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5.01.023

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| **Section:** | Prescription Drugs | **Effective Date:** | July 1, 2024 |
| **Subsection:** | Anti-infective Agents | **Original Policy Date:** | October 1, 2013 |
| **Subject:** | Ketoconazole | **Page:** | 1 of 5 |

***Last Review Date:*** June 13, 2024

# 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 indications: 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).

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 hepatitides). 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** if the conditions indicated below are met.

Ketoconazole tablets may be considered **investigational** 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:
    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 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 2024. National Comprehensive Cancer Network, Inc. Accessed on April 18, 2024.

## 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<br>Removal of baseline tests (serum gamma-glutamyl transferase (SGGT), alkaline phosphatase, prothrombin time (PT), international normalization ratio (INR), viral hepatitides and drug interactions |
| September 2015 | Annual review |
| March 2016 | Annual editorial review and reference update<br>Policy code changed from 5.03.23 to 5.01.23 |
| December 2017 | Annual editorial review and reference update<br>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 |
| June 2023 | Annual review and reference update |
| June 2024 | Annual review and reference update |

## Keywords

**This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 13, 2024 and is effective on July 1, 2024.**