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5.01.23

Section:	Prescription Drugs	**Effective Date:**	January 1, 2019
Subsection:	Anti-infective Agents	**Original Policy Date:**	October 1, 2013
Subject:	Ketoconazole	**Page:**	1 of 6

Last Review Date: November 30, 2018

Ketoconazole

Description

Ketoconazole tablets

Background
Ketoconazole is a strong antifungal agent that is taken by mouth. It works by weakening the structure and function of the fungal cell membrane. Ketoconazole should only be used for patients with serious fungal infections when other fungal medications have not worked because it can cause liver damage. Treatment should be continued only until the fungal infection goes away, which is usually 6 months or less (1-2).

Regulatory Status
FDA-approved indication: Ketoconazole 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 oral tablets should not be a first-line treatment for any fungal infection. Ketoconazole should be used for the treatment of certain fungal infections, known as endemic mycoses, only when alternative antifungal therapies are not available or tolerated (2).

Ketoconazole has a boxed warning regarding serious hepatotoxicity, which may potentially result in liver transplantation or death. Some patients had no obvious risk factors for liver disease. Serious hepatotoxicity was reported both by patients receiving high doses for short treatment durations and by patients receiving low doses for long durations. The use of ketoconazole tablets is contraindicated in patients with acute or chronic liver disease (1-2).

At baseline, obtain laboratory tests (such as serum gamma-glutamyl transferase (SGGT), alkaline phosphatase, ALT, AST, total bilirubin (TBL), prothrombin time (PT), international normalization ratio (INR), and testing for viral hepatitides (1).

Prompt recognition of liver injury is essential. 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. Liver tests should be repeated to ensure normalization of values. Hepatotoxicity has been reported with restarting oral ketoconazole (rechallenge). If it is decided to restart oral ketoconazole, monitor the patient frequently to detect any recurring liver injury from the drug If possible, use of other potentially hepatotoxic drugs should be avoided in patients receiving ketoconazole tablets (1-2).

There is a boxed warning on the label stating that Ketoconazole can prolong the QT interval. Co-administration of the following drugs with ketoconazole is contraindicated: dofetilide, quinidine, pimozide, and cisapride. 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 decrease adrenal corticosteroid secretion at doses of 400 mg and higher. This effect is not shared with other azoles. Adrenal function should be monitored in patients with adrenal insufficiency or with borderline adrenal function and in patients under prolonged periods of stress (major surgery, intensive care, etc.) (1-2).

Ketoconazole has not been studied in children under 2 years of age (1).

Related policies
Cresemba, Sporanox/ Onmel

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 (ketoconazole) tablets may be considered **medically necessary** in patients that are 2 years of age and 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: b*lastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis*, and *paracoccidioidomycosis;* and if the conditions indicated below are met.

Ketoconazole (ketoconazole) is considered **investigational** in patients that are 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:
   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

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

Duration 6 months

Rationale

Summary
Ketoconazole oral tablets should not be a first-line treatment for any fungal infection and should be used only when other antifungal drugs are not available or tolerated by the patient. The use of ketoconazole tablets in candida, dermatophyte and fungal infections of the skin or nails is no longer indicated. Due to ketoconazole's ability to inhibit adrenal androgen synthesis it has been found to be useful for certain patients with castration resistant prostate cancer (2).

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. FDA Drug Safety Communication: FDA limits usage of Ketoconazole (ketoconazole) oral tablets due to potentially fatal liver injury and risk of drug interaction and adrenal gland problems. Safety Announcement July 26, 2013. Accessed on August 21, 2018.
3. NCCN Drugs & Biologics Compendium® Ketoconazole 2017. National Comprehensive Cancer Network, Inc.

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 hepatitides 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

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on November 30, 2018 and is effective January 1, 2019.