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5.01.023

Section:	Prescription Drugs	Effective Date:	January 1, 2023
Subsection:	Anti-infective Agents	Original Policy Date:	October 1, 2013
Subject:	Ketoconazole	Page:	1 of 5

Last Review Date: December 2, 2022

Ketoconazole

Description

Ketoconazole tablets

Background

Ketoconazole is an imidazole antifungal agent available as an oral tablet and various topical formulations. Ketoconazole works by weakening the structure and function of the fungal cell membrane. Due to potential for severe adverse events, ketoconazole tablets should only be used when other effective antifungal therapy is not available or tolerated and the potential benefits are considered to outweigh the potential risks. For the management of prostate cancer, ketoconazole tablets inhibit androgen (1-2).

Regulatory Status

FDA-approved indication: Ketoconazole oral is indicated for the treatment of the following systemic fungal infections in patients who have failed or who are intolerant to other therapies: *blastomycosis*, *coccidioidomycosis*, *histoplasmosis*, *chromomycosis*, and *paracoccidioidomycosis*. Ketoconazole should not be used for fungal meningitis because it penetrates poorly into the cerebrospinal fluid. Ketoconazole tablets are not indicated for the treatment of fungal infections of the skin or nails (1-2).

Off-Label Use:

Ketoconazole is an imidazole antifungal agent that inhibits adrenal androgen synthesis. Ketoconazole is a standard secondary hormonal therapy for patients with castration-resistant prostate cancer. The published dose of ketoconazole for metastatic castrate resistant prostate cancer is 200 to 400 mg three times a day (3).

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Ketoconazole has a boxed warning regarding serious hepatotoxicity, QT prolongation, and drug interactions leading to QT prolongation (1).

Serious hepatotoxicity, including cases with a fatal outcome or requiring liver transplantation has occurred with the use of oral ketoconazole. Ketoconazole tablets is contraindicated in patients with acute or chronic liver disease. Patients receiving oral ketoconazole should be informed by the prescriber of the risk and should be closely monitored. At baseline, obtain laboratory tests (e.g., serum gamma-glutamyl transferase (SGGT), alkaline phosphatase, ALT, AST, total bilirubin (TBL), prothrombin time (PT), international normalization ratio (INR), and testing for viral hepatitis). During the course of treatment, serum ALT should be monitored weekly for the duration of treatment. If ALT values increase to a level above the upper limit of normal or 30 percent above baseline, or if the patient develops symptoms, ketoconazole treatment should be interrupted, and a full set of liver tests should be obtained (1).

Ketoconazole tablets can prolong the QT interval. Co-administration of the following drugs with ketoconazole is contraindicated: dofetilide, quinidine, pimozide, cisapride, methadone, disopyramide, dronedarone and ranolazine. Ketoconazole can cause elevated plasma concentrations of these drugs which may prolong the QT interval, sometimes resulting in life-threatening ventricular dysrhythmias such as torsades de pointes (1).

Ketoconazole tablets have warnings for enhanced sedation, myopathy, ergotism, liver disease, hypersensitivity, adrenal insufficiency, adverse reactions associated with unapproved uses and hypersensitivity (1).

The safety and effectiveness of Ketoconazole in pediatric patients less than 2 years of age have not been established (1).

Related policies

Cresemba, Itraconazole, Vfend

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Ketoconazole tablets may be considered **medically necessary** in patients 2 years of age or older for the treatment of metastatic castration resistant prostate cancer or one the following systemic fungal infections in patients who have failed or who are intolerant to other therapies: *blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis*; and if the conditions indicated below are met.

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Ketoconazole tablets may be considered **investigational** in patients less than 2 years of age and for all other indications.

Prior-Approval Requirements

Age 2 years of age or older

Diagnoses

Patient must have **ONE** of the following:

1. Metastatic castration resistant (also known as hormone refractory) prostate cancer
2. Laboratory and clinical documentation of **ONE** of the infections:
 - a. *Blastomyces dermatitidis*
 - b. *Coccidioides immitis*
 - c. *Histoplasma capsulatum*
 - d. *Paracoccidioides brasiliensis*

AND ALL of the following:

1. Prior alternative antifungal therapies were not effective or tolerated
2. Absence of acute or chronic liver disease
3. Baseline liver function tests be done before start of treatment
4. During the course of treatment, serum ALT should be monitored weekly for the duration of treatment.
 - a. Treatment will be interrupted if ALT levels increase to a level above the upper limit of normal or 30 percent above baseline, or if the patient develops symptoms

Prior – Approval *Renewal* Requirements

Age 2 years of age or older

Diagnoses

Patient must have **ONE** of the following:

1. Metastatic castration resistance (also known as hormone refractory) prostate cancer
2. Laboratory and clinical documentation of **ONE** of the infections:

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- a. *Blastomyces dermatitidis*
- b. *Coccidioides immitis*
- c. *Histoplasma capsulatum*
- d. *Paracoccidioides brasiliensis*

AND ALL of the following:

1. Absence of acute or chronic liver disease
2. During the course of treatment, serum ALT should be monitored weekly for the duration of treatment.
 - a. Treatment will be interrupted if ALT levels increase to a level above the upper limit of normal or 30 percent above baseline, or if the patient develops symptoms

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Quantity 540 tablets per 90 days for prostate cancer
180 tablets per 90 days for infection

Duration 6 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Ketoconazole is an imidazole antifungal agent available as an oral tablet and various topical formulations. Ketoconazole tablets should only be used when other effective antifungal therapy is not available or tolerated and the potential benefits are considered to outweigh the potential risks. For the management of prostate cancer, ketoconazole tablets inhibit androgen. Ketoconazole tablets carry a boxed warning for hepatotoxicity, QT prolongation and drug interactions leading to QT prolongation. Ketoconazole tablets is contraindicated in patients with acute or chronic liver disease. Ketoconazole tablets have warnings for enhanced sedation, myopathy, ergotism, liver disease, hypersensitivity, adrenal insufficiency, adverse reactions

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associated with unapproved uses and hypersensitivity. The safety and effectiveness of Ketoconazole in pediatric patients less than 2 years of age have not been established (1).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of ketoconazole tablets while maintaining optimal therapeutic outcomes.

References

1. Ketoconazole [package insert]. Morgantown, WV: Mylan Pharmaceuticals, Inc.; March 2018.
2. Ketoconazole. Clinical Pharmacology [database online]. Tampa, FL: Elsevier; publication year 2021. Available from: <http://www.clinicalkey.com>.
3. NCCN Drugs & Biologics Compendium® Ketoconazole 2022. National Comprehensive Cancer Network, Inc. Accessed on October 3, 2022.

Policy History

Date	Action
October 2013	Addition to PA
May 2014	Addition of off label indication: metastatic prostate cancer
June 2015	Annual criteria review and reference update Removal of baseline tests (serum gamma-glutamyl transferase (SGGT), alkaline phosphatase, prothrombin time (PT), international normalization ratio (INR), viral hepatitis and drug interactions)
September 2015	Annual review
March 2016	Annual editorial review and reference update Policy code changed from 5.03.23 to 5.01.23
December 2017	Annual editorial review and reference update Addition of age requirement to renewal section
November 2018	Annual editorial review and reference update
December 2019	Annual review and reference update
December 2020	Annual review
June 2021	Annual editorial review and reference update
December 2021	Annual review and reference update
June 2022	Annual review and reference update
December 2022	Annual review and reference update. Changed policy number to 5.01.023

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 2, 2022 and is effective on January 1, 2023.