NATIONAL PBM BULLETIN

MAY 31, 2016

DEPARTMENT OF VETERANS AFFAIRS
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP), VISN PHARMACIST EXECUTIVES (VPEs), AND THE CENTER FOR MEDICAL SAFETY (VA MedSAFE)

KETOCONAZOLE SAFETY

I. ISSUE

A Food and Drug Administration (FDA) safety review found that oral ketoconazole continues to be prescribed for treatment of skin and nail fungal infections **despite previous label changes limiting usage of ketoconazole (Nizoral) oral tablets due to potentially fatal liver injury and risk of drug interactions as well as adrenal gland problems**.

II. BACKGROUND

According to the FDA, an office-based physician surveys database showed that in the 18 months ending in June 2015, skin and nail fungal infections comprised the only diagnoses cited for the use of oral ketoconazole. Since the 2013 labeling changes, one patient death has been reported to the FDA due to liver failure associated with oral ketoconazole prescribed to treat a fungal infection of the nails. The topical forms of ketoconazole that are applied to the skin or nails have not been associated with liver damage, adrenal problems, or drug interactions.

III. DISCUSSION

In July 2013, FDA approved label changes for ketoconazole and added a new Medication Guide to:

- **Limit ketoconazole oral tablet use**
  - The use of ketoconazole tablets in *Candida* and dermatophyte infections is no longer indicated. **Nizoral tablets should be used only when other antifungal drugs are not available or tolerated by the patient** [*Boxed Warning, Warnings, Precautions*, and *Indications and Usage* sections].
  - Nizoral tablets are indicated only for the treatment of the following fungal infections: blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis **in patients in whom other treatments have failed or who are intolerant to other therapies** [*Indications and Usage* section].
  - Nizoral tablets are **not indicated for the treatment of fungal infections of the skin or nails.**
- **Warn that ketoconazole oral tablets can cause severe liver injuries and adrenal gland problems**
  - Nizoral tablets should not be used in patients with acute or chronic liver disease [*Contraindications* section].
  - New assessment and monitoring recommendations for evaluation of hepatotoxicity should be followed [*Boxed Warning, Warnings,* and *Precautions* sections].
  - Assess the liver status of the patient before starting oral ketoconazole, with baseline laboratory tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, prothrombin time, and international normalized ratio (INR).
  - While the patient is taking oral ketoconazole, 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 of abnormal liver function, 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.

(continued on page 2)

NATIONAL PBM BULLETIN

MAY 31, 2016

DEPARTMENT OF VETERANS AFFAIRS
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP),
VISN PHARMACIST EXECUTIVES (VPEs), AND THE CENTER FOR MEDICAL SAFETY (VA MedSAFE)

KETOCONAZOLE SAFETY *(continued from page 1)*

  - Hepatotoxicity has been reported with restarting of oral ketoconazole.
  - Do not use Nizoral tablets in patients with underlying liver disease.
  - Other hepatotoxic drugs and alcohol should be avoided while taking Nizoral tablets.
  - 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.) [*Warnings* section].
- **Advise that ketoconazole oral tablets can lead to harmful drug interactions with other medications** [*Precautions* section].
  - Ketoconazole is one of the most potent inhibitors of the cytochrome P450 3A4 isoenzyme (CYP3A4). The clearance of other co-administered drugs that are metabolized by CYP3A4 is decreased by ketoconazole and can result in increased drug concentrations in plasma, which can predispose patients to potentially serious adverse reactions including QT prolongation.

This was previously addressed in Issue 7; Volume 3; July/August 2013 of *Medication Safety in Seconds*, a safety newsletter published by the VA Center for Medication Safety (VA MedSAFE) in conjunction with the National Pharmacy Benefits Management Services (PBM).

IV. PROVIDER CONSIDERATIONS/RECOMMENDATIONS

FDA recommends that:

- Health care professionals should use ketoconazole tablets only to treat serious fungal infections when no other antifungal therapies are available. **It is extremely unusual for ketoconazole to be more appropriate than other antifungal therapies.**
- Since skin and nail fungal infections in otherwise healthy persons are not life-threatening, the risks associated with oral ketoconazole outweigh the benefits.
- Providers should discuss with their patients the risks and benefits of available therapies before using any medicine to treat skin and nail fungal infections.
- Providers should instruct patients taking ketoconazole tablets to seek medical attention right away if they experience any of these signs and symptoms of liver problems, which include loss of appetite, nausea, vomiting, or abdominal discomfort; yellowing of the skin or the whites of the eyes (jaundice); unusual darkening of the urine or lightening of the stools; or pain and discomfort in the right upper abdomen where the liver is located.

Providers should continue to report any adverse reactions with the use of ketoconazole (Nizoral) by entering the information into CPRS' Allergies/ Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (1-800-FDA-1088, fax 1-800-FDA-0178, online at

(continued on page 3)

NATIONAL PBM BULLETIN

MAY 31, 2016

DEPARTMENT OF VETERANS AFFAIRS
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP),
VISN PHARMACIST EXECUTIVES (VPEs), AND THE CENTER FOR MEDICAL SAFETY (VA MedSAFE)

KETOCONAZOLE SAFETY *(continued from page 2)*

https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm, or by mail).

V. REFERENCES

FDA Drug Safety Communication: FDA warns that prescribing of Nizoral (ketoconazole) oral tablets for unapproved uses including skin and nail infections continues; linked to patient death. http://www.fda.gov/Drugs/DrugSafety/ucm500597.htm (Accessed May 19, 2016).

ACTIONS

- ***Facility Director*** *(or physician designee): Forward this document to the Facility Chief of Staff (COS).*
- ***Facility COS and Chief Nurse Executives:*** *Forward this document to all appropriate providers and health care staff (e.g.,* ***primary care providers, infectious disease providers, dermatologists, and podiatrists including contract providers, etc****.). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.*
- ***ACOS for R&D:*** *Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).*