Cushing's Syndrome/Disease

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO268

Description

Pasireotide diaspartate (Signifor) is a subcutaneous somatostatin analog solution that exerts its activity by binding to somatostatin receptors causing adrenocorticotropic hormone (ACTH) secretion to be inhibited thereby leading to decreased cortisol secretion.

Osilodrostat (Isturisa) is an orally administered cortisol synthesis inhibitor. It inhibits 11beta-hydroxylase (CYP11B1), the enzyme responsible for the final step of cortisol biosynthesis in the adrenal gland.

Levoketoconazole (Recorlev), the 2S,4R enantiomer of ketoconazole, is an orally administered steroidogenesis inhibitor that reduces endogenous cortisol levels.

Mifepristone (Korlym) is a cortisol receptor blocker indicated for hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
pasireotide diaspartate (Signifor®)	Cushing's Disease	0.3 mg/mL ampule	60 ampules/30 days
		0.6 mg/mL ampule	
		0.9 mg/mL ampule	
osilodrostat (Isturisa®)		1 mg tablets	180 tablets/30 days
		5 mg tablets	
		10 mg tablets	
levoketoconazole (Recorlev®)	Cushing's Syndrome	150 mg tablets	240 tablets/30 days
mifepristone (Korlym®)	Hyperglycemia secondary to hypercortisolism in Cushing's syndrome	300 mg tablets	120 tablets/30 days (not to exceed 20 mg/kg/day)
Provider Administered Agents*			

pasireotide pamoate (Signifor LAR®)	Acromegaly, Cushing's disease	10 mg vial	1 vial/28 days
		20 mg vial	
		30 mg vial	
		40 mg vial	
		60 mg vial	

**Medical drug that requires administration by a healthcare professional and is not available for self-administration by the member, considered one of the excluded classes under the prescription benefit*

Initial Evaluation

I. **Pasireotide diaspartate (Signifor) and osilodrostat (Isturisa)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an endocrinologist; **AND**
   C. Will not be used in combination with other agents listed in this policy (e.g., pasireotide diaspartate (Signifor), osilodrostat (Isturisa), levoketoconazole (Recorlev), and/or mifepristone (Korlym)); **AND**
   D. A diagnosis of **Cushing's disease** when the following are met:
      1. Member had inadequate response to pituitary surgical resection; **OR**
         i. Member is not a candidate for pituitary surgery; **AND**
      2. Treatment with TWO of the following has been ineffective, not tolerated, or all are contraindicated (*Please note: These agents may be subject to prior authorization or step therapy and may require an additional review):
         i. Ketoconazole; **OR**
         ii. Cabergoline (Dostinex); **OR**
         iii. Metyrapone (Metopirone)*; **OR**
         iv. Mitotane (Lysodren); **AND**
      3. The request is for pasireotide diaspartate (Signifor); **OR**
      4. The request is for osilodrostat (Isturisa); **AND**
         i. Treatment with pasireotide diaspartate (Signifor) has been ineffective, contraindicated, or not tolerated

II. **Levoketoconazole (Recorlev)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an endocrinologist; **AND**

C. Levoketoconazole (Recorlev) will not be used in combination with osilodrostat (Isturisa), pasireotide diaspartate (Signifor), and/or mifepristone (Korlym); **AND**
D. A diagnosis of **Cushing's syndrome** when the following are met:
    1. Member had inadequate response to pituitary surgical resection; **OR**
        i. Member is not a candidate for pituitary surgery; **AND**
    2. Documentation cortisol levels remained elevated despite at least a three-month trial of a therapeutic dose of oral ketoconazole; **OR**
        i. Documentation of serious adverse effect or allergy with oral ketoconazole; **AND**
    3. Treatment with ALL of the following has been ineffective, not tolerated, or all are contraindicated (*Please note: These agents may be subject to prior authorization or step therapy and may require an additional review):
        i. Cabergoline (Dostinex); **AND**
        ii. Metyrapone (Metopirone)*; **AND**
        iii. Mitotane (Lysodren); **AND**
        iv. Pasireotide diaspartate (Signifor)*

III. **Mifepristone (Korlym)** may be considered medically necessary when the following criteria are met:
A. Member is 18 years of age or older; **AND**
B. Medication is prescribed by, or in consultation with, an endocrinologist; **AND**
C. Mifepristone (Korlym) will not be used in combination with osilodrostat (Isturisa), pasireotide diaspartate (Signifor), and/or levoketoconazole (Recorlev); **AND**
D. A diagnosis of **hyperglycemia secondary to hypercortisolism in members with endogenous Cushing's syndrome** when the following are met:
    1. Member had inadequate response to pituitary surgical resection; **OR**
        i. Member is not a candidate for pituitary surgery; **AND**
    2. Member has a diagnosis of type 2 diabetes OR glucose intolerance; **AND**
        i. Baseline hemoglobin A1c (HbA1c) has been provided in this request; **AND**
    3. Documentation cortisol levels remained elevated despite at least a three-month trial of a therapeutic dose of generic oral mifepristone tablets; **OR**
        i. Documentation of serious adverse effect or allergy with generic oral mifepristone; **AND**
    4. Treatment with ALL of the following has been ineffective, not tolerated, or all are contraindicated (*Please note: These agents may be subject to prior authorization or step therapy and may require an additional review):
        i. Ketoconazole; **AND**
        ii. Cabergoline (Dostinex); **AND**
        iii. Metyrapone (Metopirone)*; **AND**
        iv. Mitotane (Lysodren); **AND**

v. Pasireotide diaspartate (Signifor)*

IV. Pasireotide diaspartate (Signifor), osilodrostat (Isturisa), levoketoconazole (Recorlev), mifepristone (Korlym) are considered not medically necessary when criteria above are not met and/or when used for:
   A. Hypertension associated with Cushing's syndrome
   B. Termination of pregnancy
   C. Induction of labor
   D. Treatment of fungal infections

V. Pasireotide diaspartate (Signifor), Osilodrostat (Isturisa), levoketoconazole (Recorlev), mifepristone (Korlym) are considered investigational when used for all other conditions, including but not limited to:
   A. Use in combination with other agents used for Cushing's syndrome
   B. Exogenous (Iatrogenic) Cushing's syndrome
   C. Acromegaly
   D. Pancreatic fistula, postoperative/prophylaxis
   E. Carcinoid syndrome
   F. Neuroendocrine tumor
   G. VIPoma
   H. Hyperglycemia secondary to Type 2 diabetes (not associated with endogenous Cushing's Syndrome)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication requested will not be used in combination with other agents listed in this policy (e.g., pasireotide diaspartate (Signifor), osilodrostat (Isturisa), levoketoconazole (Recorlev), and/or mifepristone (Korlym)); **AND**
IV. The request is for one of the following:
   A. **Pasireotide diaspartate (Signifor)**; **AND**
      1. Member has exhibited improvement or stability of disease symptoms (e.g. cortisol level has decreased from baseline); **OR**

B. **Osilodrostat (Isturisa); AND**
    1. Member has exhibited improvement or stability of disease symptoms (e.g. cortisol level has decreased from baseline); **OR**
C. **Levoketoconazole (Recorlev); AND**
    1. Documentation cortisol levels remained elevated despite at least a three-month trial of a therapeutic dose of oral ketoconazole; **OR**
        i. Documentation of serious adverse effect or allergy with oral ketoconazole; **AND**
    2. Member has exhibited improvement or stability of cortisol levels and disease symptoms (e.g., improvement in cushingoid appearance, acne, hirsutism, psychiatric symptoms, body weight); **OR**
D. **Mifepristone (Korlym); AND**
    1. Documentation cortisol levels remained elevated despite at least a three-month trial of a therapeutic dose of generic oral mifepristone tablets; **OR**
        i. Documentation of serious adverse effect or allergy with generic oral mifepristone; **AND**
    2. Member experienced a reduction in HbA1c from baseline; **AND**
    3. Member has exhibited improvement in Cushing's syndrome symptoms (e.g., cushingoid appearance, acne, hirsutism, psychiatric symptoms, and excess total body weight).

Supporting Evidence

I. Cushing's disease is a disorder that leads to excess cortisol (hypercortisolemia) and is usually due to a corticotropin (ACTH)-producing pituitary (Cushing's disease). In Cushing's syndrome, ACTH levels are not always elevated, and symptoms of high cortisol can be caused by corticosteroid or an adrenal tumor. Diagnosis and management of Cushing's syndrome is complex and requires confirmatory tests (e.g., urinary free cortisol (UFC), salivary cortisol) as well as close monitoring by, or in consultation with, an endocrinologist.

II. Cushing's disease and Cushing's syndrome are caused by pathological hypercortisolism that includes demonstrable clinical features. Hallmark symptoms of high levels of cortisol include clinical features such as weight gain, hypertension, high blood glucose, and depression. The goals of treatment are to eliminate its primary cause and achieve remission so as to eliminate the associated signs, symptoms, and comorbidities and to improve quality of life (QOL).

III. According to the Endocrine Society Clinical Practice Guidelines and Pituitary Society Consensus Guidelines for Cushing's disease, first line treatment for excess cortisol production due to Cushing's syndrome is transsphenoidal surgery (TSS) regardless of the cause. Although surgical treatment is optimal with a success rate of 80-85%, second-line medical therapy is often required when surgery is delayed, contraindicated, or unsuccessful. Repeat TSS is indicated in

patients with recurrent Cushing's syndrome symptoms and have evidence of residual visible tumor on MRI. There is low quality evidence recommending systemic therapy to treat Cushing's syndrome in the pre-operative setting. Pre-operative therapy with systemic treatment or targeted radiation may be considered for patients with aggressive Cushing's syndrome, defined as those with life-threatening severe clinical features to rapidly reduce or stabilize cortisol levels.

IV. Systemic therapy options for Cushing's consist of steroidogenesis inhibitors (i.e., ketoconazole, metyrapone, mitotane, osilodrostat, etomidate), pituitary-directed agents (i.e., cabergoline, pasireotide), and glucocorticoid antagonists (i.e., mifepristone). Only levoketoconazole (Recorlev), osilodrostat (Isturisa), and pasireotide (Signifor) are FDA-approved to treat Cushing's in patients which pituitary surgery is not an option or has not been curative. Ketoconazole, metyrapone, mitotane, etomidate, and cabergoline are used off-label.

V. Guidelines recommend steroidogenesis inhibitors (i.e., ketoconazole, osilodrostat, metyrapone, etomidate) as first-line pharmacologic therapy following non-curative surgery or in patients for whom surgery was not an option. Among these therapies, ketoconazole is strongly recommended due to ease of dose titration and availability. Efficacy of ketoconazole in Cushing's syndrome is based on several retrospective trials that report UFC normalization in 45-50% of patients. IV anesthetic, etomidate, has a rapid onset of action, but use is limited to acute treatment of severe hypercortisolism due to Cushing's syndrome. Second-line systemic therapies may include any of the remaining agents (i.e., pituitary-directed agents, glucocorticoid antagonists, etc.) as treatment selection is individualized based on severity of disease, clinical manifestations, cost, drug accessibility, and safety profile. As of February 2023, guidelines have not been updated with regard to place in therapy for osilodrostat (Isturisa) or levoketoconazole (Recorlev) for the treatment of Cushing's syndrome.

VI. Guidelines do not specify a preferred treatment algorithm, nor do they indicate that treatment failure to one agent precludes treatment with another agent in the same class. The Pituitary Society guidelines recommend switching therapies when cortisol levels remain elevated despite treatment on maximum tolerated dose for 2-3 months.

VII. There is a lack of head-to-head trials showing superior safety or efficacy comparing levoketoconazole to ketoconazole, cabergoline (Dostinex), metyrapone (Metopirone), mitotane (Lysodren), or pasireotide diaspartate (Signifor). Given the known safety, established efficacy, and cost-effectiveness of these therapies, pasireotide diaspartate (Signifor) remains the preferred specialty agent by this plan due to efficacy, safety, and cost. Osilodrostat (Isturisa), levoketoconazole (Recorlev), and mifepristone (Korlym) are significantly more costly than pasireotide diaspartate (Signifor), despite not having any evidence of improved clinical efficacy or safety.

VIII. The safety and efficacy of pasireotide diaspartate (Signifor), osilodrostat (Isturisa), levoketoconazole (Recorlev), and mifepristone (Korlym) has been studied in patients 18 years of age or older, and there is no published data to support its use in pediatric patients.

IX. The efficacy of pasireotide was demonstrated in a 12-month, randomized, Phase III study. The study looked at 162 patients with Cushing's disease with persistent or recurrent disease despite pituitary surgery or new patients whom surgery was not indicated or who had had refused surgery. Cushing's disease was defined by a mean 24-hour urinary free cortisol (UFC) level of at least 1.5 times the upper limit of the normal range (ULN). Patients enrolled were randomized to receive pasireotide at 0.6 mg twice daily (n = 82) or 0.9 mg twice daily (n = 80). Three months after randomization patients were reassessed for efficacy, which was defined as having a 24-hour UFC ≤2.0 ULN or equal to their baseline values. If they were considered responders they were continued at their randomized dose until month six. If the patient did not fall into those responder parameters the patient and provider were unblinded and their dose was increased by 0.3 mg bid. At month six all the patients were transferred into the open label portion of the study, where their dose of pasireotide could be increased (to a max of 1200 mg bid) to achieve UFC under the upper limit of the normal range. At this time doses could also be decreased if needed for adverse events.

- The primary outcome was the proportion of patients who achieved normalization of mean 24-hour UFC levels (UFC ≤ULN) after 6 months of treatment without a dose increase of pasireotide. Secondary outcomes included signs and symptoms of Cushing's disease including morning cortisol levels, blood pressure, LDL and weight changes (please review study for others).
- Results showed after 6 months, 15% (12 patients) and 26% (21 patients) of patients in the 0.6 mg and 0.9 mg groups respectively reached the primary endpoint (normalization of mean 24-hour urinary free cortisol UFC levels). Secondary outcomes also showed statistically significant changes including: diastolic blood pressure: −3.7 mm Hg P=0.03, LDL cholesterol: −15 mg/deciliter P<0.001 and weight: −6.7 kg P<0.001.
- The open label portion of the study showed continuing benefits with 13% of patients in the 0.6 mg group and 25% of those in the 0.9 mg group had urinary free cortisol levels at or below the upper limit of the normal range at month 12.

X. The safety and efficacy of osilodrostat (Isturisa) was assessed in one 48-week, prospective, multicenter, open-label, phase III trial with a double-blind, placebo-controlled, randomized withdrawal period in 137 patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative. The trial included patients who were previously treated (87.6% had previous pituitary surgery and 74.5% had previous medical therapy for Cushing's disease, including ketoconazole, metyrapone, cabergoline, and pasireotide (Signifor/Signifor LAR).

- The primary efficacy outcome was the proportion of patients maintaining complete response a mean urinary free cortisol (mUFC) ≤ upper limit of normal (ULN) without a dose increase during the randomized withdrawal period at week 34. At the time of the randomization (Week 26) all (100%) randomized patients were biochemically controlled (mUFC ≤ ULN).

- At the end of the 8-week randomized withdrawal period (Week 34 of study), the complete response rate in the osilodrostat (Isturisa) group dropped to 86.1% but was higher than that in the placebo group (29.4%).
- About 53% of patients met the key secondary endpoint, the proportion of patients with mUFC≤ULN at week 24 (end of open-label osilodrostat treatment period 2) without dose-up titration weeks 13-24.
- Most common adverse reactions (incidence >20%) were adrenal insufficiency, fatigue, nausea, headache, and edema.
- Although osilodrostat (Isturisa) showed a statistically significant improvement in the control of the cortisol levels, clinical significance, durability of response, meaningfulness of these results are unknown and the quality of evidence is low.

XI. Ketoconazole is a racemic mixture of two enantiomers, one of which is levoketoconazole. Levoketoconazole (Recorlev) is the pure (2S, 4R) enantiomer and is FDA approved for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome for whom pituitary surgery is not an option or has not been curative.

XII. Levoketoconazole (Recorlev) has not been evaluated against ketoconazole for the treatment of hypercortisolemia in patients with Cushing's syndrome, therefore comparative safety and efficacy remain uncertain. However, the chemical entity in ketoconazole is the same as levoketoconazole (Recorlev); therefore, both products are expected to produce a similar efficacy and safety profile for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome, even in the absence of an FDA-labeled indication for ketoconazole. Furthermore, medical necessity for levoketoconazole (Recorlev) is limited to members that have a documented serious intolerance (e.g., allergy reaction, serious adverse event, life-threatening reaction that required hospitalization) or treatment failure with generic oral ketoconazole. If a member has a contraindication to ketoconazole, it is presumed that treatment with levoketoconazole would also be contraindicated, given similar warnings and side effect profile.

XIII. Levoketoconazole (Recorlev) has been studied in two phase 3 studies for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome for whom pituitary surgery is not an option or has not been curative.

- The SONICS trial was a 6-month open-label, single arm, dose-titration study (n=95) with a 21-week run-in period; patients who did not achieve a stable therapeutic dose during this dose titration phase did not continue in the study. The primary efficacy endpoint was the proportion of patients with normalized mean urinary free cortisol (mUFC) response of at the end of a 6-month maintenance phase without a dose increase. About 30% of patients on levoketoconazole achieved a normalized mUFC (95% CI: 21.7%- 41.2%; p=0.0154) at 6 months. Significant mean improvements in comorbidity biomarkers and clinical signs and symptoms were also seen (glucose metabolism, total cholesterol, LDL, HDL, body weight, and hirsutism (women)). Approximately 15% of patients had at least one treatment-related serious adverse event, which include reversible liver-related adverse events, QT

prolongation, and adrenal insufficiency. Routine laboratory assessments showed ALT increases above the ULN in 41% of patients at any time. Notably, 51% of study participants discontinued therapy with the most common reasons being adverse events and inefficacy.

- The LOGICS trial was 6-month double-blind, randomized, placebo-controlled withdrawal and rescue/restoration study of patients who completed the SONICS trial (n=12) or were treatment-naïve (n=72). A total of 84 patients were enrolled in the study, of whom 44 entered the randomized withdrawal phase and were assigned 1:1 to placebo or levoketoconazole. The primary outcome was the proportion of patients with loss of mUFC response, which was met with a 40% loss of response in the levoketoconazole group compared to 95% of patients in the placebo group (p=0.0002). A secondary endpoint, mUFC normalization, was met with 50% of patients achieving normalized mUFC in the levoketoconazole group compared to 4.5% of patients on placebo (95% CI: 19.2-67.9; P=0.0015). Approximately 48% of patients discontinued the study before the double-blind phase due to treatment related adverse events. Additionally, 95% of patients required rescue therapy due to high mUFC levels during the randomized withdrawal phase.

XIV. Long term safety and efficacy of levoketoconazole has not been established; however, an ongoing trial (OPTIC study) is currently evaluating long-term use of levoketoconazole in patients that have completed the SONICS and LOGICS trials.

XV. The overall quality of evidence for levoketoconazole (Recorlev) is considered low due to open-label study design, lack of an active or meaningful comparator given high volume of concomitant rescue therapy, and high attrition rate. While UFC is a clinically meaningful, objective endpoint correlated with improvement of hypercortisolism in Cushing's syndrome, concerns listed above limit confidence that medication is providing a clinically meaningful benefit over available treatments for Cushing's syndrome. Additionally, levoketoconazole use was associated with serious safety concerns including hepatotoxicity and QT prolongation.

XVI. It is known that patients with Cushing's have various lab abnormalities and may develop type 2 diabetes secondary to elevated cortisol levels. The difference between mifepristone (Korlym) and the other agents for Cushing's is that mifepristone (Korlym) was evaluated for treating hyperglycemia secondary to hypercortisolism in patients with CS who have T2DM. Korlym has not been evaluated to lower cortisol levels, however mifepristone has been used off-label for this; no other drugs approved for CS have such an indication.

XVII. Mifepristone acts as a rapid acting glucocorticoid receptor antagonist. The safety and efficacy of mifepristone (Korlym) for the treatment of endogenous Cushing's syndrome was studied in an uncontrolled, open-label, 24-week, multicenter clinical study that enrolled 50 participants. Those participants exhibited clinical and biochemical evidence of hypercortisolemia despite first-line intervention via surgical treatment and radiotherapy. Per label, the reasons for medical treatment was failed surgery, recurrence of disease, and a poor medical candidate for surgery. The study was split into two cohorts: diabetes and hypertension. The primary efficacy endpoint

for the diabetes cohort was a ≥25% reduction from baseline in glucose AUC and was conducted in the modified intent-to-treat population (n=25); 15 of 25 patients (60%) were treatment responders (95% CI: 39%, 78%) and were found to have a mean A1c reduction of 1.1% at 24 weeks. As for the hypertension cohort, there were no changes in mean systolic and diastolic blood pressures at the end of the trial relative to baseline in the modified intent-to-treat population (n=21). Participants in the study showed varying degrees of improvement in Cushing's syndrome manifestations such as cushingoid appearance, acne, hirsutism, striae, psychiatric symptoms, and excess total body weight.

XVIII. The overall quality of evidence for mifepristone (Korlym) is considered low due to open-label study design, small sample size, lack of an active or meaningful comparator, high attrition rate, and absence of a statistically significant different in the hypertension cohort. While reduction in glucose AUC is a clinically meaningful, objective endpoint correlated with improvement of hypercortisolism in Cushing's syndrome, concerns listed above limit confidence that medication is providing a clinically meaningful benefit over available treatments for Cushing's syndrome. In clinical trials for Signifor, Isturisa, and Recorlev, metabolic lab values, including glucose, were evaluated as secondary outcomes with improvements in glucose lowering, blood pressure, and weight. Close monitoring for severe hypokalemia, clinical signs of adrenal insufficiency, and QT prolongation may limit the use of mifepristone in clinical practice.

XIX. Mifepristone (Korlym) has not been evaluated against generic mifepristone for the treatment of hyperglycemia secondary to hypercortisolism in Cushing's syndrome, therefore comparative safety and efficacy remain uncertain. However, the chemical entity in generic mifepristone tablets is the same as mifepristone (Korlym) therefore, both products are expected to produce a similar efficacy and safety profile for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome, even in the absence of an FDA-labeled indication for mifepristone. Documentation of medical necessity for mifepristone (Korlym) is required, as the recommended dose can be obtained with the generic mifepristone, providing a significant price differential (6 – 10x difference). Medical necessity for mifepristone (Korlym) is limited to members that have a documented serious intolerance (e.g., allergy reaction, serious adverse event, life-threatening reaction that required hospitalization) or treatment failure with generic oral mifepristone. If a member has a contraindication to mifepristone, it is presumed that treatment with mifepristone (Korlym) would also be contraindicated, given similar warnings and side effect profile.

Investigational or Not Medically Necessary Uses

I. The agents referenced in this policy have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Exogenous (Iatrogenic) Cushing's syndrome

i. The treatment of Cushing's syndrome due to exogenous therapy is to stop the glucocorticoid. Safety and efficacy of pasireotide diaspartate (Signifor), osilodrostat (Isturisa), levoketoconazole (Recorlev), and mifepristone (Korlym) has only been established for endogenous Cushing's (e.g. ACTH dysregulation caused by tumor, etc), there is currently limited evidence to suggest the use of the agents in this policy in the setting of exogenous (iatrogenic) Cushing's syndrome.

B. Agents in the policy used in combination
   i. Approved treatments are not to be used in combination with other specialty medications listed in this policy used to treat Cushing's given lack of scientific evidence to safely recommend their use as dual therapy. Sufficient data is not currently available to support the safety and efficacy of pasireotide diaspartate (Signifor), osilodrostat (Isturisa), levoketoconazole (Recorlev), and mifepristone (Korlym) use in combination with other agents listed in these criteria. Osilodrostat (Isturisa) and Pasireotide diaspartate (Signifor) have not been studied in combination with one another or with agents used for Cushing's syndrome (levoketoconazole (Recorlev) and/or mifepristone (Korlym), etc.). Levoketoconazole (Recorlev) has not been studied in combination with osilodrostat (Isturisa), pasireotide diaspartate (Signifor), or mifepristone (Korlym).
   ii. In practice, ketoconazole has been used in combination with metyrapone or osilodrostat to maximize cortisol level lowering when monotherapy has been ineffective; triple therapy (ketoconazole/pasireotide/cabergoline and ketoconazole/metyrapone/mitotane) has also been used in patients with uncontrolled cortisol levels and presence of visible tumor post-resection. However, quality of evidence supporting combination use is low and there are significant safety concerns due to additive toxicity (QT prolongation, hepatotoxicity).

C. Acromegaly
   i. Pasireotide diaspartate (Signifor) subcutaneous syringe does not carry an FDA approval in the setting of acromegaly; however, Pasireotide pamoate (Signifor LAR) product is approved in this setting. Notably, coverage of pasireotide pamoate (Signifor LAR) under the pharmacy benefit is excluded due to provider administration exclusion. Other somatostatin agents used in acromegaly include Sandostatin LAR, Sandostatin, and somatuline.

D. Pancreatic fistula, postoperative; prophylaxis
   i. Limited data evaluating pasireotide diaspartate (Signifor) demonstrated reduction in relative risk only, therefore use of pasireotide diaspartate (Signifor) for prophylaxis or postoperative treatment of pancreatic fistula is considered experimental and investigational.

E. Carcinoid syndrome

i. Pasireotide diaspartate (Signifor) failed to demonstrate statistically significant benefit for the treatment of carcinoid syndrome. Additionally, use is not recognized by NCCN guidelines, therefore use of pasireotide diaspartate (Signifor) for carcinoid syndrome is considered experimental and investigational.

F. Neuroendocrine tumor (NETS)
   i. Pasireotide diaspartate (Signifor) failed to improve symptom control or tumor response in clinical trials evaluating treatment for NETS. Additionally, use is not recognized by NCCN guidelines, therefore use pasireotide diaspartate (Signifor) for NETs is considered experimental and investigational.

G. Vasoactive intestinal peptide tumors (VIPomas) [pancreatic neuroendocrine (islet cell) tumor, insulinoma, glucagonoma, somatostatinoma, and gastrinoma]
   i. Pasireotide diaspartate (Signifor) failed to improve symptom control or tumor response in clinical trials evaluating treatment for VIPoma. Additionally, use is not recognized by NCCN guidelines, therefore use pasireotide diaspartate (Signifor) for VIPoma is considered experimental and investigational. Appropriate treatment options may include injectable octreotide (e.g. generic octreotide acetate, Sandostatin, Bynfezia Pen).

H. Treatment of fungal infections
   i. Safety and efficacy of levoketoconazole (Recorlev) has not been established for treating fungal infections and should not be substituted for ketoconazole when used to treat fungal infections. Additionally, drugs or interventions that a treating licensed health care provider recommends are considered medically necessary if the level of service, intervention, or prescription drug recommended for the condition is cost-effective compared to alternative interventions. Therefore, it is considered not medically necessary.

I. Type 2 diabetes unrelated to endogenous Cushing's Syndrome
   i. Safety and efficacy of mifepristone (Korlym) has only been established for hyperglycemia secondary to hypercortisolism in members with endogenous Cushing's syndrome; therefore, hyperglycemia due to type 2 diabetes alone is considered experimental and investigational.

J. Hypertension associated with Cushing's syndrome
   i. In the SEISMIC clinical trial evaluating mifepristone, the hypertension cohort demonstrated no changes in mean systolic and diastolic blood pressures at the end of the trial relative to baseline in the modified intent-to-treat population (n=21). Therefore, use of mifepristone is considered not medically necessary for any symptoms outside of hyperglycemia (e.g. hypertension, weight loss, cortisol induced-psychosis) related symptoms secondary to hypercortisolism.

K. Termination of pregnancy and induction of labor

i. Although the active ingredient, mifepristone, at a lower strength is indicated for both termination of pregnancy and induction of labor, mifepristone (Korylm) has not been approved by the FDA or studied in those indications. Therefore, mifepristone (Korylm) is considered not medically necessary.

Appendix

I. Levoketoconazole (Recorlev)
   A. The recommended initial dosing of levoketoconazole is 150 mg twice daily and dosing is titrated by 150 mg daily every 2-3 weeks until an adequate clinical response is achieved based on cortisol levels and patient tolerability. The maximum recommended dosage is 1,200 mg per day in divided doses.
   B. Levoketoconazole (Recorlev) carries black box warning for hepatotoxicity and is contraindicated in patients with cirrhosis, elevated LFT defined as baseline AST or ALT > 3 times the upper limit of normal, acute liver disease or poorly controlled chronic liver disease, extensive metastatic liver disease, or recurrent symptomatic cholelithiasis. Cases of serious hepatoxicity were reported in patients taking levoketoconazole (Recorlev) and therefore treatment with levoketoconazole (Recorlev) is contraindicated in patients with a prior history of drug induced liver injury with ketoconazole or any azole antifungal therapy that required treatment discontinuation (serious and fatal hepatotoxicity have been reported in patients taking oral ketoconazole). Baseline liver function tests should be obtained prior to starting therapy and continuously monitored throughout treatment.
   C. Levoketoconazole (Recorlev) also carries a black box warning for QT prolongation and is contraindicated with other drugs that prolong the QT interval, in patients with a prolonged QTcF interval of greater than 470 msec at baseline, and in patients with a history of torsade's de pointes, ventricular tachycardia, ventricular fibrillation, or long QT syndrome (including first-degree family history). A baseline electrocardiogram (ECG) function test should be obtained prior to starting therapy.

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
octreotide (Sandostatin, Bynfezia Pen, Mycapssa)	Acromegaly
	Metastatic carcinoid tumor
	Vasoactive intestinal peptide tumor (VIPoma)
pegvisomant (Somavert)	Acromegaly

Cushing's Syndrome/Disease

EOCCO POLICY

Policy Implementation/Update

Action and Summary of Changes	Date

Created new Cushing's Syndrome Policy, combining Isturisa, Signifor, Recorlev, and Korlym policies: Added criteria to avoid combination Cushing's agent use in initial and renewal. Updated E/I (added VIPoma), supporting evidence, references. Added related policies.
• Isturisa policy
  ○ Removed documentation of baseline UFC level.
• Korlym policy
  ○ Updated from trial of 2 to trial of all generic available agents in Cushing's, including generic mifepristone and trial of Signifor. Require documentation of medical necessity for generic mifepristone in renewal criteria.
	02/2023

Previous reviews
• Pasireotide diaspartate (Signifor)
  ○ Changed criteria regarding previous therapy to require treatment with two agents to have been ineffective, not tolerated, or contraindicated. Updated the example for improvement or stability of disease symptoms
  ○ Removal of UFC 24-hour urinary free cortisol level (UFC). Addition of age requirement and addition of previous trial of ketoconazole, metyrapone, or mitotane.
• Mifepristone (Korlym)
  ○ Changed criteria regarding previous therapy to require treatment with two agents to have been ineffective, not tolerated, or contraindicated. Updated renewal language to reflect new standard language. Updated supporting evidence.
  ○ Transitioned criteria to policy with the following updates: defined surgery in the policy, removed pregnancy question, addition of supporting evidence, and addition of investigational diagnoses along with supporting evidence.
	08/2020
	12/2019
	08/2020
	10/2019

Policy created • Levoketoconazole (Recorlev) • Osilodrostat (Isturisa) • Pasireotide diaspartate (Signifor) • Mifepristone (Korlym)	03/2022 07/2020 07/2013 09/2012