Pharmacy Policy Bulletin

Title:	Cushing's Disease Agents
Policy #:	Rx.01.132

Application of pharmacy policy is determined by benefits and contracts. Benefits may vary based on product line, group, or contract. Some medications may be subject to precertification, age, quantity, or formulary restrictions (ie limits on non-preferred drugs). Individual member benefits must be verified.

This pharmacy policy document describes the status of pharmaceutical information and/or technology at the time the document was developed. Since that time, new information relating to drug efficacy, interactions, contraindications, dosage, administration routes, safety, or FDA approval may have changed. This Pharmacy Policy will be regularly updated as scientific and medical literature becomes available. This information may include new FDA-approved indications, withdrawals, or other FDA alerts. This type of information is relevant not only when considering whether this policy should be updated, but also when applying it to current requests for coverage.

Members are advised to use participating pharmacies in order to receive the highest level of benefits.

Intent:

The intent of this policy is to communicate the medical necessity criteria for **pasireotide (Signifor®), osilodrostat (Isturisa®)**, **mifepristone (Korlym®), and levoketoconazole (Recorlev®)** as provided under the member's prescription drug benefit.

Description:

Cushing's disease is caused by an adrenocorticotropic hormone (ACTH) secreting pituitary tumor. Surgical intervention is required for optimal treatment of Cushing's disease. When surgery is delayed, contraindicated, or unsuccessful, medical therapy may be required. Cabergoline and pasireotide are medications that target the tumor and may help normalize urinary free cortisol.

Pasireotide (Signifor®) exerts its pharmacological activity via binding to somatostatin receptors (SSTRs). Pasireotide binds and activates the SSTRs, resulting in inhibition of ACTH secretion, which leads to decreased cortisol secretion.

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

Mifepristone (Korlym®) is a selective antagonist of the progesterone receptor at low doses and blocks the glucocorticoid receptor (GR-II) at higher doses. Mifepristone has high affinity for the GR-II receptor but little affinity for the GR-I (MR, mineralocorticoid) receptor. In addition, mifepristone appears to have little or no affinity for estrogen, muscarinic, histaminic, or monoamine receptors.

Levoketoconazole (Recorlev®) inhibits key steps in the synthesis of cortisol and testosterone, principally those mediated by CYP11B1 (11β hydroxylase), CYP11A1 (the cholesterol side-chain cleavage enzyme, the first step in the conversion of cholesterol to pregnenolone), and CYP17A1 (17α-hydroxylase).

Pasireotide (Signifor®) is indicated for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.

Osilodrostat (Isturisa®) is indicated for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.

Mifepristone (Korlym®) indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.

Levoketoconazole (Recorlev®) is indicated for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome for whom surgery is not an option or has not been curative

Policy:

Cushing's Disease

INITIAL CRITERIA Pasireotide (Signifor®) or osilodrostat (Isturisa®) is approved when ALL of the following are met:

1. Diagnosis of Cushing's disease; and
2. Member has failed surgery or is not a candidate for surgery; and
3. Member is 18 years of age or older; and
4. Prescribed by or in consultation with an endocrinologist; and
5. For Osilodrostat (Isturisa®) only, inadequate response or inability to tolerate pasireotide (Signifor® [LAR])

Initial Authorization duration: 6 months

REAUTHORIZATION CRITERIA Pasireotide (Signifor®) or osilodrostat (Isturisa®) is re-approved when ALL of the following are met:

1. Documentation of positive clinical response to therapy (i.e., reduction in cortisol levels, improvement in signs or symptoms of the disease); and
2. Prescribed by or in consultation with an endocrinologist

Reauthorization duration: 2 years

INITIAL CRITERIA Levoketoconazole (Recorlev®) is approved when ALL of the following are met:

1. Diagnosis of Cushing's syndrome; and
2. Member is 18 years of age or older; and
3. Member is being treated for endogenous hypercortisolemia (e.g., pituitary adenoma, ectopic tumor, adrenal adenoma); and
4. One of the following:
    a. Member is not a candidate for surgery; or
    b. Surgery has not been curative; and
5. Inadequate response or inability to tolerate oral ketoconazole; and
6. Prescribed by or in consultation with an endocrinologist

Initial authorization duration: 12 months

REAUTHORIZATION CRITERIA Levoketoconazole (Recorlev®) is re-approved when there is documentation of positive clinical response to therapy as demonstrated by one of the following:

1. Normalization of urinary free cortisol (UFC); or
2. At least a 50% decrease in UFC levels

Reauthorization duration: 2 years

Hyperglycemia secondary to Cushing's Syndrome

INITIAL CRITERIA Mifepristone (Korlym®) is approved when ALL of the following are met:

1. Hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance; and
2. Member has failed surgery or is not a candidate for surgery; and
3. Prescribed by or in consultation with an endocrinologist; and
4. Member is not pregnant; and
5. Member is 18 years of age or older

Initial Authorization duration: 6 months

REAUTHORIZATION CRITERIA Mifepristone (Korlym®) is re-approved when ALL of the following are met:

1. Documentation of positive clinical response to therapy (e.g., improved, or stable glucose tolerance while on therapy); and
2. Prescribed by or in consultation with an endocrinologist

Reauthorization duration: 2 years

Black Box Warning as shown in the drug Prescribing Information:

Mifepristone (Korlym®)

TERMINATION OF PREGNANCY

Mifepristone is a potent antagonist of progesterone and cortisol via the progesterone and glucocorticoid (GR-II) receptors, respectively. The antiprogestational effects will result in the termination of pregnancy. Pregnancy must therefore be excluded before the initiation of treatment with KORLYM and prevented during treatment and for one month after stopping treatment by the use of a non-hormonal medically acceptable method of contraception unless the patient has had a surgical sterilization, in which case no additional contraception is needed. Pregnancy must also be excluded if treatment is interrupted for more than 14 days in females of reproductive potential.

Levoketoconazole (Recorlev®)

HEPATOTOXICITY AND QT PROLONGATION

Cases of hepatotoxicity with fatal outcome or requiring liver transplantation have been reported with oral ketoconazole. Some patients had no obvious risk factors for liver disease. RECORLEV is associated with serious hepatotoxicity. Evaluate liver enzymes prior to and during treatment.

RECORLEV is associated with dose-related QT interval prolongation. QT interval prolongation may result in life threatening ventricular dysrhythmias such as torsades de pointes. Perform ECG prior to and during treatment.

Guidelines:

Refer to the specific manufacturer's prescribing information for administration and dosage details and any applicable Black Box warnings.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable benefit contract, the applicable drug(s) identified in this policy is (are) covered under the prescription drug benefits of the Company’s products when the medical necessity criteria listed in this pharmacy policy are met. Any services that are experimental/investigational or cosmetic are benefit contract exclusions for all products of the Company.

References:

Nieman LK. Medical therapy of hypercortisolism (Cushing's syndrome). UpToDate. August 2022. Available at: https://www.uptodate.com/contents/medical-therapy-of-hypercortisolism-cushings-syndrome?source=search_result&search=cushings%20disease&selectedTitle=8~100#H1. Accessed October 05, 2022.

Nieman LK. Overview of the treatment if Cushing's syndrome. UpToDate. November 2021. Available at: https://www.uptodate.com/contents/overview-of-the-treatment-of-cushings-syndrome?source=search_result&search=cushings%20disease%20management&selectedTitle=1~100#H4. Accessed October 05, 2022.

Isturisa® (osilodrostat) [prescribing information]. Lebanon, NJ: Recordati Rare Disease, Inc.; March 2020. Available from: https://www.isturisa.com/pdf/isturisa-prescribing-information.pdf. Accessed October 05, 2022.

Korlym® (mifepristone) [prescribing information]. Menlo Park, CA: Corcept Therapeutics Inc.; November 2019. Available from: https://www.korlym.com/wp-content/uploads/2018/01/K-00017-NOV-2019_electronic-PI_r8_FINAL.pdf. Accessed October 05, 2022.

Recorlev® (levoketoconazole) [prescribing information]. Chicago, IL: Xeris Pharmaceuticals, Inc.; December 2021. Available from: https://www.recorlev.com/full-prescribing-information.pdf. Accessed October 05, 2022.

Signifor® (pasireotide) [package insert]. East Hanocer, NJ. Novartis Pharmaceuticals Corporation. June 2020. Available at: https://www.signiforlar.com/pdf/signifor-lar-pi.pdf. Accessed October 05, 2022.

Applicable Drugs:

Inclusion of a drug in this table does not imply coverage. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

Brand name	Generic name
Signifor®	Pasireotide
Isturisa®	Osilodrostat
Korlym®	Mifepristone
Recorlev®	Levoketoconazole

Cross References:

Off-Label Use policy Rx.01.33
Quantity Level Limits for Pharmaceuticals Covered Under the Prescription Drug Benefit Rx.01.76

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P&T Approval Date:	September 15, 2022
Policy Effective Date:	January 01, 2023
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