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RESEARCH**

APPLICATION NUMBER:
202107Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Korlym™ safely and effectively. See full prescribing information for Korlym.

Korlym™ (mifepristone) 300 mg Tablets

Initial U.S Approval 2000

WARNING: TERMINATION OF PREGNANCY

See full prescribing information for complete boxed warning.

Mifepristone has potent antiprogesterational effects and will result in the termination of pregnancy. Pregnancy must therefore be excluded before the initiation of treatment with Korlym, or if treatment is interrupted for more than 14 days in females of reproductive potential.

INDICATIONS AND USAGE

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 have failed surgery or are not candidates for surgery.

Important Limitations of Use (1.1)

- Do not use for the treatment of type 2 diabetes mellitus unrelated to endogenous Cushing's syndrome.

DOSAGE AND ADMINISTRATION

- Administer once daily orally with a meal (2).
- The recommended starting dose is 300 mg once daily (2).
- Renal impairment: do not exceed 600 mg once daily.
- Mild-to-moderate hepatic impairment: do not exceed 600 mg once daily. Do not use in severe hepatic impairment.

Based on clinical response and tolerability, the dose may be increased in 300 mg increments to a maximum of 1200 mg once daily. Do not exceed 20 mg/kg per day (2).

DOSAGE FORMS AND STRENGTHS

- 300 mg tablet

CONTRAINDICATIONS

- Pregnancy (4.1, 8.1)
- Use of simvastatin or lovastatin and CYP 3A substrates with narrow therapeutic range (4.2)
- Concurrent long-term corticosteroid use (4.3)

- Women with history of unexplained vaginal bleeding (4.4)
- Women with endometrial hyperplasia with atypia or endometrial carcinoma (4.4)

WARNINGS AND PRECAUTIONS

- Adrenal insufficiency:** Patients should be closely monitored for signs and symptoms of adrenal insufficiency (5.1).
- Hypokalemia:** Hypokalemia should be corrected prior to treatment and monitored for during treatment (5.2).
- Vaginal bleeding and endometrial changes:** Women may experience endometrial thickening or unexpected vaginal bleeding. Use with caution if patient also has a hemorrhagic disorder or is on anti-coagulant therapy (5.3).
- QT interval prolongation:** Avoid use with QT interval-prolonging drugs, or in patients with potassium channel variants resulting in a long QT interval (5.4).
- Use of Strong CYP3A Inhibitors:** Concomitant use can increase mifepristone plasma levels significantly. Use only when necessary and limit mifepristone dose to 300 mg (5.6).

ADVERSE REACTIONS

Most common adverse reactions in Cushing's syndrome ($\geq 20\%$): nausea, fatigue, headache, decreased blood potassium, arthralgia, vomiting, peripheral edema, hypertension, dizziness, decreased appetite, endometrial hypertrophy

To report suspected adverse reactions, contact Concept Therapeutics at 1-855-844-3270 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Drugs metabolized by CYP3A: Administer drugs that are metabolized by CYP3A at the lowest dose when used with Korlym (7.1).
- CYP3A inhibitors: Caution should be used when Korlym is used with strong CYP3A inhibitors. Limit mifepristone dose to 300 mg per day when used with strong CYP3A inhibitors (5.6, 7.2).
- CYP3A inducers: Do not use Korlym with CYP3A inducers (7.3).
- Drugs metabolized by CYP2C8/2C9: Use the lowest dose of CYP2C8/2C9 substrates when used with Korlym (7.4).
- Drugs metabolized by CYP2B6: Use of Korlym should be done with caution with bupropion and efavirenz (7.5).
- Hormonal contraceptives: Do not use with Korlym (7.6).

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Discontinue drug or discontinue nursing (8.3).

See Section 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide

FULL PRESCRIBING INFORMATION: Contents*

1 INDICATIONS AND USAGE

LIMITATIONS OF USE:

2 DOSAGE AND ADMINISTRATION

- 2.1 Adult Dosage
- 2.2 Dosing in Renal Impairment
- 2.3 Dosing in Hepatic Impairment

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

- 4.1 Pregnancy
- 4.2 Drugs Metabolized by CYP3A
- 4.3 Corticosteroid Therapy Required for Lifesaving Purposes
- 4.4 Women with Risk of Vaginal Bleeding or Endometrial Changes
- 4.5 Known Hypersensitivity to Mifepristone

5 WARNINGS AND PRECAUTIONS

- 5.1 Adrenal Insufficiency
- 5.2 Hypokalemia
- 5.3 Vaginal Bleeding and Endometrial Changes
- 5.4 QT Interval Prolongation
- 5.5 Exacerbation/Deterioration of Conditions Treated with Corticosteroids
- 5.6 Use of Strong CYP3A Inhibitors
- 5.7 *Pneumocystis jiroveci* Infection
- 5.8 Potential Effects of Hypercortisolemia

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Laboratory Tests
- 6.3 Vaginal Bleeding and Endometrial Changes
- 6.4 Additional Data from Clinical Trials

- 6.4.1 Adrenal Insufficiency

- 6.4.2 Rash

7 DRUG INTERACTIONS

- 7.1 Drugs Metabolized by CYP3A
- 7.2 CYP3A Inhibitors
- 7.3 CYP3A Inducers
- 7.4 Drugs Metabolized by CYP2C8/2C9
- 7.5 Drugs Metabolized by CYP2B6
- 7.6 Use of Hormonal Contraceptives

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment
- 8.8 Females of Reproductive Potential

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Cushing's Syndrome

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

- 17.1 Importance of Preventing Pregnancy

*Sections or subsections omitted from the full prescribing information are not listed

Korlym™ (mifepristone) 300 mg tablets for oral use

FULL PRESCRIBING INFORMATION

WARNING: TERMINATION OF PREGNANCY

Mifepristone is a potent antagonist of progesterone and cortisol via the progesterone and glucocorticoid (GR-II) receptors, respectively. The antiprogesterational 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.

1 INDICATIONS AND USAGE

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 have failed surgery or are not candidates for surgery.

LIMITATIONS OF USE:

- Korlym should not be used in the treatment of patients with type 2 diabetes unless it is secondary to Cushing's syndrome.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Dosage

The recommended starting dose is 300 mg orally once daily. Korlym must be given as a single daily dose. Korlym should always be taken with a meal. Patients should swallow the tablet whole. Do not split, crush, or chew tablets.

Dosing and titration

The daily dose of Korlym may be increased in 300 mg increments. The dose of Korlym may be increased to a maximum of 1200 mg once daily but should not exceed 20 mg/kg per day. Increases in dose should not occur more frequently than once every 2-4 weeks. Decisions about dose increases should be based on a clinical assessment of tolerability and degree of improvement in Cushing's syndrome manifestations. Changes in glucose control, anti-diabetic medication requirements, insulin levels, and psychiatric symptoms may provide an early assessment of response (within 6 weeks) and may help guide early dose titration. Improvements in cushingoid appearance, acne, hirsutism, striae, and body weight occur over a longer period of time and, along with measures of glucose control, may be used to determine dose changes beyond the first 2 months of therapy. Careful and gradual titration of Korlym accompanied by monitoring for recognized adverse reactions (*See Warnings and Precautions 5.1 and 5.2*) may reduce the risk of severe adverse reactions. Dose reduction or even dose discontinuation may be needed in some

clinical situations. If Korlym treatment is interrupted, it should be reinitiated at the lowest dose (300 mg). If treatment was interrupted because of adverse reactions, the titration should aim for a dose lower than the one that resulted in treatment interruption.

2.2 Dosing in Renal Impairment

No change in initial dose of Korlym is required in renal impairment. The maximum dose should be limited to 600 mg. *[See Renal Impairment (8.6) and Clinical Pharmacology (12.3)]*

2.3 Dosing in Hepatic Impairment

No change in the initial dose of Korlym is required in mild to moderate hepatic impairment. The maximum dose should be limited to 600 mg. Korlym should not be used in severe hepatic impairment. *[See Hepatic Impairment (8.7) and Clinical Pharmacology (12.3)]*

3 DOSAGE FORMS AND STRENGTHS

Korlym is supplied as a light yellow to yellow oval-shaped tablet debossed with “Corcept” on one side and “300” on the other. Each tablet contains 300 mg of mifepristone. The tablets are not scored.

4 CONTRAINDICATIONS

4.1 Pregnancy

Korlym is contraindicated in women who are pregnant. Pregnancy must be excluded before the initiation of treatment with Korlym or if treatment is interrupted for more than 14 days in females of reproductive potential. Nonhormonal contraceptives should be used during and one month after stopping treatment in all women of reproductive potential. *[See Use in Specific Populations 8.8]*

4.2 Drugs Metabolized by CYP3A

Korlym is contraindicated in patients taking simvastatin, lovastatin, and CYP3A substrates with narrow therapeutic ranges, such as cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus, due to an increased risk of adverse events. *[See Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*

4.3 Corticosteroid Therapy Required for Lifesaving Purposes

Korlym is contraindicated in patients who require concomitant treatment with systemic corticosteroids for serious medical conditions or illnesses (e.g., immunosuppression after organ transplantation) because Korlym antagonizes the effect of glucocorticoids.

4.4 Women with Risk of Vaginal Bleeding or Endometrial Changes

Korlym is contraindicated in the following:

- Women with a history of unexplained vaginal bleeding
- Women with endometrial hyperplasia with atypia or endometrial carcinoma

4.5 Known Hypersensitivity to Mifepristone

Korlym is contraindicated in patients with prior hypersensitivity reactions to mifepristone or to any of the product components.

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