

FDA Drug Safety Communication: FDA limits usage of Nizoral (ketoconazole) oral tablets due to potentially fatal liver injury and risk of drug interactions and adrenal gland problems

Safety Announcement

[7-26-2013] The U.S. Food and Drug Administration (FDA) is taking several actions related to Nizoral (ketoconazole) oral tablets, including limiting the drug's use, warning that it can cause severe liver injuries and adrenal gland problems and advising that it can lead to harmful drug interactions with other medications. FDA has approved label changes and added a new Medication Guide to address these safety issues. As a result, Nizoral oral tablets should not be a first-line treatment for any fungal infection. Nizoral should be used for the treatment of certain fungal infections, known as endemic mycoses, only when alternative antifungal therapies are not available or tolerated.

The topical formulations of Nizoral have not been associated with liver damage, adrenal problems, or drug interactions. These formulations include creams, shampoos, foams, and gels applied to the skin, unlike the Nizoral tablets, which are taken by mouth.

Liver Injury (Hepatotoxicity)

Nizoral tablets can cause liver injury, which may potentially result in liver transplantation or death. FDA has revised the Boxed Warning, added a strong recommendation against its use (contraindication) in patients with liver disease, and included new recommendations for assessing and monitoring patients for liver toxicity (see Additional Information sections).

Serious liver damage has occurred in patients receiving high doses of Nizoral for short periods of time as well as those receiving low doses for long periods. Some of these patients had no obvious risk factors for liver disease. The liver injury is sometimes reversible upon stopping the drug, but that is not always possible.

Adrenal Gland Problems (Adrenal Insufficiency)

Nizoral tablets may cause adrenal insufficiency by decreasing the body's production of hormones called corticosteroids. Corticosteroids are produced by the adrenal glands, which are small glands located on top of each kidney. Corticosteroids affect the body's balance of water and salts and minerals (electrolytes). Health care professionals should monitor adrenal function in patients taking Nizoral tablets who have existing adrenal problems or in patients who are under prolonged periods of stress such as those who have had a recent major surgery or who are under intensive care in the hospital.

Drug Interactions

Nizoral tablets may interact with other drugs a patient is taking and can result in serious and potentially life-threatening outcomes, such as heart rhythm problems. All medications that a patient is currently taking should be assessed for possible interactions with [Nizoral tablets](#).

In summary, the drug label for [Nizoral tablets](#) has been updated to include the following information:

- Limitation of the usage of Nizoral tablets by removing indications in which the risk outweighs the benefits. 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.
- A new contraindication that Nizoral tablets should not be used in patients with acute or chronic liver disease (*Contraindications* section).
- Updated information on the risk of liver injury, or hepatotoxicity, with new assessment and monitoring recommendations (*Boxed Warning, Warnings, and Precautions* sections).
- Updated information on drug interactions (*Precautions* section).
- A warning regarding adrenal insufficiency with recommendations for monitoring populations at risk (*Warnings* section).

FDA has also approved a new patient Medication Guide containing information on the potential risks associated with Nizoral tablets, which must be dispensed with every prescription for the drug.

On July 26, 2013, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) announced their negative risk-benefit assessment for oral ketoconazole-containing medicines used to treat infections caused by dermatophytes and yeasts and recommended suspensions of these medicines throughout the European Union (EU). The EMA public announcement of the recommendation to suspend the marketing authorizations of ketoconazole for oral use as antifungal treatment is available at

http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/07/WC500146613.pdf.

In addition to the indications for treatment of infections caused by dermatophytes and *Candida*, the previous US drug label also included indications for the following serious fungal infections: blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. In the

revised US drug label, indications for dermatophyte and *Candida* infections have been removed and the indications for treatment of blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis have been retained only for patients in whom other antifungal treatments have failed or are not tolerated.

FDA will continue to evaluate the safety of Nizoral tablets and will communicate with the public again if additional information becomes available.

Facts about Nizoral (ketoconazole) tablets

- Antifungal drug indicated for the treatment of the following fungal infections when alternatives are not available or not tolerated: blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. Nizoral tablets should not be used for fungal meningitis because it penetrates poorly into the cerebrospinal fluid.
- During 2012, approximately 5.2 million ketoconazole prescriptions were dispensed, of which 609,000 (12%) were for the tablet formulation.¹
- The most common diagnoses associated with the use of oral ketoconazole tablets in outpatient settings over recent years have included superficial skin and nail fungal infections as reported by office-based physicians.²

Additional Information for Patients

- Nizoral tablets may cause liver problems, including life-threatening liver failure or death.
- Nizoral tablets can cause problems with the usual production of corticosteroid hormones and may interact negatively with other medications.
- Contact your health care professional right away if you take Nizoral tablets and experience any of these signs and symptoms of liver problems:
 - Loss of appetite, nausea, vomiting, or abdominal discomfort
 - Fever, feeling unwell, or unusual tiredness
 - Yellowing of the skin or the whites of the eyes (jaundice)
 - Unusual darkening of the urine or lightening of the stools
 - Pain or discomfort in the right upper abdomen, where the liver is located
- Contact your health care professional if you are taking Nizoral tablets for any non-life-threatening infection or if you are unsure, or if you have liver or adrenal problems.
- If you take other medications besides Nizoral tablets, it is important to discuss these medications with your health care professionals, including the prescriber and the pharmacist.

- Your health care professional may order laboratory tests to monitor how your liver is working while you are taking Nizoral tablets and if you develop signs and symptoms of liver problems.
- Do not drink alcohol or use drugs or medications (e.g., acetaminophen) that can cause liver problems while taking Nizoral tablets.
- Carefully read the patient Medication Guide that comes with your ketoconazole prescription.
- Discuss any questions or concerns about Nizoral tablets with your health care professional.
- Report any side effects that you experience to your health care professional and the FDA MedWatch program, using the information in the Contact FDA box at the bottom of the page.

Additional Information for Health Care Professionals

- Nizoral tablets should be used only for the treatment of certain life-threatening mycoses when the potential benefits outweigh the risks and alternative therapeutic options are not available or tolerated.
- Prompt recognition of liver injury is essential.
 - 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.
 - 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.
- Review all concomitant medications for the potential for drug interactions with 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.)
- Report adverse events involving Nizoral tablets to the FDA MedWatch program, using the information in the Contact FDA box at the bottom of the page.

Data Summary

FDA conducted a comprehensive benefit-risk assessment of the safety and efficacy of Nizoral (ketoconazole) tablets in the context of the drug's labeled indications for the treatment of superficial and systemic fungal infections, which resulted in the changes to the drug's label.

Hepatotoxicity

Serious hepatic injury was identified as the major toxicity for Nizoral tablets and was noted to be unrelated to dose, duration, or indication for treatment. In conducting the benefit-risk assessment, spontaneous adverse event reports of ketoconazole-induced liver injury, including fatalities and liver transplantations, retrieved from the FDA Adverse Event Reporting System (AERS) were assessed independently by a hepatology expert in FDA. The overall risk for ketoconazole-induced serious liver injury appeared higher than that associated with other azole antifungal drugs as assessed from pharmacoepidemiologic studies.

One published study in the U.K. General Practice Research Database suggested a risk of acute liver injury (defined as patients presenting with symptoms of liver disorder: nausea, vomiting, abdominal pain and/or jaundice requiring referral to a specialist or hospitalization and free of history of liver disease and other chronic illnesses in the past 5 years) of approximately 1 in 500 patients, and analysis of liver transplantation data indicates that hepatotoxicity from ketoconazole accounted for proportionately more liver transplants than hepatotoxicity from other antifungal drugs³. However, in view of various methodological limitations, there was uncertainty in quantifying precise estimates of the risk of acute liver injury for Nizoral tablets compared to other marketed oral azole antifungals.

Adrenal Insufficiency

Through its inhibition of the cytochrome P450 isoenzyme system, ketoconazole can block production of adrenal steroids. This accounts for clinically important endocrinologic abnormalities observed in some patients (particularly when the drug is administered at high dosages), including gynecomastia in men and menstrual irregularities in women.

Drug Interactions

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. Thus, the co-administration of ketoconazole with some other drugs is restricted or contraindicated in the [drug labels](#).

In conclusion, ketoconazole should not be a first-line treatment for any fungal infection. Ketoconazole is not recommended for the treatment of any form of candidiasis or any superficial fungal infection. Ketoconazole may be considered in the treatment of certain life-threatening systemic mycoses in patients for whom alternate antifungal drugs are not available or cannot be tolerated.

References

1. IMS Health, Vector One®: National. Data extracted June 2013
2. Encuity Research, LLC., Treatment Answers™. Data extracted June 2012
3. Garcia Rodriguez, Duque A, Castellsaque J, et al., A cohort study on the risk of acute liver injury among users of ketoconazole and other antifungal drugs. *Br J Clin Pharmacol* 1999 Dec.; 48(6):847-852.