15.4% (p = 0.0006) and 20.0% (p < 0.0001) for Signifor LAR 40 mg and 60 mg, respectively, at 6 months.

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08/01/2013	Medical Policy Committee review
08/21/2013	Medical Policy Implementation Committee approval. New policy.
08/07/2014	Medical Policy Committee review
08/20/2014	Medical Policy Implementation Committee approval. No change to coverage.
04/02/2015	Medical Policy Committee review
04/20/2015	Medical Policy Implementation Committee approval. No change to coverage. Added a new product, Signifor LAR, to the policy and updated all sections to reflect changes.
04/07/2016	Medical Policy Committee review
04/20/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
04/06/2017	Medical Policy Committee review
04/19/2017	Medical Policy Implementation Committee approval. No change to coverage.
04/05/2018	Medical Policy Committee review
04/18/2018	Medical Policy Implementation Committee approval. No change to coverage.
04/04/2019	Medical Policy Committee review
04/24/2019	Medical Policy Implementation Committee approval. No change to coverage.
04/02/2020	Medical Policy Committee review
04/08/2020	Medical Policy Implementation Committee approval. Added new indication for Signifor LAR with criteria and relevant background information.
04/01/2021	Medical Policy Committee review
04/14/2021	Medical Policy Implementation Committee approval. No change to coverage.
04/07/2022	Medical Policy Committee review
04/13/2022	Medical Policy Implementation Committee approval. No change to coverage.
04/06/2023	Medical Policy Committee review
04/12/2023	Medical Policy Implementation Committee approval. No change to coverage.
04/04/2024	Medical Policy Committee review
04/10/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/03/2025	Medical Policy Committee review
04/09/2025	Medical Policy Implementation Committee approval. Updated Signifor LAR criteria to clarify that doses above the labeled maximum dose are considered investigational.

Next Scheduled Review Date: 04/2026

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Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J2502 Delete codes effective 05/01/2025: J3490, J3590
ICD-10 Diagnosis	All Related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.