BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

ISTURISA® (osilodrostat) oral
KORLYM™ (mifepristone) oral
Mifepristone oral
RECORLEV® (levoketoconazole) oral
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and/or Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Medical Necessity Requirements for ISTURISA (osilodrostat)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a physician specializing in the diagnosis or in consultation with an Endocrinologist

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Indication

- Confirmed diagnosis of *endogenous* hypercortisolemia with Cushing's syndrome for whom surgery is not an option or has not been curative

Age Requirement

- 18 years or older

Baseline Clinical Evaluation

- Serum potassium and magnesium corrected if abnormal
- Electrocardiogram (ECG)

Alternative Therapies

- Failure contraindication, intolerance, or not a candidate for **TWO** of the following:
  - Ketoconazole monotherapy
  - Metopirone (metyrapone) monotherapy
  - Ketoconazole with Metopirone (metyrapone)
  - Ketoconazole with mitotane

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Documentation Requirements

- A completed request form must be submitted including:
  - Chart notes
  - Lab results
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration

- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualification

- Continues to be seen by a physician specializing in the diagnosis or in consultation with an Endocrinologist

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Clinical Response

- Achieved and maintains **THREE** of the following:
  - Urinary free cortisol less than or equal to upper limit of normal
  - Cortisol levels within normal limits
  - No symptoms consistent with Cushing's disease such as cushingoid appearance, acne, hirsutism, striae, psychiatric symptoms, and excess total body weight
  - No evidence of hypocortisolism or adrenal insufficiency
  - No evidence of disease progression

Adherence

- Adherence to the prescribed therapy regimen has been documented

Safety

- No significant adverse effects such as severe hypocortisolism, adrenal insufficiency, QTc prolongation, uncontrolled hypokalemia

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Documentation Requirements

- Chart notes
- Lab results
- Supporting clinical documentation

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year

Medical Necessity Requirements for KORLYM (mifepristone) and Mifepristone generic

Criteria for Initial Therapy:

Prescriber Qualifications

- Prescribed by a physician specializing in the diagnosis or in consultation with an Endocrinologist

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KORLYM™ (mifepristone) oral
Mifepristone oral
RECORLEV® (levoketoconazole) oral
Generic Equivalent (if available)

Indication

- Hyperglycemia is secondary to hypercortisolism in *endogenous* Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or not a candidate for surgery

Age Requirement

- 18 years or older

Baseline Clinical Evaluation

- Hypercortisolism not due to chronic corticosteroid use
- Poorly controlled diabetes mellitus or glucose elevation despite treatment with anti diabetic therapy
- Negative pregnancy test for women of childbearing potential
- Serum potassium corrected if abnormal

Alternative Therapies

- Failure, contraindication, intolerance, or not a candidate for **TWO** of the following:
  - Ketoconazole monotherapy
  - Metopirone (metyrapone) monotherapy
  - Ketoconazole with Metopirone (metyrapone)
- For brand Korlym: failure, contraindication, or intolerance to generic mifepristone

Brand Specific Criteria

- **For brand Korlym**: failure, contraindication, or intolerance to **THREE** generic equivalents (if available) of **mifepristone**. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No FDA label contraindications such as:
  - Pregnancy
  - Unexplained vaginal bleeding
  - Endometrial hyperplasia with atypia or endometrial cancer
  - Concurrent use with CYP3A metabolized drugs (i.e., simvastatin lovastatin) and CYP3A substrates with narrow therapeutic ranges (i.e., cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus)
  - Concurrent use with systemic corticosteroid for a medical condition where corticosteroid use is for lifesaving purposes (such as immunosuppression in organ transplantation or an autoimmune disorder)
- No severe hepatic impairment

- No concurrent use with drugs causing QT prolongation or strong CYP3A inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, and St. John's Wort)
- Women of childbearing potential must use non hormonal contraception during and for 1 month after therapy

Additional Requirements
- Not to be used for the treatment of type 2 diabetes mellitus unrelated to endogenous Cushing's syndrome

Documentation Requirements
- A completed request form must be submitted including:
  - Chart notes
  - Lab results
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration
- 2 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):
Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualification
- Continues to be seen by a physician specializing in the diagnosis or in consultation with an Endocrinologist

Clinical Response
- Achieved and maintains **TWO** of the following:
  - At least 25 percent reduction in glucose from baseline
  - At least 2 percent reduction in HgA1c from baseline
  - Reduction in Cushing's symptoms (e.g., cushingoid appearance, acne, hirsutism, striae, psychiatric symptoms, and excess total body weight)

Adherence
- Adherence to the prescribed therapy regimen has been documented

Safety
- No FDA label contraindications or significant adverse drug effects such as:
  - Pregnancy
  - Unexplained vaginal bleeding

  - Endometrial hyperplasia with atypia or endometrial cancer
  - Concurrent use with CYP3A metabolized drugs (i.e., simvastatin lovastatin) and CYP3A substrates with narrow therapeutic ranges (i.e., cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus)
  - Concurrent use with systemic corticosteroid for a medical condition where corticosteroid use is for lifesaving purposes (such as immunosuppression in organ transplantation or an autoimmune disorder)
  - Adrenal insufficiency
  - Severe or uncorrectable hypokalemia
  - Severe QT interval prolongation
- No severe hepatic impairment
- No concurrent use with drugs causing QT prolongation or in an individual with potassium channel variants that result in a long QT interval
- No concurrent use with strong CYP3A inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, and St. John's Wort)
- Women of childbearing potential must use non hormonal contraception during and for 1 month after therapy

Additional Requirements

- Not to be used for the treatment of type 2 diabetes mellitus unrelated to endogenous Cushing's syndrome

Documentation Requirements

- Chart notes
- Lab results
- Supporting clinical documentation

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year

Medical Necessity Requirements for RECORLEV (levoketoconazole)

Criteria for Initial Therapy:

Prescriber Qualifications

- Prescribed by a physician specializing in the diagnosis or in consultation with an Endocrinologist

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Generic Equivalent (if available)

Indication

- *Endogenous* hypercortisolemia in Cushing's syndrome where pituitary surgery is not an option or has not been curative

Age Requirement

- 18 years or older

Baseline Clinical Evaluation

- Serum potassium and magnesium corrected if abnormal
- Liver tests (ALT, AST, total bilirubin)
- Electrocardiogram (ECG)

Alternative Therapies

- Failure, contraindication, intolerance, to **TWO** of the following:
  - Ketoconazole monotherapy
  - Metopirone (metyrapone) monotherapy
  - Ketoconazole with Metopirone (metyrapone)
  - Ketoconazole with mitotane

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No FDA label contraindications such as:
  - Cirrhosis
  - Acute liver disease or poorly controlled chronic liver disease
  - Baseline AST or ALT greater than 3 times upper limit of normal
  - Recurrent symptomatic cholelithiasis
  - Prior drug induced liver injury due to ketoconazole or any azole antifungal therapy
  - Extensive metastatic liver disease
  - Concomitant use with drugs that cause QT prolongation associated with ventricular arrhythmias, including torsades de pointes
  - Prolonged QTcF interval greater than 470 msec at baseline, history of torsades de pointes, ventricular tachycardia, ventricular fibrillation, or prolonged QT syndrome
  - Hypersensitivity to levoketoconazole, ketoconazole or any excipient
  - Concomitant use with drugs that are sensitive substrates of CYP3A4 or CYP3A4 and P gp substrates

- No fungal infection
- Not using chronic glucocorticosteroids
- No significant interacting drugs

Documentation Requirements

- A completed request form must be submitted including:
  - Chart notes
  - Lab results
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration

- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualification

- Continues to be seen by a physician specializing in the diagnosis or in consultation with an Endocrinologist

Clinical Response

- Achieved and maintains **THREE** of the following:
  - Urinary cortisol less than or equal to upper limit of normal
  - Cortisol levels within normal limits
  - No symptoms consistent with Cushing's disease (e.g., cushingoid appearance, acne, hirsutism, striae, psychiatric symptoms, and excess total body weight)
  - No evidence of hypocortisolism
  - No evidence of disease progression

Adherence

- Adherence to the prescribed therapy regimen has been documented

Safety

- No FDA label contraindications or significant adverse drug effects such as:
  - Cirrhosis
  - Acute liver disease or poorly controlled chronic liver disease
  - Baseline AST or ALT greater than 3 times upper limit of normal

  - Recurrent symptomatic cholelithiasis
  - Prior drug induced liver injury due to ketoconazole or any azole antifungal therapy
  - Extensive metastatic liver disease
  - Concomitant use with drugs that cause QT prolongation associated with ventricular arrhythmias, including torsades de pointes
  - Prolonged QTcF interval greater than 470 msec at baseline, history of torsades de pointes, ventricular tachycardia, ventricular fibrillation, or prolonged QT syndrome
  - Hypersensitivity to levoketoconazole, ketoconazole or any excipient
  - Concomitant use with drugs that are sensitive substrates of CYP3A4 or CYP3A4 and P gp substrates
  - Significant or recurrent elevations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin
  - First episode or recurrent QTc prolongation greater than 500 msec
  - Severe hypocortisolism
  - Adrenal insufficiency
- No significant interacting drugs

Documentation Requirements

- Chart notes
- Lab results
- Supporting clinical documentation

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Off-Label Use Requests:

Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. Off-Label Use of Non-Cancer Medications

2. Off-Label Use of Cancer Medications

Description:

Isturisa (osilodrostat) is a cortisol synthesis inhibitor 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 inhibits 11 β-

hydroxylase (CYP11B1), the enzyme responsible for the final step of cortisol biosynthesis in the adrenal gland, thereby lowering cortisol levels.

Korlym (mifepristone) is a cortisol receptor blocker 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 who have failed surgery or are not candidates for surgery. Korlym should not be used in the treatment of patients with type 2 diabetes unless it is secondary to Cushing's syndrome. Mifepristone acts as an antagonist at the progesterone receptor (PR), glucocorticoid receptor type II (GR-II), and androgen receptor (AR). It does not bind to either the estrogen receptor (ER) or mineralocorticoid receptor (MR). Antagonism of the progesterone receptors occurs at low doses whereas antagonism of the glucocorticoid receptors occurs at higher doses. Mifepristone inhibits the actions of exogenous and endogenous glucocorticoids and progestins.

Recorlev (levoketoconazole), a cortisol synthesis inhibitor, is indicated for the treatment of endogenous hypercortisolemia in **Cushing's syndrome** where pituitary surgery is not an option or has not been curative. *In vitro*, levoketoconazole 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). Ketoconazole tablets contain equal parts levoketoconazole and dextroketoconazole in a racemic mixture, Levoketoconazole is the 2S, 4R enantiomer of ketoconazole. The safety and effectiveness of Recorlev (levoketoconazole) for the treatment of fungal infections have not been established. Recorlev (levoketoconazole) is not approved for the treatment of fungal infections.

Cushing's **syndrome**, also known as hypercortisolism, is an uncommon disorder that occurs because of excess cortisol. It can come from chronic use of corticosteroid medications or tumor of the pituitary or adrenal glands producing too much cortisol. Cushing's **disease** is a specific type of Cushing syndrome caused by a benign tumor located in the pituitary gland that secretes too much adrenocorticotropic hormone (ACTH), which in turn increases cortisol.

Endogenous Cushing syndrome is most often caused by hormone-secreting tumors of the adrenal glands or the pituitary. **Exogenous** Cushing syndrome is most commonly due to chronic use of glucocorticoid medications that cause iatrogenic Cushing's syndrome.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Signs and symptoms of Cushing's syndrome	
More Common	**Less Common**

Decreased libido	ECG abnormalities or atherosclerosis
Obesity/weight gain	Striae
Plethora	Edema
Round face	Proximal muscle weakness
Menstrual changes	Osteopenia or fracture
Hirsutism	Headache
Hypertension	Backache
Ecchymoses	Recurrent infections
Lethargy, depression	Abdominal pain
Dorsal fat pad	Acne
Abnormal glucose tolerance	Female balding

Recorlev (levoketoconazole): Some Package Label Interactions: [Note: not a complete list]

CYP3A4 or CYP3A4 and P-gp Substrates That May Prolong QT

Bosutinib, cisapride, clarithromycin, cobimetinib, crizotinib, disopyramide, dofetilide, dronedarone, eliglustat (in patients that are poor or intermediate metabolizers of CYP2D6 and in patients taking strong or moderate CYP2D6 inhibitors), ivabradine, methadone, midostaurin, nicardipine, pimozide, quinidine, and ranolazine

Sensitive CYP3A4 or CYP3A4 and P-gp Substrates

Alfentanil, avanafil, buspirone, conivaptan, dabigatran etexilate, darifenacin, darunavir, digoxin, ebastine, everolimus, fexofenadine, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, and vardenafil

Strong CYP3A4 Inhibitors

Antivirals (e.g., ritonavir, ritonavir-boosted darunavir, ritonavir boosted fosamprenavir, saquinavir)
Glucocorticoid and progesterone receptor antagonists (e.g., mifepristone)
Others clarithromycin, conivaptan, tipranavir

Strong CYP3A4 Inducers

Antibacterials (e.g., isoniazid, rifabutin, rifampicin), Anticonvulsants (e.g., carbamazepine, phenytoin), Antivirals (e.g., efavirenz, nevirapine), Cytotoxic agents (e.g., mitotane)

Gastric Acid Suppressors

Avoid use of H2- receptor antagonists and proton pump inhibitors

Sucralfate

Avoid use

Some drugs that cause QT interval prolongation: [Note: not a complete list]

Amiodarone, sotalol, quinidine, procainamide, levofloxacin, moxifloxacin, haloperidol, quetiapine, methadone, others

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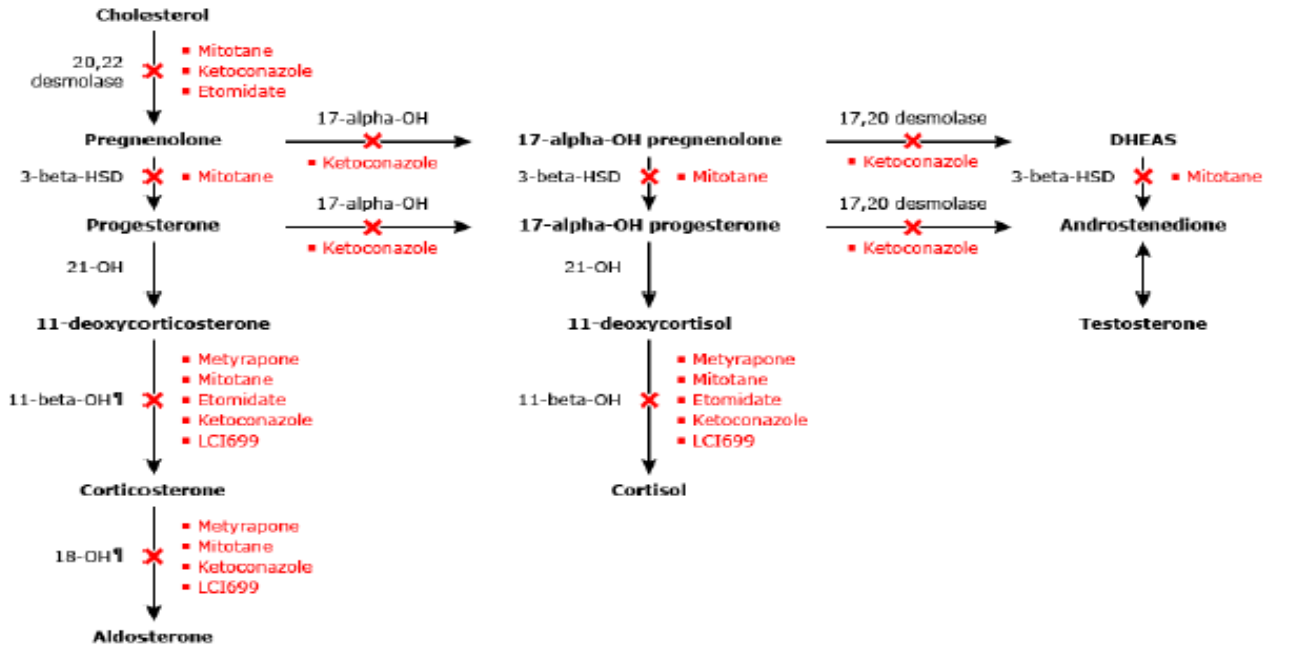
Steroidogenesis in adrenal cortex affected by specific enzyme inhibitors*



Steroidogenesis in the adrenal cortex denoting the specific pathways inhibited by ketoconazole (KTZ), metyrapone (MTR), mitotane, etomidate, and newer steroidogenesis inhibitors.

17-alpha-OH: 17-alpha-hydroxylase; DHEAS: dehydroepiandrosterone sulfate; 3-beta-HSD: 3-beta-hydroxysteroid dehydrogenase; 21-OH: 21-hydroxylase; 11-beta-OH: 11-beta-hydroxylase; LCI699: osilodrostat; 18-OH: 18-hydroxylase.
* Refer to UpToDate table for nomenclature used for steroidogenic enzymes.
¶ Aldosterone synthase.

Resources:

Isturisa (osilodrostat) product information, revised by Recordati Rare Diseases, Inc. 11-2025 Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 12, 2026.

Korlym (mifepristone) product information, revised by Corcept Therapeutics Incorporated 09-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 12, 2026.

Mifepristone product information, revised by Corcept Therapeutics Incorporated 09-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 12, 2026.

Recorlev (levoketoconazole) product information, revised by Xeris Pharmaceuticals, Inc. 06-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 12, 2026.

Nieman LK. Overview of the treatment of Cushing's syndrome. In: UpToDate, Lacroix A, Rubinow K (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through March 2026. Topic last updated April 02, 2025. Accessed April 20, 2026.

Nieman LK. Medical therapy of hypercortisolism (Cushing's syndrome). In: UpToDate, Lacroix A, Rubinow K (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through March 2026. Topic last updated March 25, 2026. Accessed April 20, 2026.

Nieman LK. Epidemiology and clinical manifestations of Cushing's syndrome. In: UpToDate, Lacroix A, Rubinow K (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through March 2026. Topic last updated February 28, 2024. Accessed April 20, 2026.

Nieman LK. Establishing the diagnosis of Cushing's syndrome. In: UpToDate, Lacroix A, Mulder JE. (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through March 2026. Topic last updated December 03, 2025. Accessed April 20, 2026.

Nieman LK. Establishing the cause of Cushing' syndrome. In: UpToDate, Lacroix A, Rubinow K (Eds), UpToDate, Waltham, MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through March 2026. Topic last updated December 03, 2025. Accessed April 20, 2026.

Nieman LK, Biller BM, Findling JW. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015;100(8):2807-2831. Accessed June 23, 2020. Re-evaluated April 20, 2026.