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PHARMACY / MEDICAL POLICY – 5.01.548

Pharmacotherapy of Cushing's Disease and Acromegaly

Effective Date:	Mar. 1, 2025	RELATED POLICIES:
Last Revised:	Feb. 11, 2025	None
Replaces:	N/A	

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RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

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Introduction

The pituitary gland is about the size of a pea. It's just behind the bridge of the nose and is attached to the brain with nerve fibers. Despite its small size, it plays a very large role in controlling other glands throughout the body. For this reason, the pituitary is often called the master gland. The pituitary gland also produces other hormones, including ACTH and growth hormone. In Cushing's disease, a pituitary tumor causes the pituitary gland to produce too much ACTH. The ACTH then signals the adrenal glands to produce cortisol. Removing the tumor often allows the pituitary gland to return to producing normal levels of ACTH, which then lowers the cortisol levels. Acromegaly is a condition that results in enlargement of the hands, feet, and face. It's caused by the pituitary gland producing too much growth hormone. A noncancerous tumor on the pituitary gland is the most common cause of acromegaly. Specific drugs may be used to treat Cushing's disease or acromegaly when surgery or other medications didn't work or can't be used. This policy describes when specific drugs to treat these conditions may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity

Bynfezia Pen (octreotide) SC	**Bynfezia Pen (octreotide) may be considered medically necessary for the treatment of acromegaly when all the following criteria are met:**
	• The individual is aged 18 years or older
	AND
	• Has a documented diagnosis of acromegaly established by one of the following tests:
	  ○ Elevated serum insulin-like growth factor-1 (IGF-1)
	  ○ Inadequate suppression of growth hormone levels (> 1 ng/mL) two hours after oral glucose tolerance test
	AND
	• Had an inadequate response to surgery or radiation therapy or surgery and radiation therapy is not appropriate
	AND
	• Has tried generic octreotide first and had an inadequate response or intolerance to generic octreotide
	
	Bynfezia Pen (octreotide) may be considered medically necessary for the treatment of adult individuals with unresectable, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) when:
	• The individual is aged 18 years or older
	AND
	• Has tried generic octreotide first and had an inadequate response or intolerance to generic octreotide
	
	Note: A GEP-NET is a rare type of tumor that can grow in the pancreas or other areas of the gut, such as the stomach, small intestine, rectum, colon, or appendix.
	
	Bynfezia Pen (octreotide) may be considered medically necessary for the treatment of adults with carcinoid syndrome when:

Drug	Medical Necessity
	• The individual is aged 18 years or older **AND** • Has tried generic octreotide first and had an inadequate response or intolerance to generic octreotide **Bynfezia Pen (octreotide) may be considered medically necessary for the treatment of profuse watery diarrhea associated with vasoactive intestinal peptide tumors (VIPomas) in adults when:** • The individual is aged 18 years or older **AND** • Has tried generic octreotide first and had an inadequate response or intolerance to generic octreotide

Isturisa (osilodrostat) oral	**Isturisa (osilodrostat) may be considered medically necessary for treatment of Cushing's disease when all the following criteria are met:**
	• The individual is aged 18 years or older
	AND
	• Has a documented diagnosis of Cushing's disease established by any of the following tests:
	  ○ 24-hour urinary free-cortisol test
	  ○ Late-night salivary cortisol test
	  ○ Overnight low-dose dexamethasone suppression test
	  ○ Dexamethasone-corticotropin-releasing hormone (CRH) test
	AND
	• Has failed pituitary surgery, or is not a surgical candidate
	AND
	• Has tried generic ketoconazole first and had an inadequate response or intolerance to generic ketoconazole
	AND
	• The dose is limited to 60 mg per day (taken as 30 mg twice daily)

Korlym (mifepristone) oral	**Korlym (mifepristone) may be considered medically necessary for the treatment of hyperglycemia in individuals with Cushing's syndrome when all the following criteria are met:** • The individual is aged 18 years or older

Drug	Medical Necessity
	AND • Has type 2 diabetes mellitus or glucose intolerance **AND** • Hyperglycemia is secondary to Cushing's syndrome **AND** • Has failed pituitary surgery, or is not a surgical candidate **AND** • Has tried and had an inadequate response or intolerance to generic mifepristone

• **Brand lanreotide SC**
• **Somatuline Depot (lanreotide) SC**
	Brand lanreotide and Somatuline Depot (lanreotide) may be considered medically necessary for the treatment of acromegaly when all the following criteria are met:
	• The individual is aged 18 years or older
	AND
	• Has a documented diagnosis of acromegaly established by one of the following tests:
	  ○ Elevated serum insulin-like growth factor-1 (IGF-1)
	  ○ Inadequate suppression of growth hormone levels (> 1 ng/mL) two hours after oral glucose tolerance test
	AND
	• Had an inadequate response to surgery or radiation therapy or surgery and radiation therapy is not appropriate
	
	Brand lanreotide and Somatuline Depot (lanreotide) may be considered medically necessary for the treatment of adult individuals with unresectable, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs).
	
	Note: A GEP-NET is a rare type of tumor that can grow in the pancreas or other areas of the gut, such as the stomach, small intestine, rectum, colon, or appendix.
	
	Brand lanreotide and Somatuline Depot (lanreotide) may be considered medically necessary for the treatment of adults with carcinoid syndrome.

Drug	Medical Necessity
	Brand lanreotide and Somatuline Depot (lanreotide) may be considered medically necessary for the treatment of profuse watery diarrhea associated with vasoactive intestinal peptide tumors (VIPomas) in adults.
Generic mifepristone oral	**Generic mifepristone may be considered medically necessary for the treatment of hyperglycemia in individuals with Cushing's syndrome when all the following criteria are met:** • The individual is aged 18 years or older **AND** • Has type 2 diabetes mellitus or glucose intolerance **AND** • Hyperglycemia is secondary to Cushing's syndrome **AND** • Has failed pituitary surgery, or is not a surgical candidate

Mycapssa (octreotide) oral	**Mycapssa (octreotide) may be considered medically necessary for the treatment of acromegaly when all the following criteria are met:**
	• The individual is aged 18 years or older
	AND
	• Has a documented diagnosis of acromegaly established by one of the following tests:
	  ○ Elevated serum insulin-like growth factor-1 (IGF-1)
	  ○ Inadequate suppression of growth hormone levels (> 1 ng/mL) two hours after oral glucose tolerance test
	AND
	• Had an inadequate response to surgery or radiation therapy or surgery and radiation therapy is not appropriate
	AND
	• Has already responded to and tolerated octreotide or lanreotide
	AND
	• The dose prescribed is ≤ 80 mg daily

Octreotide, generic SC/IV	**Generic octreotide may be considered medically necessary for the treatment of acromegaly when all the following criteria are met:** • The individual is aged 18 years or older **AND**

Drug	Medical Necessity

	• Has a documented diagnosis of acromegaly established by one of the following tests:
	  ○ Elevated serum insulin-like growth factor-1 (IGF-1)
	  ○ Inadequate suppression of growth hormone levels (> 1 ng/mL) two hours after oral glucose tolerance test
	AND
	• Had an inadequate response to surgery or radiation therapy or surgery and radiation therapy is not appropriate
	
	Generic octreotide may be considered medically necessary for the treatment of adult individuals with unresectable, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs).
	
	Note: A GEP-NET is a rare type of tumor that can grow in the pancreas or other areas of the gut, such as the stomach, small intestine, rectum, colon, or appendix.
	
	Generic octreotide may be considered medically necessary for the treatment of adults with carcinoid syndrome.
	
	Generic octreotide may be considered medically necessary for the treatment of profuse watery diarrhea associated with vasoactive intestinal peptide tumors (VIPomas) in adults.

Recorlev (levoketoconazole) oral	**Recorlev (levoketoconazole) may be considered medically necessary for the treatment of endogenous hypercortisolemia (high cortisol) in individuals with Cushing's syndrome when the following criteria are met:**
	• The individual is aged 18 years or older
	AND
	• Has a documented diagnosis of Cushing's syndrome established by any of the following tests:
	  ○ 24-hour urinary free-cortisol test
	  ○ Late-night salivary cortisol test
	  ○ Overnight low-dose dexamethasone suppression test
	  ○ Dexamethasone-corticotropin-releasing hormone (CRH) test

Drug	Medical Necessity
	AND • Has failed surgery or is not a surgical candidate **AND** • Has tried generic ketoconazole first and had an inadequate response or intolerance to generic ketoconazole **AND** • The dose prescribed is ≤ 1,200 mg daily

Sandostatin (octreotide) SC/IV	**Sandostatin (octreotide) may be considered medically necessary for the treatment of acromegaly when all the following criteria are met:**
	• The individual is aged 18 years or older
	AND
	• Has a documented diagnosis of acromegaly established by one of the following tests:
	  ○ Elevated serum insulin-like growth factor-1 (IGF-1)
	  ○ Inadequate suppression of growth hormone levels (> 1 ng/mL) two hours after oral glucose tolerance test
	AND
	• Had an inadequate response to surgery or radiation therapy or surgery and radiation therapy is not appropriate
	AND
	• Has tried generic octreotide first and had an inadequate response or intolerance to generic octreotide
	
	Sandostatin (octreotide) may be considered medically necessary for the treatment of adult individuals with unresectable, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) when:
	• The individual is aged 18 years or older
	AND
	• Has tried generic octreotide first and had an inadequate response or intolerance to generic octreotide
	
	Note: A GEP-NET is a rare type of tumor that can grow in the pancreas or other areas of the gut, such as the stomach, small intestine, rectum, colon, or appendix.

Drug	Medical Necessity
	Sandostatin (octreotide) may be considered medically necessary for the treatment of adults with carcinoid syndrome when: • The individual is aged 18 years or older **AND** • Has tried generic octreotide first and had an inadequate response or intolerance to generic octreotide **Sandostatin (octreotide) may be considered medically necessary for the treatment of profuse watery diarrhea associated with vasoactive intestinal peptide tumors (VIPomas) when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has tried generic octreotide first and had an inadequate response or intolerance to generic octreotide

• **Generic long-acting octreotide depot IM**
• **Sandostatin LAR Depot (octreotide) IM**
	Generic long-acting octreotide depot and Sandostatin LAR Depot (octreotide) may be considered medically necessary for the treatment of acromegaly when all the following criteria are met:
	• The individual is aged 18 years or older
	AND
	• Has a documented diagnosis of acromegaly established by one of the following tests:
	  ○ Elevated serum insulin-like growth factor-1 (IGF-1)
	  ○ Inadequate suppression of growth hormone levels (> 1 ng/mL) two hours after oral glucose tolerance test
	AND
	• Had an inadequate response to surgery or radiation therapy or surgery and radiation therapy is not appropriate
	
	Generic long-acting octreotide depot and Sandostatin LAR Depot (octreotide) may be considered medically necessary for the treatment of adult individuals with unresectable, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

Drug	Medical Necessity
	Note: A GEP-NET is a rare type of tumor that can grow in the pancreas or other areas of the gut, such as the stomach, small intestine, rectum, colon, or appendix. **Generic long-acting octreotide depot and Sandostatin LAR Depot (octreotide) may be considered medically necessary for the treatment of adults with carcinoid syndrome.** **Generic long-acting octreotide depot and Sandostatin LAR Depot (octreotide) may be considered medically necessary for the treatment of profuse watery diarrhea associated with vasoactive intestinal peptide tumors (VIPomas) in adults.**

Signifor (pasireotide) SC	**Signifor (pasireotide) may be considered medically necessary for the treatment of Cushing's disease when all the following criteria are met:**
	• The individual is aged 18 years or older
	AND
	• Has a documented diagnosis of Cushing's disease established by any of the following tests:
	  ○ 24-hour urinary free-cortisol test
	  ○ Late-night salivary cortisol test
	  ○ Overnight low-dose dexamethasone suppression test
	  ○ Dexamethasone-corticotropin-releasing hormone (CRH) test
	AND
	• Has failed pituitary surgery, or is not a surgical candidate
	AND
	• Has tried generic ketoconazole first and had an inadequate response or intolerance to generic ketoconazole

Signifor LAR (pasireotide) IM	**Signifor LAR (pasireotide) may be considered medically necessary for the treatment of Cushing's disease when all the following criteria are met:** • The individual is aged 18 years or older **AND** • Has a documented diagnosis of Cushing's disease established by any of the following tests:

Drug	Medical Necessity
	○ 24-hour urinary free-cortisol test ○ Late-night salivary cortisol test ○ Overnight low-dose dexamethasone suppression test ○ Dexamethasone-corticotropin-releasing hormone (CRH) test **AND** • Has failed pituitary surgery, or is not a surgical candidate **AND** • Has tried generic ketoconazole first and had an inadequate response or intolerance to generic ketoconazole **Signifor LAR (pasireotide) may be considered medically necessary for the treatment of acromegaly when all the following criteria are met:** • The individual is aged 18 years or older **AND** • Has a documented diagnosis of acromegaly established by one of the following tests: ○ Elevated serum insulin-like growth factor-1 (IGF-1) ○ Inadequate suppression of growth hormone levels (> 1 ng/mL) two hours after oral glucose tolerance test **AND** • Had an inadequate response to surgery or radiation therapy or surgery and radiation therapy is not appropriate
Somavert (pegvisomant) SC	**Somavert (pegvisomant) may be considered medically necessary for the treatment of acromegaly when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has a documented diagnosis of acromegaly established by one of the following tests: ○ Elevated serum insulin-like growth factor-1 (IGF-1) ○ Inadequate suppression of growth hormone levels (> 1 ng/mL) two hours after oral glucose tolerance test **AND** • Had an inadequate response to surgery or radiation therapy or surgery and radiation therapy is not appropriate

Drug	Investigational
As listed	**All other uses of the medications listed in this policy are considered investigational.** **The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews for all drugs listed in the policy may be approved up to 12 months.** **All other reviews for all drugs listed in policy may be approved up to 12 months.**
Re-authorization criteria	**Non-formulary exception reviews and all other reviews for re-authorization of all drugs listed in policy may be approved up to 12 months as long as the drug-specific coverage criteria are met, and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.**

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis, relevant history, physical evaluation, and medication history

Coding

Code	Description
HCPCS	
J1930	Injection, lanreotide, (Somatuline Depot) 1mg

Code	Description
J2502	Injection, pasireotide (Signifor LAR) long acting, 1 mg
J2353	Injection, octreotide, depot form for intramuscular injection, (Sandostatin, Sandostatin LAR Depot, Bynfenzia Pen SC) 1 mg
J2354	Injection, octreotide, nondepot form for subcutaneous or intravenous injection, 25 mcg
J3490	Unclassified drugs (Use to report Lanreotide & Signifor)
J3590	Unclassified biologics (Use to report Lanreotide & Somavert)

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Benefit Application

Pharmacy Benefit

Isturisa (osilodrostat), Korlym (mifepristone), generic mifepristone, Mycapssa (octreotide), and Recorlev (levoketoconazole) are managed through the pharmacy benefit.

Medical / Pharmacy Benefit

Brand lanreotide, Bynfezia Pen (octreotide), generic octreotide, Sandostatin (octreotide), Signifor (pasireotide), Somatuline Depot (lanreotide), and Somavert (pegvisomant) are managed through both the pharmacy benefit and medical benefit.

Medical Benefit

Generic long-acting octreotide depot, Sandostatin LAR Depot (octreotide), and Signifor LAR (pasireotide) are managed through the medical benefit.

Evidence Review

Description

Cushing's syndrome is a classic constellation of symptoms caused by long-term exposure to excessively high levels of circulating corticosteroid hormones. The most common cause of Cushing's syndrome is exogenous glucocorticoid administration. However, symptoms may result from endogenous causes including ACTH-dependent and ACTH-independent Cushing's. ACTH-dependent disease makes up 80% of endogenous cases and is due to pituitary adenoma in 85% of cases and ectopic tumor secretion in 15% of cases. Cushing's disease refers to pituitary tumors that secrete ACTH.

Cushing's syndrome occurs in 1-3 individuals/million persons yearly with a prevalence of 40 cases/million persons, more frequently in females (3:1). Cushing's disease occurs more rarely than Cushing's syndrome and incidence peaks in the third to fourth decade.

The pituitary produces many hormones including TSH, growth hormone, ACTH, luteinizing hormone, follicle stimulating hormone, prolactin, and vasopressin. Pituitary adenomas can result in overproduction of ACTH, resulting in excess cortisol production from the adrenal glands. The hypothalamic-pituitary-adrenal (HPA) axis no longer retains its circadian rhythm and hypercortisolism occurs. Excess cortisol results in a wide constellation of symptoms including truncal obesity, hypertension, impaired glucose tolerance, dyslipidemia, increased risk of arterial thrombosis, psychiatric and cognitive disorders, osteoporosis, muscle and skin atrophy, impaired immune function, and hyperandrogenism. Quality of life (QOL) is frequently impaired. Morbidity and mortality is increased due to increased infections as well as cardiovascular disease resulting from increased cardiovascular risk factors such as hypertension, DM, and dyslipidemia. Estimated 5-year survival in untreated individuals is 50%. With treatment, chances of death remain 2-4 times greater than the average population.

Treatment Alternatives for Cushing's Disease

The preferred treatment for Cushing's disease is transsphenoidal surgery (TSS), which results in long-term remission rates of 60-90% with a recurrence risk of 26% within 10-years. Poor outcomes are seen with larger tumor size and repeat surgeries. Individuals with persistent disease after surgery can be treated with pituitary irradiation; however, months to years of treatment may be required before an effect is seen. Bilateral adrenalectomy may also be

performed; however, the pituitary adenoma remains in situ, negative feedback effects of cortisol are lost, and replacement gluco- and mineralocorticoids are required.

Medical therapy is used with unsuccessful surgery, individuals without an adenoma image on MRI, those undergoing radiotherapy which is not yet effective, individuals with severe complications of Cushing's, and individuals ineligible for surgery. Cushing's disease can be treated with drugs that target the adenoma, adrenal ACTH receptors or glucocorticoid receptors. Drugs which target the pituitary include the somatostatin analog, pasireotide, and the dopamine agonist cabergoline. Cabergoline is a dopamine agonist that targets dopamine receptor subtype 2 (D2R), which is expressed in 80% of ACTH-secreting pituitary adenomas and is useful when Cushing's disease is associated with urinary free cortisol (UFC) values up to twice normal.

Adrenal-targeting drugs include ketoconazole, metyrapone, and mitotane. These agents act by inhibiting steroid formation. Ketoconazole's actions are linked to inhibition of CYP 450 enzymes. Metyrapone decreases cortisol secretion, but usually not too normal, in individuals with Cushing's disease and is primarily used as adjunctive therapy in individuals with mild disease or after pituitary irradiation. Mifepristone is the only agent available which blocks glucocorticoid receptors, more specifically the cortisol and progesterone receptors. Mifepristone is FDA indicated for individuals with Cushing's syndrome with diabetes or glucose intolerance that require glycemic control.

Recorlev (levoketoconazole)

Levoketoconazole is an adrenal steroidogenesis inhibitor. It is the 2S,4R enantiomer of racemic ketoconazole and is the active enantiomer for steroidogenesis inhibition. Levoketoconazole inhibits enzymes involved in steroidogenesis including CYP11A1, CYP17A1, CYP11B1, and CYP11B2 (see Figure 2). In vitro studies indicate levoketoconazole is approximately twice as potent than ketoconazole in steroidogenesis inhibition. Levoketoconazole differs from ketoconazole in that it is 12-fold less potent than ketoconazole towards inhibition of liver enzymes. However, based on pharmacologic studies, levoketoconazole and ketoconazole appear to have the same effects on lipid metabolism and antifungal activity. Also, the impact of both drugs on CYP enzymes appears similar; therefore, drug interactions are expected to be similar with both drugs.

Levoketoconazole has been studied in two small, fair quality, Phase 3 trials (SONICS and LOGICS). The SONICS trial was a multicenter, single-arm, open-label, nonrandomized, Phase 3 trial which included 94 adults with a confirmed diagnosis of endogenous CS with mUFC ≥1.5 times the ULN and either an abnormal dexamethasone suppression test or an abnormal late

night salivary cortisol. Those with QT prolongation, abnormal electrocardiogram (ECG), hepatic disease, uncontrolled hypertension, or poorly controlled DM were excluded. The trial included a 2-21 week dose titration phase followed by a 6 month maintenance phase, and a 6 month extension. Individuals began levoketoconazole at 150 mg po BID which was then titrated to response with a max of 600 mg po BID. Those with an established therapeutic dose (defined as mUFC <ULN or max dose levoketoconazole with a clinically meaningful partial response) were eligible to continue to the maintenance phase. A total of 94 individuals began the titration phase; however, 17/94 (18%) discontinued the study, leaving 77 individuals who entered the maintenance phase; an additional 17% of individuals discontinued the study during the maintenance phase. The primary endpoint was complete response in the maintenance phase, defined as mUFC below the ULN during the maintenance phase without a dose change. At the end of the maintenance phase, levoketoconazole met the primary endpoint; 30.9% of individuals were considered responders ($p=0.0154$ vs null hypothesis of ≤20% responders). The per protocol analysis of the same endpoint found 45% of individuals were considered responders ($p=0.0001$). Additionally, 36.1% of individuals met criteria for mUFC normalization regardless of dose change and 45.7% had normalized mUFC or ≥50% decrease in mUFC. Significant improvement was noted in comorbidity biomarkers for fasting blood glucose (FBG), hemoglobin A1c (HbA1c), total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and body weight ($p<0.0001$ for all comparisons); however, no significant change was noted in systolic blood pressure (SBP), diastolic blood pressure (DBP), or C-reactive protein (CRP). Significant improvement also occurred in clinical signs and symptoms including hirsutism in women ($p=0.0008$), acne ($p=0.0063$), and peripheral edema ($p=0.03$). The CushingQoL score significantly improved ($p<0.0001$) at both assessment points (3 and 6 months), exceeding the MID at the 6-month mark only. The mean change in Beck Depression Inventory-II (BDI-II) score significantly improved at 6 months (-4.3, $p=0.0043$) and exceeded the minimum important difference (MID). Lastly, individuals completing the maintenance phase were eligible to enter the extended phase.1 A total of 60 individuals entered the extension phase of the trial with 55.1% and 40.9% of individuals achieving mUFC ≤ULN at Month 9 and 12, respectively. Improvements in hirsutism ($p<0.0001$), CushingQoL (13.2, $p<0.0001$), and BDI-II (-5.4%, $p=0.0016$) were maintained during the extension phase; however, changes in acne and peripheral edema were no longer significant.

The LOGICS trial was a multicenter, double-blind, placebo-controlled, randomized, Phase 3 withdrawal trial which included 84 individuals who either completed the SONICS trial (12 individuals) or met the SONICS inclusion criteria. Individuals entered an open-label, 14-19 week dose titration phase for levoketoconazole (150-600 mg po BID). Those with a stable dose of levoketoconazole and normalized mUFC for 4 weeks entered the 8-week, double-blind, placebo-controlled, randomized withdrawal period where individuals were randomized to

levoketoconazole or placebo. Individuals who completed the randomized withdrawal period continued on to restoration period without a change in treatment unless rescue criteria were met. Rescue criteria included 1) relapse of hypercortisolemia, 2) partial loss of cortisol response and deterioration in ≥1 biomarker, 3) clinical deterioration and deterioration in ≥2 biomarkers without loss of cortisol response. The primary endpoint was the proportion of individuals with loss of mUFC response during the randomized withdrawal period where loss of response was defined as mUFC ≥1.5 times the ULN or >40% increase in mUFC above baseline. Overall, 84 individuals entered the titration phase of the trial and 44 continued on to the withdrawal period, resulting in a 47% discontinuation rate. The primary outcome of loss of response during the withdrawal period occurred 40.9% of individuals with levoketoconazole compared to 95.5% with placebo (p=0.0002). At the end of the withdrawal period, 50% of individuals on levoketoconazole and 4.5% of individuals on placebo had normalized mUFC (p=0.0015). Additionally, total cholesterol and LDL significantly increased in the placebo group compared to levoketoconazole during the withdrawal phase (p=0.0004 and 0.0056, respectively). No change was seen in FBC, HbA1c or CRP. The median time to rescue for individuals randomized to placebo was 22 days.

Serious AEs occurred in 15% of individuals in the SONICS trial; of these, four were considered probably or definitely related to treatment (increased LFTs [one individual], QT prolongation [two individuals], and adrenal insufficiency [one individual]). Additionally, serious adverse events (SAEs) occurred in 16% of individuals in the LOGICS trial; those considered drug related were hepatoxicity (three individuals), gastroenteritis (one individual), and hypokalemia (one individual). Common AEs in the Phase 3 trials were nausea (29%-32%), headache (21%-28%), hypokalemia (28%), peripheral edema (19%), hypertension (17%-19%), fatigue (16%), and diarrhea (15%), increased ALT (15%).1-3 Most AEs were of mild to moderate intensity.

Treatment Alternatives for Acromegaly

The goals of therapy are to lower the serum insulin-like growth factor 1 (IGF-1), and serum growth hormone (GH) concentrations. For an individual who has microadenoma/macroadenoma, which is resectable, transsphenoidal surgery is preferred. If adenoma is not resectable (or individual is not a candidate for surgery), then the preferred treatment would be a long-acting somatostatin analog, such as octreotide or lanreotide. If somatostatin analog treatment with or without cabergoline is not effective, adding pegvisomant may be necessary (note this approach has NOT been approved by the FDA). If adenoma size keeps increasing despite the use of somatostatin analog with pegvisomant, radiotherapy or repeat surgery may be warranted.

Signifor LAR (pasireotide)

Signifor LAR (pasireotide) is a cyclohexapeptide somatostatin analogue. Pasireotide binds to and activates somatostatin receptors. This results in the inhibition of ACTH, leading to decreased cortisol secretion. Of the five somatostatin receptors (hsst1-5), the somatostatin receptor hsst5 is overexpressed on corticotroph adenomas in individuals with Cushing's disease. Pasireotide preferentially binds to hsst1,2,3,5 and has 40-fold higher affinity for hsst5 than octreotide. The dose of pasireotide is titrated based on response and tolerability. Treatment response is defined as a clinically meaningful decrease in 24-hour UFC and/or improved signs and symptoms of Cushing's disease. The maximum decrease in UFC typically occurs after 2 months of therapy. If dose reductions are necessary due to AEs, reductions of 0.3 mg are recommended. Caution is recommended with drugs which prolong the QT interval. Cyclosporine levels may decrease with pasireotide and a dose increase of cyclosporine may be required to maintain cyclosporine levels. Bromocriptine levels may increase with pasireotide and a dose reduction of bromocriptine may be necessary.

Pasireotide has been studied in a phase II and a phase III trial for Cushing's disease. Both trials assessed changes in urinary free cortisol (UFC) level, a biomarker, rather than clinical symptoms of Cushing's disease. The phase III trial randomized 162 individuals to pasireotide 600 mcg or 900 mcg subcutaneously twice daily for 6 months. No comparator arm was included. Pasireotide was considered efficacious based on the predefined study efficacy criteria of >15% responder rate which was achieved with both doses of pasireotide (15% 600 mcg, 26% 900 mcg); however, the study was not powered to compare study arms. Changes in clinical symptoms of Cushing's disease were considered secondary endpoints. Significant changes were noted in weight (-6.7 kg, $p<0.001$) as well as systolic (-6 mm Hg, $p=0.03$) and diastolic blood pressure (-3.7 mm Hg, $p=0.03$). However, changes in antihypertensive medications were allowed during the trial and may have influenced the latter results. Lastly, the open-label, 15-day, phase II trial in 29 individuals found 17% of individuals normalized UFC with pasireotide 600 mcg. None of the pasireotide trials were of long enough duration to assess changes in mortality. Trial sizes are small due to the limited number of individuals with Cushing's disease. Lastly, none of the trials included a comparator arm. Use of a placebo arm was considered unethical, and, at the time of trial design, no other medications were FDA approved for Cushing's. Since that time, mifepristone (Korlym) has received approval for the control of hyperglycemia due to hypercortisolism in individuals with Cushing's syndrome with diabetes mellitus (DM) or glucose intolerance that failed or are not eligible for surgery.

Pasireotide (Signifor LAR) in the setting of acromegaly was approved based on two multicenter Phase III studies, C2305 and C2402, which respectively examined medically naïve individuals, who have had prior surgery, or for whom surgery was not an option, and individuals with acromegaly inadequately controlled on first generation somatostatin analogs. In both studies, higher rates of full biochemical control (defined as mean GH level <2.5mcg/L and normal IGF-1 levels) were achieved with Signifor LAR compared to a first generation somatostatin analog. A crossover extension to C2305 showed 17.3% (14/81) of individuals that did not reach biochemical control (GH still ≥ 2.5 mcg/L and IGF-1 still above normal) were able to achieve control of both GH and IGF-1 after switching to pasireotide. Zero out of thirty-eight individuals switching to octreotide achieved control. Pasireotide individuals had more hyperglycemic adverse effects (27.2% vs. 13.2%)

A 12-month, multicenter, double-blind RCT superiority study (n=358) determined that pasireotide was superior to octreotide in acromegaly individuals. Individuals studied were medically naïve. Individuals could have had a prior pituitary surgery, or otherwise refused surgery or had surgery contraindicated. The primary outcome was growth hormone falling under 2.5 µg/L as well as normal IGF-1 at month 12. Significantly more pasireotide LAR individuals achieved control than octreotide LAR individuals (31.3% vs 19.2%, p value = 0.007). Pasireotide individuals had a significantly higher rate of hyperglycemia (57.3% vs. 21.7). Acromegaly guidelines available at this time do not recommend pasireotide as a first line option due to a shorter history of efficacy and safety vs. other somatostatin analogs.

An open-label, multicenter, single-arm, expanded-treatment study (2017) evaluated the safety profile of Signifor LAR administered intramuscularly every 28 days in 44 adult individuals with active acromegaly for an average of 37.6 weeks. There were 25 grade ≥3 treatment-emergent adverse events reported in 11 individuals (25%), with 27.3% of those experiencing grade ≥3 hyperglycemia. There were 21 individuals (48%) who needed to initiate antidiabetic medications. Overall, hyperglycemia-related adverse events were most common, but they were generally manageable.

Somavert (pegvisomant)

Somavert selectively binds to growth hormone (GH) receptors on cell surfaces, where it blocks the binding of endogenous GH, and thus interferes with GH signal transduction. Inhibition of GH action results in decreased serum concentrations of insulin-like growth factor-I (IGF-I), as well as other GH-responsive serum proteins, including IGF binding protein-3 (IGFBP-3), and the acid-labile subunit (ALS).

Somavert has been studied in a randomized, double-blinded, placebo-controlled, 12-week study evaluating the safety and efficacy of Somavert 10 mg, 15 mg, or 20 mg in individuals with acromegaly. Following withdrawal from previous medical therapy, the 80 individuals randomized to treatment with Somavert received a subcutaneous (SC) loading dose, followed by 10, 15, or 20 mg/day SC. The three groups that received Somavert showed dose-dependent reductions in serum levels of IGF-I, free IGF-I, IGFBP-3, and ALS compared with placebo at all post-baseline visits. After 12 weeks of treatment, the mean serum IGF-I concentration decreased from baseline by 4.0%, 26.7%, 50.1%, and 62.5% in the placebo, 10 mg, 15 mg, and 20 mg arms, respectively. This difference was significant in all treatment arms compared to placebo. Normalization of serum IGF-I concentrations were achieved in 10%, 54%, 81%, and 89% of subjects in the placebo, 10 mg, 15 mg, and 20 mg arms, respectively. In individuals treated with Somavert 15 mg or 20 mg daily, there were significant decreases in ring size, soft-tissue swelling, the degree of excessive perspiration, and fatigue.

Somavert is contraindicated in individuals with a history of hypersensitivity to any of its components.

Korlym (mifepristone)

Korlym (mifepristone) is a glucocorticoid receptor-II (GR-II) antagonist that has high affinity for the GR-II receptor but little affinity for the GR-I (mineralocorticoid) receptor. It also blocks progesterone receptors. There appears to be little or no affinity for estrogen, muscarinic, histaminic, or monoamine receptors. The approval of mifepristone for the treatment of hyperglycemia due to hypercortisolism secondary to Cushing's syndrome was primarily based on results from one 24 week, phase III, multicenter, open-label, single arm study (Study of the Efficacy and Safety of Mifepristone in the treatment of Endogenous Cushing's Syndrome [SEISMIC]). Results showed significant clinical, metabolic, and health-related quality of life improvements in 50 individuals, the majority of whom had failed multiple therapeutic modalities. While the strength of evidence of efficacy is weak, the authors and FDA approval suggests benefits outweigh risks for this orphan indication with unmet need. An extension study for SEISMIC participants examining long-term safety and efficacy is ongoing. Numerous case reports and small retrospective studies of mifepristone use for hypercortisolism are also available in the literature. The majority of individuals in these reports had failed multiple therapeutic modalities, including surgery, prior to use of mifepristone. Doses of the agent ranged from 200 to 2000 mg/day for up to 2 years. Most publications reported improvements in the clinical manifestations of the condition. Mifepristone has a large potential for drug-drug

interactions via the CYP3A4, CYP2C8 and CYP2C9 pathways. Its efficacy data remains limited, and long-term data is unavailable.

Summary

Interpretation of available data on the efficacy and safety of most drugs currently used in the treatment of Cushing's disease is difficult. Published study designs have varied considerably with only a few small prospective, randomized, controlled studies available. Furthermore, there is significant variation in clinical outcomes or biochemical parameters used as the primary endpoint (e.g., urine free cortisol [UFC], serum and salivary cortisol, and plasma ACTH), and reference values derived from a sufficiently large population are largely lacking, especially for some of the more recently developed assays. Unfortunately, criteria for defining a clear and effective response to treatment, and for disease control, are insufficient at this time.

Sandostatin LAR Depot (octreotide)

Octreotide exerts pharmacologic actions similar to the natural hormone, somatostatin. It is an even more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. For the treatment of acromegaly, the clinical trials of Sandostatin LAR Depot were performed in individuals who had been receiving octreotide injection for a period of weeks to as long as 10 years. The acromegaly studies with Sandostatin LAR Depot were performed in individuals who achieved GH levels of < 10 ng/mL (and, in most cases < 5 ng/mL) while on subcutaneous octreotide injection. However, some individuals enrolled were partial responders to subcutaneous octreotide injection, i.e., GH levels were reduced by > 50% on subcutaneous octreotide injection compared to the untreated state, although not suppressed to < 5 ng/mL.

Sandostatin LAR Depot was evaluated in three clinical trials in acromegalic individuals. In 2 of the clinical trials, a total of 101 individuals were entered who had, in most cases, achieved a GH level < 5 ng/mL on octreotide injection given in doses of 100 mcg or 200 mcg three times daily. Most individuals were switched to 20 mg or 30 mg doses of Sandostatin LAR Depot given once every 4 weeks for up to 27 to 28 injections. A few individuals received doses of 10 mg and a few required doses of 40 mg. Growth hormone and IGF-1 levels were at least as well controlled with Sandostatin LAR Depot as they had been on octreotide injection and this level of control remained for the entire duration of the trials.

A third trial was a 12-month study that enrolled 151 individuals who had a GH level < 10 ng/mL after treatment with octreotide injection (most had levels < 5 ng/mL). The starting dose of

Sandostatin LAR Depot was 20 mg every 4 weeks for 3 doses. Thereafter, individuals received 10 mg, 20 mg, or 30 mg every 4 weeks, depending upon the degree of GH suppression. GH and IGF-1 were at least as well controlled on Sandostatin LAR Depot as they had been on octreotide injection.

For the 88 individuals who received 27 to 28 injections in the first two trials, a mean GH level of < 2.5 ng/mL was observed in 47% receiving Sandostatin LAR Depot. Over the course of the trials, 42% of individuals maintained mean growth hormone levels of < 2.5 ng/mL and mean normal IGF-1 levels.

For the 122 individuals who received all 12 injections in the third trial, a mean GH level of < 2.5 ng/mL was observed in 66% receiving Sandostatin LAR Depot. Over the course of the trial, 57% of individuals maintained mean growth hormone levels of < 2.5 ng/mL and mean normal IGF-1 levels.

In all 3 trials, GH, IGF-1, and clinical symptoms were similarly controlled on Sandostatin LAR Depot as they had been on octreotide injection. Of the 25 individuals who completed the trials and were partial responders to octreotide injection (GH > 5.0 ng/mL but reduced by > 50% relative to untreated levels), 1 individual (4%) responded to Sandostatin LAR Depot with a reduction of GH to < 2.5 ng/mL and 8 individuals (32%) responded with a reduction of GH to < 5.0 ng/mL.

Somatuline Depot (lanreotide)

Lanreotide is an octapeptide analog of natural somatostatin. The mechanism of action of lanreotide is believed to be similar to that of natural somatostatin. Lanreotide has a high affinity for human somatostatin receptors (SSTR) 2 and 5 and a reduced binding affinity for human SSTR1, 3, and 4. Activity at human SSTR2 and 5 is the primary mechanism believed responsible for GH inhibition. Like somatostatin, lanreotide is an inhibitor of various endocrine, neuroendocrine, exocrine, and paracrine functions.

The effect of Somatuline Depot on reducing GH and IGF-levels and control of symptoms in individuals with acromegaly was studied in 2 long-term, multiple-dose, randomized, multicenter studies.

Study 1 was a 1-year study that included a 4-week, double-blind, placebo-controlled phase; a 16-week single-blind, fixed-dose phase; and a 32-week, open-label, dose-titration phase. Individuals with active acromegaly, based on biochemical tests and medical history, entered a

12-week washout period if there was previous treatment with a somatostatin analog or a dopaminergic agonist.

Upon entry, individuals were randomly allocated to receive a single, deep subcutaneous injection of Somatuline Depot 60, 90, or 120 mg or placebo. Four weeks later, individuals entered a fixed-dose phase where they received 4 injections of Somatuline Depot followed by a dose-titration phase of 8 injections for a total of 13 injections over 52 weeks (including the placebo phase). Injections were given at 4-week intervals. During the dose-titration phase of the study, the dose was titrated twice (every fourth injection), as needed, according to individual GH and IGF-1 levels.

A total of 108 individuals (51 males, 57 females) were enrolled in the initial placebo-controlled phase of the study. Half (54/108) of the individuals had never been treated with a somatostatin analog or dopamine agonist or had stopped treatment for at least 3 months prior to their participation in the study and were required to have a mean GH level greater than 5 ng/mL at their first visit. The other half of the individuals had received prior treatment with a somatostatin analog or a dopamine agonist before study entry and at study entry were required to have a mean GH concentration greater than 3 ng/mL and at least a 100% increase in mean GH concentration after washout of medication.

In the double-blind phase of Study 1, a total of 52 (63%) of the 83 lanreotide-treated individuals had a greater than 50% decrease in mean GH from baseline to Week 4, including 52%, 44%, and 90% of individuals in the 60, 90, and 120 mg groups, respectively, compared to placebo (0%, 0/25). In the fixed-dose phase at Week 16, 72% of all 107 lanreotide-treated individuals had a decrease from baseline in mean GH of greater than 50%, including 68% (23/34), 64% (23/36), and 84% (31/37) of individuals in the 60, 90, and 120 mg lanreotide treatment groups, respectively. Efficacy achieved in the first 16 weeks was maintained for the duration of the study.

Study 2 was a 48-week, open-label, uncontrolled, multicenter study that enrolled individuals who had an IGF-1 concentration 1.3 times or greater than the upper limit of the normal age-adjusted range. Individuals receiving treatment with a somatostatin analog (other than Somatuline Depot) or a dopaminergic agonist had to attain this IGF-1 concentration after a washout period of up to 3 months.

Individuals were initially enrolled in a 4-month, fixed-dose phase where they received 4 deep subcutaneous injections of Somatuline Depot 90 mg, at 4-week intervals. Individuals then entered a dose-titration phase where the dose of Somatuline Depot was adjusted based on GH and IGF-1 levels at the beginning of the dose-titration phase and, if necessary, again after another 4 injections. Individuals titrated up to the maximum dose (120 mg) were not allowed to titrate down again.

After 48 weeks of treatment with Somatuline Depot at 4-week intervals, 43% (27/63) of the acromegalic individuals in this study achieved normal age-adjusted IGF-1 concentrations. Mean IGF-1 concentrations after treatment completion were 1.3 ± 0.7 times the upper limit of normal compared to 2.5 ± 1.1 times the upper limit of normal at baseline.

The reduction in IGF-1 concentrations over time correlated with a corresponding marked decrease in mean GH concentrations. The proportion of individuals with mean GH concentrations less than 2.5 ng/mL increased significantly from 35% to 77% after the fixed-dose phase and 85% at the end of the study. At the end of treatment, 24/63 (38%) of individuals had both normal IGF-1 concentrations and a GH concentration of less than or equal to 2.5 ng/mL and 17/63 individuals (27%) had both normal IGF-1 concentrations and a GH concentration of less than 1 ng/mL.

2014 Update

Updated per literature search from July 1, 2013, through October 31, 2014. No changes required.

2015 Update

Updated per the package insert on June 2, 2015. Purpose of the update is to include a recently added indication (12/14) for the use of pasireotide (Signifor LAR) in the setting of acromegaly.

2016 Update

Updated the rationale section for pasireotide and mifepristone per the literature search conducted from July 1, 2016, through December 7, 2016. No policy criteria changes were made with this review. References updated.

2017 Update

A literature search was conducted from December 1, 2016 through November 2, 2017. No policy criteria changes were made with this review. References updated.

2018 Update

A literature search was conducted from November 1, 2017 through October 31, 2018. No policy criteria changes were made with this review. References updated.

2019 Update

A literature search was conducted from November 1, 2018 through August 28, 2019. Reviewed all FDA-approved indications for drugs in policy and made additional updates to Signifor LAR (pasireotide) to clarify Signifor LAR is indicated for both acromegaly and Cushing's disease. Policy criteria rewritten and revised for Korlym (mifepristone) to reflect prescribing information. Added policy criteria for Somavert (pegvisomant). References updated.

2020 Update

Reviewed prescribing information for all drugs in policy and conducted a literature search from November 1, 2019 through November 30, 2020. No new information was identified and policy statements remain unchanged.

2021 Update

Added coverage criteria for the octreotide products (Bynfezia Pen, generic octreotide, Mycapssa, Sandostatin, and Sandostatin LAR Depot) for the treatment of acromegaly. Included coverage for adults with gastroenteropancreatic neuroendocrine tumors (GEP-NETs), carcinoid syndrome, and the treatment of profuse watery diarrhea associated with VIPomas. Added coverage criteria for Somatuline Depot (lanreotide) for the treatment of acromegaly, GEP-NETs, carcinoid syndrome, and the treatment of profuse watery diarrhea associated with VIPomas. Reviewed prescribing information for Korlym (mifepristone), Signifor (pasireotide), Signifor LAR (pasireotide), and Somavert (pegvisomant) and conducted a literature search on the management of Cushing's disease. No new information was identified and policy statements remain unchanged for management of Cushing's disease.

2022 Update

Reviewed prescribing information for all drugs in policy and the medical management of Cushing's syndrome. Updated references and added Recorlev (levoketoconazole) clinical trial information. Added coverage criteria for Recorlev (levoketoconazole) for treatment of endogenous hypercortisolemia (high cortisol) in individuals with Cushing's syndrome. Updated criteria for Isturisa (osilodrostat), Signifor (pasireotide), and Signifor LAR (pasireotide) for the treatment of Cushing's disease to require the individual has tried generic ketoconazole first and had an inadequate response or intolerance to generic ketoconazole. The requirement to use cabergoline AND Metopirone (metyrapone) or Lysodren (mitotane) was removed. Added a note on definition of a gastroenteropancreatic neuroendocrine tumor (GEP-NET).

2023 Update

Reviewed prescribing information for all drugs in policy and no new evidence found that could change the policy statements.

2024 Update

Reviewed prescribing information for all drugs in policy. Added coverage criteria for generic mifepristone. Updated coverage criteria for Korlym (mifepristone) to require trial and failure with generic mifepristone.

2025 Update

Reviewed prescribing information for all drugs in policy and no new evidence was identified that could change the policy statements. Added generic long-acting octreotide depot with the same coverage criteria as Sandostatin LAR Depot (octreotide). Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.

References

1. Van der Pas R, de Herder WW, Hofland LJ, Feelders RA. Recent developments in drug therapy for Cushing's disease. Drugs 2013 June 5 [Epub ahead of print].
2. Castinetti F, Moragne I, Conte-Devolx B, and Brue T. Cushing's disease. Orpahnet J Rare Dis 2012;7:41-50.
3. Hammer GD, Tyrell JB, Lamborn KR, et al. Transsphenoidal microsurgery for Cushing's disease: initial outcome and long-term results. J Clin Endocrinol Metab 2004;89(12):6348-6357.
4. Dekkers OM, Biermasz NR, Pereira AM, et al. Mortality in patients treated for Cushing's disease is increased, compared with patients treated for nonfunctioning pituitary macroadenoma. J Clin Endocrinol Metab 2007;92(3):976-981.
5. Fleseriu M, Petersenn S. Medical management of Cushing's disease: what is the future? Pituitary 2012;15:330-341.
6. Niemann LK, Biller BM, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2008;93:1526-1540.
7. Biller BM, Grossman AB, Stewart PM, et al. Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab 2008;93:2454-2462.
8. Colao A, Petersenn S, Newell-Price J, et al. A 12-month phase 3 study of pasireotide in Cushing's disease. N Engl J Med 2012;366:914-924.
9. Boscaro M, Ludlam WH, Atkinson B, et al. Treatment of pituitary-dependent Cushing's disease with the multireceptor ligand somatostatin analog pasireotide (SOM230): a multicenter, phase II trial. J Clin Endocrinol Metab 2009;94:115-122.
10. Feelders RA, de Bruin C, Pereira AM, et al. Pasireotide alone or with cabergoline and ketoconazole in Cushing's disease. N Engl J Med 2010;362(19):1846-1847.
11. Biller BMK, et al. Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab 2008; 93(7):2454–2462.
12. Fleseriu M, et al; SEISMIC Study Investigators. Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing's syndrome. J Clin Endocrinol Metab 2012;97:2039-2049.
13. Blasey CM, et al. A multisite trial of mifepristone for the treatment of psychotic depression: a site-by-treatment interaction. Contemp Clin Trial 2009;284-288.
14. Blasey CM, et al. Efficacy and safety of mifepristone for the treatment of psychotic depression. J Clin Psychopharmacol 2011;31:436-440.
15. Patil CG, et al. Late recurrences of Cushing's disease after initial successful transsphenoidal surgery. J Clin Endocrinol Metab 2008; 93(2):358–362.
16. Colao A, et al. Pasireotide versus octreotide in acromegaly: a head-to-head superiority study. J Clin Endocrinol Metab. 2014; 99(3):791-9
17. Katznelson L, et al. Acromegaly: an endocrine society clinical practice guideline. J Endocrinol Metab. 2014; 99(11): 3933-3951
18. Bronstein MD, et al. Switching patients with acromegaly from octreotide to pasireotide improves biochemical control: crossover extension to a randomized, double-blind, phase III study. BMC Endocr Disord. 2016: 16(16). doi: 10.1186/s12902-016-0096-8
19. Wildemberg LE and Gadelha MR. Pasireotide for the treatment of acromegaly. Expert Opinion on Pharmacotherapy. 2016. 4:579-588
20. Fleseriu M, Rusch E, Geer EB, et al. Safety and tolerability of pasireotide long-acting release in acromegaly-results from the acromegaly, open-label, multicenter, safety monitoring program for treating patients who have a need to receive medical therapy (ACCESS) study. Endocrine. 2017;55(1):247-55.

21. Muhammad A, van der Lely AJ, Delhanty PJD, et al. Efficacy and Safety of Switching to Pasireotide in Patients With Acromegaly Controlled With Pegvisomant and First-Generation Somatostatin Analogues (PAPE Study). J Clin Endocrinol Metab. 2018 Feb 1;103(2):586-595.
22. Lacroix A, Gu F, Gallardo W, Pivonello R,, et al. Efficacy and safety of once-monthly pasireotide in Cushing's disease: a 12 month clinical trial. Lancet Diabetes Endocrinol. 2018 Jan;6(1):17-26. doi: 10.1016/S2213-8587(17)30326-1. Epub 2017 Oct 12.
23. Lynnette N , Beverly B, James F, M Hassan M, et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015 Aug;100(8):2807-31. doi: 10.1210/jc.2015-1818. Epub 2015 Jul 29.
24. Fleseriu M, Pivonello R, Elenkova A, et al. Efficacy and safety of levoketoconazole in the treatment of endogenous Cushing's syndrome (SONICS): a phase 3, multicentre, open-label, single-arm trial. Lancet Diabetes Endocrinol. 2019;7(11):855-865.
25. Zacharieva S, Pivonello R, Elenkova A, et al. Safety and efficacy of levoketoconazole in the treatment of endogenous Cushing's syndrome (LOGICS): results from a double-blind, placebo-controlled, randomized withdrawal study. J Endocrine Soc. 2021;5(Supple_1):A526.
26. Geer EB, Salvatori R, Elenkova A, et al. Levoketoconazole improves clinical signs and symptoms and patient-reported outcomes in patients with Cushing's syndrome. Pituitary. 2021;24:104-115.
27. Pivonello R, Ferrigno R, De Martino MC, et al. Medical treatment of Cushing's disease: an overview of the current and recent clinical trials. Front Endocrinol. 2020;11:648.
28. Nieman L, Lacroix A, Martin K. Medical therapy of hypercortisolism (Cushing's syndrome). UpToDate: topic last updated January 16, 2025. Available at: **https://www.uptodate.com/contents/medical-therapy-of-hypercortisolism-cushing-syndrome**. Accessed January 28, 2025.
29. Korlym (mifepristone) prescribing information. Corcept Therapeutics; Menlo Park, CA. Revised September 2024.
30. Signifor (pasireotide) injection prescribing information. Novartis Pharmaceuticals Corporation; East Hanover, NJ. Revised July 2024.
31. Signifor LAR (pasireotide) injection prescribing information. Recordati Rare Diseases Inc; Lebanon, NJ. Revised July 2024.
32. Somavert (pegvisomant) prescribing information. Pfizer Inc; New York, NY. Revised July 2023.
33. Bynfezia Pen (octreotide acetate) prescribing information. Sun Pharmaceuticals Industries, Inc.; Cranbury, NJ. Updated September 2024.
34. Mycapssa (octreotide) prescribing information. MW Encap Ltd., Scotland, UK. Revised March 2022.
35. Sandostatin (octreotide acetate) prescribing information. Novartis Pharmaceuticals Corporation.; East Hanover, NJ. Revised July 2024.
36. Sandostatin LAR Depot (octreotide acetate) prescribing information. Novartis Pharmaceuticals Corporation.; East Hanover, NJ. Revised July 2024.
37. Somatuline Depot (lanreotide) prescribing information. Ipsen Biopharmaceuticals, Inc.; Cambridge, MA. Updated July 2024.
38. Recorlev (levoketoconazole) prescribing information. Xeris Pharmaceuticals, Inc.; Chicago, IL. Revised June 2023.

History

Date	Comments
10/14/13	New policy. Add to Prescription Drug section. *Pasireotide (Signifor)* and *mifepristone (Korlym)* considered medically necessary to treat Cushing's disease when criteria are met.
12/17/14	Annual Review. Policy updated with literature review; no change in policy statement.
06/09/15	Annual Review. Policy scope expanded to address acromegaly; title expanded to include acromegaly. Medically necessary policy statement added for acromegaly with criteria of inadequate response to surgery and/or not a surgical candidate.
01/19/16	Coding update. New HCPCS code J2502, effective 1/1/16, added to policy.
01/01/17	Annual Review, approved December 13, 2016. Policy updated with literature review.
12/01/17	Annual Review, approved November 21, 2017. Policy was updated with literature review. Reference added. No policy changes were made.
12/01/18	Annual Review, approved November 21, 2018. No changes; references update.
10/01/19	Annual Review, approved September 10, 2019. Criteria updated for Korlym (mifepristone), Signifor (pasireotide) and Signifor LAR (pasireotide). New policy criteria added for Somavert (pegvisomant).
08/01/20	Interim Review, approved July 14, 2020. Added coverage criteria for Isturisa (osilodrostat) for the treatment of Cushing's disease.
01/01/21	Annual Review, approved December 17, 2020. No changes to policy statements.
05/01/21	Annual Review, approved April 13, 2021. Added coverage criteria for Bynfezia Pen (octreotide), generic octreotide, Sandostatin (octreotide), and Sandostatin LAR Depot (octreotide) for the treatment of acromegaly, gastroenteropancreatic neuroendocrine tumors (GEP-NETs), carcinoid syndrome, and treatment of the profuse watery diarrhea associated with VIPomas. Added coverage criteria for Mycapssa (octreotide) for the treatment of acromegaly. Added coverage criteria for Somatuline Depot (lanreotide) for the treatment of acromegaly, GEP-NETs, carcinoid syndrome, and treatment of the profuse watery diarrhea associated with VIPomas. Updated coverage criteria for Signifor LAR (pasireotide) and Somavert (pegvisomant) for the treatment of acromegaly adding requirements for patient age and documented diagnosis of acromegaly. Coverage for Bynfezia Pen (octreotide), generic octreotide, Sandostatin (octreotide), Sandostatin LAR Depot (octreotide), and Somatuline Depot (lanreotide) becomes effective for dates of service on or after August 6, 2021, following 90-day provider notification. Added HCPCS codes J2353, J2354, J3490, J3590, J1930.
09/01/21	Interim Review, approved August 24, 2021. Updated Korlym (mifepristone) criteria to state Cushing's syndrome.
05/01/22	Annual Review, approved April 12, 2022. Added coverage criteria for Recorlev (levoketoconazole) for treatment of endogenous hypercortisolemia (high cortisol) in patients with Cushing's syndrome. Updated criteria for Isturisa (osilodrostat), Signifor (pasireotide), and Signifor LAR (pasireotide) for the treatment of Cushing's disease to require the patient has tried generic ketoconazole first and had an inadequate

Date	Comments
	response or intolerance to generic ketoconazole. The requirement to use cabergoline AND Metopirone (metyrapone) or Lysodren (mitotane) was removed. Added a note on definition of a gastroenteropancreatic neuroendocrine tumor (GEP-NET).
02/01/23	Interim Review, approved January 23, 2023. Added brand lanreotide to policy with the identical coverage criteria as Somatuline Depot (lanreotide). Changed the wording from "patient" to "individual" throughout the policy for standardization. Added Lanreotide to HCPC code J3490 and J3590.
08/01/23	Annual Review, approved July 24, 2023. No changes to the policy statements.
04/01/24	Annual Review, approved March 12, 2024. Added coverage criteria for generic mifepristone. Updated coverage criteria for Korlym (mifepristone) to require trial and failure with generic mifepristone.
03/01/25	Annual Review, approved February 11, 2025. Added generic long-acting octreotide depot with the same coverage criteria as Sandostatin LAR Depot (octreotide). Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.