RATIONALE FOR INCLUSION IN PA PROGRAM

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).

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).

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).
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 of the following systemic fungal infections in patients who have failed or who are intolerant to other therapies: *blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis,* and *paracoccidioidomycosis*; prior alternative antifungal therapies were not effective or tolerated, absence of acute or chronic liver disease, baseline liver function tests be done before start of treatment; during the course of treatment, serum ALT should be monitored weekly for the duration of treatment and stopped if ALT levels increase to a level above the upper limit of normal or 30 percent above baseline, or if the patient develops symptoms.

Ketoconazole (ketoconazole) is considered **investigational** in patients that are less than 2 years of age or in patients who do not have metastatic castration resistance prostate cancer or a confirmed systemic fungal infection of *blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis,* or *paracoccidioidomycosis*.

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

**References**