Original Effective Date: 11/01/2018
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Last P&T Approval/Version: 07/26/2023
Next Review Due By: 07/2024
Policy Number: C15367-A

Signifor (pasireotide diaspartate)

PRODUCTS AFFECTED

Signifor (pasireotide diaspartate), Signifor LAR (pasireotide)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Cushing's Disease, Acromegaly

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review.

A. CUSHING'S DISEASE:
1. Diagnosis of Cushing's Disease
   AND
2. Documentation that pituitary surgery was not curative for the member OR member is not a candidate for pituitary surgery

AND

3. Documentation of baseline urinary or serum cortisol levels [DOCUMENTATION REQUIRED]
   AND
4. Prescriber attests to obtaining baseline Fasting serum glucose test, Oral glucose tolerance test, Hemoglobin A1c test (HbA1c), and anti-hyperglycemic medication doses or number of medications
   AND
5. Documentation of trial and failure, or labeled contraindication to Steroidogenesis inhibitor such as ketoconazole tablets, Metopirone (metyrapone capsules), or Lysodren (mitotane tablets) for the treatment of Cushing's syndrome
   AND
6. Prescriber attests that member does not have any of the following conditions: (a) cholelithiasis; (b) poorly controlled diabetes mellitus (HbA1c 8% or greater at time pasireotide is initiated); (c) severe liver impairment (Child-Pugh C); and (d) elevated QTc interval (500 milliseconds or greater)

B. ACROMEGALY (SIGNIFOR LAR ONLY):
   1. (a) Documentation of transsphenoidal surgery that was not curative (growth hormone level > 5ng/mL or IGF-1 level > 1.9 U/mL, males & >2.2 U/mL, females)
      OR
      (b) Documentation that member is not a surgical candidate due to high risk from medical comorbidities OR the tumor is largely unresectable
      AND
   2. Documentation of adequate trial/failure, intolerance, or contraindication to ALL guideline preferred drugs: (a) Three months of octreotide LAR or lanreotide LAR at a maximum tolerated dose, AND (b) cabergoline as a single agent or as an add-on to octreotide, lanreotide or pegvisoman
      AND
   3. Prescriber attests that member does not have any of the following conditions: (a) cholelithiasis; (b) poorly controlled diabetes mellitus (HbA1c 8% or greater at time pasireotide is initiated); (c) severe liver impairment (Child-Pugh C); and (d) elevated QTc interval (500 milliseconds or greater)

CONTINUATION OF THERAPY:

A. CUSHING'S DISEASE:
   1. Documentation member has had a decrease in urinary free cortisol or serum cortisol from baseline levels [DOCUMENTATION REQUIRED]
      AND
   2. Prescriber attests to an improvement in, or stabilization of, glucose tolerance (or improved glycemic control) as assessed by: Fasting serum glucose test, Oral glucose tolerance test, Hemoglobin A1c test (HbA1c) or Decrease in anti-hyperglycemic medication doses or number of medications
      AND
   3. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

B. ACROMEGALY:
   1. (a) Documentation of growth hormone level <5 ng/mL OR IGF-1 level <1.9 U/mL for males or <2.2 U/mL for females
      OR
      (b) Documentation of clinical improvement (e.g., reduction in tumor size, decreased headaches, improved cardiovascular or respiratory symptoms)
      AND
   2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

DURATION OF APPROVAL:

Initial authorization: 6 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with a board-certified endocrinologist or physician who specializes in the treatment of Cushing's disease [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:
18 years of age and older

QUANTITY:
SIGNIFOR: 0.9mg twice a day
SIGNIFOR LAR: Acromegaly: Maximum 60mg once every 4 weeks (28 days); Cushing's Disease: Maximum 40mg once every 4 weeks (28 days)

Maximum Quantity Limits –
SIGNIFOR: 60 ampules/30 days
SIGNIFOR LAR: 1 vial per 28 days

PLACE OF ADMINISTRATION:
Signifor (pasireotide diaspartate): The recommendation is that injectable medications in this policy will be for pharmacy or medical benefit coverage and the subcutaneous injectable products administered in a place of service that is a non-hospital facility-based location.

Signifor (pasireotide) LAR-- intramuscular: The recommendation is that injectable medications in this policy will be for pharmacy or medical benefit coverage and the intramuscular injectable products administered in a place of service that is a non-hospital facility-based location.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Subcutaneous, Intramuscular (LAR)

DRUG CLASS:
Somatostatic Agents

FDA-APPROVED USES:
Signifor (pasireotide diaspartate):- Indicated 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 (pasireotide): Indicated for the treatment of patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option, and for patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Cushing's disease
Cushing's disease is caused by pituitary adrenocorticotropic hormone-secreting tumors. First-line treatment is targeted at removing or destroying the tumor either by a transsphenoidal surgery or pituitary radiation therapy.

Cushing's syndrome
Cushing's syndrome is a manifestation of hypercortisolism, which can be secondary to a number of sources, chiefly, an ACTH-secreting pituitary tumor, a non-pituitary or "ectopic" ACTH-secreting tumor, or an adrenal adenoma or carcinoma that produces cortisol. Primary treatment is surgical, but when it is ineffective or cannot be performed, medical therapy is indicated.

Pasireotide is not recommended to treat other types of Cushing's Syndrome. The NCCN Guidelines Version 3.2018 - Neuroendocrine and Adrenal Tumors section Evaluation and Treatment of Cushing's Syndrome makes no mention for the use of pasireotide in Cushing's Syndrome caused by non- pituitary tumors. "Medical management of hypercortisolism is achieved with adrenostatic agents, including ketoconazole, mitotane, and/or mifepristone. Ketoconazole is most commonly used (at doses of 400-1200 mg/d) because of its easy availability and relatively tolerable toxicity profile. The data supporting use of other individual drugs for the management of Cushing's disease are limited.
Octreotide or lanreotide can also be considered for ectopic Cushing's syndrome if the tumor is somatostatin scintography-positive, although it may be less effective in controlling ectopic ACTH secretion than it is in other contexts. Bilateral adrenalectomy is generally recommended when medical management of ectopic Cushing's syndrome fails."

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of SIGNIFOR and SIGNIFOR LAR are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to pasireotide include: Severe hepatic impairment (i.e., Child-Pugh Class C).

Inconclusive or Non-Supportive Evidence

For neuroendocrine tumors, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. (RG B)
Pasireotide is a promising somatostatin analogue for the treatment of epithelial neoplasms that undergo neuroendocrine differentiation because it binds with high affinity to somatostatin receptors1, 2, 3, and 5. Pasireotide may have a role in the treatment of octreotide-resistant carcinoid tumors. In a phase III, multicenter, randomized controlled trial, 110 adults with metastatic neuroendocrine digestive tract tumors and inadequately controlled carcinoid symptoms were assigned to administration of either long-acting octreotide or long-acting pasireotide. After 6 months, the study was halted because carcinoid symptom control appeared to be comparable between the 2 therapies; however, progression-free survival was superior for those treated with pasireotide (12 months vs 7 months). A phase II open-label multicenter study of members with advanced neuroendocrine tumors and carcinoid syndrome whose symptoms were inadequately controlled by octreotide showed that, of 44 members evaluated for efficacy, 27% had complete or partial symptom control over 15 days of treatment with pasireotide. A phase II open-label study of 29 members with metastatic neuroendocrine tumors found that pasireotide administration was associated with median progression-free survival of 11 months, although 79% of members had significant hyperglycemia.
Case reports and series have suggested possible utility of pasireotide for insulinoma. Review articles have stated that further studies are needed to better define the role, if any, of pasireotide for therapy of neuroendocrine tumors.

For postoperative pancreatic fistula prevention, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. (RG B) A randomized study of 300 members undergoing pancreaticoduodenectomy or distal pancreatectomy assigned members to 7 days of pasireotide or placebo on the morning of surgery.

Pasireotide administration was associated with significantly lower occurrence of pancreatic leak, fistula, or abscess as compared with placebo (9% vs 21%, respectively); significant hyperglycemia and dose- limiting nausea were higher in those receiving pasireotide.

OTHER SPECIAL CONSIDERATIONS:

Recommended treatment for hypercortisolism (Cushing's Syndrome) (Nieman) – Recommended approaches to treatment include surgical removal of the pituitary corticotropin- secreting tumor, radiation therapy with or without medical therapy, or medical therapy when surgery and or radiation have not been effective, or adrenalectomy (surgical or medical with mitotane). Medical therapy may include adrenal enzyme blockers (ketoconazole and/or metopirone), adrenolytic agents (mitotane), pituitary agents (cabergoline, pasireotide), or glucocorticoid receptor antagonists (mifepristone).
Recommended medical treatments and dosing
Cabergoline - Cushing syndrome (off-label use): Oral: Initial: 0.5 mg once weekly or 1 mg weekly (given as 0.5 mg twice weekly); may increase by 0.5 to 1 mg weekly at 1- or 2-month intervals until complete and sustained normalization of urinary free cortisol (UFC) levels; maximum: 7 mg weekly (given as 1 mg once daily) (ES [Neiman 2015]; Godbout 2010; Pivonello 2009) Ketoconazole - Cushing syndrome (off-label use): Oral: Initial: 400 to 600 mg daily in 2 or 3 divided doses; may increase dose by 200 mg daily every 7 to 28 days up to a maximum of 1,200 mg daily in 2 or 3 divided doses; dosage range: 200 to 1,200 mg daily; mean effective dose in most studies: 600 to 800 mg daily in 2 divided doses (Castinetti 2014; ES [Nieman 2015]; Miller 1993)
Metopirone - Cushing syndrome (off-label use): Oral: Initial: 250 mg 4 times a day; dosage range: 500 mg to 6,000 mg daily in divided doses every 6 to 8 hours; maximum daily dose: 6,000 mg (Biller 2008; ES [Neiman 2015]) Mitotane - Cushing syndrome (off-label use): Oral: Initial: 500 mg 3 times daily (Biller 2008); may increase dose rapidly during the first 4 to 6 weeks up to a maximum of 4,000 mg to 8,000 mg per day in 3 divided doses, with the largest dose given in the evening to minimize discomfort (Baudry 2012; ES [Neiman 2015]; Schteingart 1980); after achieving control of cortisol secretion, gradually taper to the minimal dose required to maintain remission (Baudry 2012)

Mifepristone – Hyperglycemia in members with Cushing syndrome (Korlym): Oral: Initial dose: 300 mg once daily. Dose may be increased in 300 mg increments at intervals of ≥2 to 4 weeks based on tolerability and symptom control. Maximum dose: 1,200 mg once daily, not to exceed 20 mg/kg/day. If treatment is interrupted, reinitiate at 300 mg daily or a dose lower than the dose that caused the treatment to be stopped if interruption due to adverse reactions Dosage adjustment of Korlym in members already being treated with strong CYP3A inhibitor therapy: Initial: 300 mg once daily; may increase dose as clinically indicated (maximum dose: 600 mg/day). Dosage adjustment of Korlym in members who require initiation of strong CYP3A inhibitor therapy:
If current dose is 300 mg/day: No dosage adjustment necessary.
If current dose is 600 mg/day: Reduce dose to 300 mg once daily; if clinically indicated may increase dose to a maximum of 600 mg once daily.
If current dose is 900 or 1200 mg/day: Reduce dose to 600 mg once daily.
Note: Pasireotide is listed as a step therapy option in the Molina Clinical Policy for KORLYM-mifepristone for treating hyperglycemia secondary to Cushing's syndrome. Recommended treatment for Acromegaly (Melmed and Katznelson) –
Surgical removal of the pituitary growth hormone-secreting adenoma is recommended as first-line unless surgery is declined, the member is a poor surgical candidate, or it is anticipated that the adenoma is not fully resectable. Surgical debulking for macroadenomas close to the chiasm and followed by medical therapy. Medical therapy options include bromocriptine, octreotide, lanreotide, pegvisomant, or abergoline. In the setting of residual disease after surgery, medical therapy is indicated. Radiation therapy is recommended if medical therapy has been ineffective or not was tolerated.
Recommended medical treatments and dosing –

Octreotide – Acromegaly: SubQ, IV: Initial: 50 mcg 3 times/day; titrate to achieve growth hormone levels <5 ng/mL or IGF-I (somatomedin C) levels <1.9 units/mL in males and <2.2 units/mL in females. Usual effective dose: 100 mcg 3 times/day; range: 300 to 1,500 mcg/day. Doses above 300 mcg/day rarely result in additional benefit; if increased dose fails to provide additional benefit, the dose should be reduced. Note: Should be withdrawn yearly for a 4-week interval (8 weeks for depot injection) in members who have received irradiation. Resume if levels increase and signs/symptoms recur. IM depot injection: Members must be stabilized on subcutaneous octreotide for at least 2 weeks before switching to the long-acting depot. Upon switch: 20 mg IM intragluteally every 4 weeks for 3 months, then the dose may be modified based upon response.

Lanreotide – Acromegaly: SubQ: Initial dose: 90 mg once every 4 weeks for 3 months; after initial 3 months, continue monitoring and adjust dose as necessary based on clinical response of member, growth hormone (GH) levels, and/or insulin-like growth factor 1 (IGF-1) levels Pegvisomant – Acromegaly: SubQ: Initial loading dose: 40 mg; maintenance dose: 10 mg once daily following initial loading dose; doses may be adjusted by 5 mg increments or decrements in 4- to 6- week intervals based on IGF-I concentrations (maximum maintenance dose: 30 mg daily) Cabergoline – Acromegaly (off-label use): The initial dose of cabergoline should be 0.5 mg once a week or 0.25 mg twice a week. The dose should be increased, if necessary, to 1 mg twice a week. Higher doses are not likely to decrease GH further. The presence of hyperprolactinemia does not consistently predict GH and IGF- 1 response.
Bromocriptine - Acromegaly: Oral: Initial: 1.25 to 2.5 mg daily increasing by 1.25 to 2.5 mg daily as necessary every 3 to 7 days; usual dose: 20 to 30 mg daily (maximum: 100 mg/day) Endocrinology Society Guidelines –
5.1 We recommend medical therapy in a member with persistent disease following surgery. (1|QQQQ)
5.2 In a member with significant disease (i.e., with moderate-to-severe signs and symptoms of GH excess and without local mass effects), we suggest use of either a SRL or pegvisomant as the initial adjuvant medical therapy. (2|QQEE)
5.3 In a member with only modest elevations of serum IGF-1 and mild signs and symptoms of GH excess, we suggest a trial of a dopamine agonist, usually cabergoline, as the initial adjuvant medical therapy. (2|QQEE)

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
J3490	Unclassified drugs (Signifor, pasireotide diaspartate)
J2502	Injection, pasireotide long acting, 1 mg

AVAILABLE DOSAGE FORMS:
Signifor SOLN 0.3MG/ML
Signifor SOLN 0.6MG/ML
Signifor SOLN 0.9MG/ML
Signifor LAR SRER 10MG
Signifor LAR SRER 20MG
Signifor LAR SRER 30MG

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Diagnosis Required Medical Information Continuation of Therapy Duration of Approval Prescriber Requirements Age Restrictions Quantity FDA-Approved Uses Contraindications/Exclusions/Discontinuation Available Dosage Forms References	Q3 2023
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Place of Administration Coding/Billing Information	Q3 2022
Q2 2022 Established tracking in new format	Historical changes on file