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Dear Dr. Hamburg and Dr. Woodcock:

Public Citizen, a consumer advocacy organization with more than 350,000 members and supporters nationwide, hereby petitions the Food and Drug Administration (FDA), pursuant to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(e), and 21 C.F.R. § 10.30, to immediately require the removal from the market of the oral form of the antifungal agent ketoconazole¹ because the drug's risks of fatal liver failure and adrenal insufficiency, and its numerous drug interactions, outweigh its limited benefits in treating fungal infections.

¹ For the remainder of this document, unless otherwise indicated, "ketoconazole" refers only to oral formulations of ketoconazole approved in the U.S., and not to other formulations (e.g., topical), which do not carry the same safety concerns and which are not covered in the petition's requests.

I. STATEMENT OF GROUNDS

A. Background

Ketoconazole was approved in 1981 for the treatment of several fungal infections, and there are currently several generic versions on the market² (the original manufacturer recently withdrew its brand-name version, Nizoral, from the market³). Originally, ketoconazole was indicated to treat several systemic⁴ and nonsystemic fungal infections.⁵ In addition to these approved indications, ketoconazole has sometimes been used off-label to treat endocrine disorders, such as Cushing's syndrome, and androgen-dependent prostate cancer⁶ because of its ability to suppress adrenal and testicular steroid production, respectively, at high doses.⁷ In 2012, approximately 5.2 million ketoconazole prescriptions were dispensed, of which 609,000 (12 percent) were for tablet formulations, with nonsystemic fungal infections treated in outpatient clinics representing the most common use.⁸ By 2014, 462,000 prescriptions were still dispensed for the drug.⁹

On July 26, 2013, the FDA issued a safety communication removing several of ketoconazole's approved indications, including fungal dermatophyte (skin, hair, and nail) infections and various systemic candida infections, due to the drug's severe risks of liver injury, adrenal gland dysfunction, and numerous medication interactions.¹⁰ The FDA also mandated that a medication guide be distributed with the drug, informing patients of these risks and restricted uses.

Ketoconazole's hepatotoxic effects were apparent soon after its approval. In 1983, the FDA required that a black-box warning be added to the label about fatal hepatotoxicity.¹¹ Over the ensuing three decades, more evidence has accumulated quantifying the drug's hepatic effects relative to those of other antifungal agents. Liver injury caused by oral ketoconazole has been

² Food and Drug Administration. CDER Regulatory Briefing. Benefit-Risk Assessment of Oral Ketoconazole Tablets. January 4, 2013. Page 3. Internal memo obtained by Public Citizen, hereafter cited as "FDA Memo" **and enclosed at the end of this petition.**

³ Food and Drug Administration. FDA Approved Drug Products. Nizoral is listed as "discontinued", with the last label change implemented in February 2014. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>. Accessed January 28, 2015.

⁴ As used in this document, "systemic" fungal infections refer to non-superficial (i.e., skin, hair, or nail) fungal infections that affect one or more internal organs, or the entire body.

⁵ FDA Memo, p. 3.

⁶ FDA Memo, p. 3.

⁷ FDA Memo, p. 6.

⁸ Food and Drug Administration. 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. July 26, 2013. <http://www.fda.gov/Drugs/DrugSafety/ucm362415.htm>. Accessed January 13, 2015.

⁹ IMS Health data. Obtained on January 30, 2015.

¹⁰ Food and Drug Administration. 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. July 26, 2013. <http://www.fda.gov/Drugs/DrugSafety/ucm362415.htm>. Accessed January 13, 2015. On October 16, 2013, the FDA further recommended that pharmaceutical companies and researchers avoid using oral ketoconazole and instead use other strong inhibitors of the CYP3A enzyme in drug interaction studies in healthy subjects. See: Food and Drug Administration. FDA Drug Safety Communication: FDA advises against using oral ketoconazole in drug interaction studies due to serious potential side effects. October 16, 2013. <http://www.fda.gov/Drugs/DrugSafety/ucm371017.htm>. Accessed January 13, 2015.

¹¹ FDA Memo, p. 3.

estimated to occur in one of 500 patients, and one per 750 person-months of exposure, with no history of liver disease.¹² Liver damage can be severe, leading to liver transplant or death in some patients, including in those without a history of liver disease. Although other antifungal medications in the same class also can cause liver damage, the risk is considerably higher with ketoconazole.¹³ Oral ketoconazole also can cause adrenal insufficiency, affecting the body's balance of water, salts, and electrolytes, and can interact with numerous drugs, leading to potentially fatal heart rhythm disturbances.¹⁴

However, despite these risks, the agency still has allowed the drug to be marketed for five systemic fungal infections (blastomycosis, histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, and chromomycosis) as a last resort if other antifungals fail or are not tolerated, and only in those without pre-existing liver disease (see Table 1, page 11).¹⁵

The same day as the FDA's July 2013 announcement, a key committee of the European Medicines Agency (EMA; the European equivalent of the FDA) recommended that all oral formulations of ketoconazole be removed from the European market because it concluded that the drug's risks outweighed its benefits for all indications.¹⁶ That agency stated that there were "inadequate data to support the efficacy of ketoconazole when other treatments have failed or are not tolerated, or resistance has been detected" and that proposals (similar to the FDA's) to mitigate the drug's risks would not be "sufficient to reduce the risk of hepatotoxicity to an acceptable level" in light of the drug's uncertain benefits.¹⁷ (While the EMA has since recommended bringing ketoconazole back on the European market for the treatment of Cushing's syndrome,¹⁸ its 2013 decision to remove the antifungal indications for all oral formulations of ketoconazole still stands. In addition, the FDA has not approved ketoconazole for treatment of Cushing's syndrome in the U.S.)

¹² Food and Drug Administration. 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. July 26, 2013. <http://www.fda.gov/Drugs/DrugSafety/ucm362415.htm>. Accessed January 20, 2015.

¹³ European Medicines Agency. European Medicines Agency recommends suspension of marketing authorisations for oral ketoconazole. July 26, 2013. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/07/news_detail_001855.jsp. Accessed January 20, 2015.

¹⁴ Food and Drug Administration. 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. July 26, 2013. <http://www.fda.gov/Drugs/DrugSafety/ucm362415.htm>. Accessed January 20, 2015.

¹⁵ Food and Drug Administration. 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. July 26, 2013. <http://www.fda.gov/Drugs/DrugSafety/ucm362415.htm>. Accessed January 20, 2015.

¹⁶ European Medicines Agency. European Medicines Agency recommends suspension of marketing authorisations for oral ketoconazole. July 26, 2013. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/07/news_detail_001855.jsp. Accessed January 13, 2015.

¹⁷ European Medicines Agency. European Medicines Agency recommends suspension of marketing authorisations for oral ketoconazole. July 26, 2013. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/07/news_detail_001855.jsp. Accessed January 20, 2015.

¹⁸ European Medicines Agency. Ketoconazole HRA recommended for approval in Cushing's syndrome. September 26, 2014. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/09/news_detail_002174.jsp. Accessed January 20, 2015.

Public Citizen has learned that six months before the FDA's July 2013 announcement restricting ketoconazole, a team of FDA experts at the Office of Surveillance and Epidemiology (OSE; hereafter referred to as the "OSE review team" or "OSE reviewers") reached a different conclusion, agreeing instead with the eventual assessment of the EMA's Committee for Medicinal Products for Human Use with respect to the risk-benefit ratio of oral ketoconazole for fungal infections. The OSE review team included 14 scientists, including two hepatologists with expertise in drug-induced liver damage, Drs. John Senior and Leonard Seeff.¹⁹ Public Citizen obtained a copy of an internal memo (enclosed at the end of this petition), dated January 4, 2013, in which the OSE review team concluded that, in the context of **all** of the drug's labeled indications, **"it was unable to view the risk of serious potentially life-threatening hepatic injury as tolerable for the potential benefit of ketoconazole treatment."**²⁰ [Emphasis added]

We agree with the conclusion of the OSE reviewers and the EMA that ketoconazole should be banned because there are no patients for whom the benefits of ketoconazole outweigh its risks and there are other effective, safer therapies for the fungal infections for which ketoconazole is still used today. Much of the supporting evidence outlined in this petition derives from the OSE review team's memo, an exhaustive analysis of all relevant data since ketoconazole's approval in 1981, which forms the basis of its recommendation to ban the drug, supplemented by additional medical publications and guidelines issued by the Infectious Diseases Society of America.

B. Safety discussion: Ketoconazole uniquely toxic

Given the overall consensus (including on the part of the aforementioned OSE reviewers and the EMA) on the nature and scale of the risks of ketoconazole, this petition will only briefly discuss the drug's risks, relying mainly on OSE reviewers' recent analysis.

1. Hepatotoxicity

a. Pathophysiology

The pathophysiology of ketoconazole-associated liver injury is not completely understood. Studies have shown that a metabolite of ketoconazole known as N-deacetyl ketoconazole is transformed into N-deacetyl-N-hydroxyketoconazole.²¹ This metabolite is further transformed into smaller products that are toxic to hepatocytes, including hepatocellular mitochondria, where function is impaired. The resulting injury is primarily a hepatocellular pattern, with increased alanine aminotransferase levels, although some cases of reported liver injury reflected cholestatic and mixed hepatocellular/cholestatic patterns.²²

¹⁹ We have learned that the OSE review team consisted of the following scientists: Fred Sorbello, Chris Jones, Andy Mosholder, Hina Mehta, Leonard Seeff, Vicky Borders-Hemphill, Neha Gada, Judy Staffa, Linda Scarazzini, Bindi Nikhar, Kelly Cao, Beth Maloney, John Senior, and Laura Governale.

²⁰ FDA Memo, p. 48.

²¹ FDA Memo, p. 5.

²² FDA Memo, p. 4.

b. Literature review

A 1999 observational study of the U.K. General Practice Research Database (GPRD) was the most rigorous study reviewed in the OSE review team's analysis²³ and formed the basis for the estimate of the incidence of ketoconazole-induced hepatotoxicity presented in the FDA's July 2013 safety communication.²⁴ Garcia-Rodriguez et al. conducted a retrospective cohort study of British patients in the GPRD, a database of electronic medical records submitted by a network of general practitioners in the U.K., to determine the risk of liver injury from several antifungal drugs, including ketoconazole.²⁵ Patients without a recent history of liver disease or a number of other serious illnesses who received one or more prescriptions for an antifungal drug were included in the analysis. The authors estimated that acute liver injury associated with ketoconazole use occurred in one in 500 patients, far exceeding the estimated incidence for the other four antifungal drugs studied.²⁶ When accounting for duration of exposure, the incidence was approximately one per 750 person-months of exposure.

Janssen Pharmaceuticals, the original manufacturer of ketoconazole, presented an early estimate of the incidence of ketoconazole-induced "symptomatic hepatic reactions" of only one in 10,000-15,000.²⁷ However, the OSE review team pointed out that the study had many limitations, not the least of which was a reliance on voluntary adverse event reports to estimate incidence.²⁸ (It is estimated that as few as 2 to 20 percent of all adverse events are reported to the FDA.²⁹) Analyzing the Janssen data, Stricker et al. estimated a true incidence of one in 1,000 or greater after adjusting for likely underreporting of adverse events,³⁰ which more closely resembles the one-in-500 estimate formulated by Garcia-Rodriguez et al.

A Taiwanese randomized trial of 211 subjects without liver disease found that four of 137 subjects (3 percent) randomized to ketoconazole acquired clinical hepatitis, and 24 (18 percent) had asymptomatic transaminase elevations, compared with none of the 74 griseofulvin-treated subjects.³¹ However, the OSE review team thought that a clinical hepatitis incidence of 3 percent was unusually high and inconsistent with other clinical trial data showing an incidence of less than 1 percent.

²³ FDA Memo, p. 15; Garcia-Rodriguez LA, Duque A, Castellsague J, Perez-Gutthann S, Stricker BH. A cohort study on the risk of acute liver injury among users of ketoconazole and other antifungal drugs. *Br J Clin Pharmacol*. 1999;48(6):847-852.

²⁴ 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. July 26, 2013. <http://www.fda.gov/Drugs/DrugSafety/ucm362415.htm>. Accessed January 13, 2015.

²⁵ FDA Memo, p. 15.

²⁶ FDA Memo, p. 16.

²⁷ FDA Memo, p. 17; Janssen PAJ, Cauwenbergh G, Symoens J. Hepatic reactions during ketoconazole treatment: A 1 year update. Beerse, Belgium: Janssen Pharmaceutica; 1983. [As reported in: Lewis JH, Zimmerman J, Benson GD, et al. Hepatic injury associated with ketoconazole therapy. *Gastroenterology*. 1984;86:503-513]

²⁸ FDA Memo, p. 18.

²⁹ Hazell L, Shakir SA. Under-reporting of adverse drug reactions: A systematic review. *Drug Saf*. 2006;29:385-396.

³⁰ FDA Memo, p. 18; Stricker B, Blok A, Bronkhorst F, Van Parys G, Desmet V. Ketoconazole-associated hepatic injury. *J Hepatol*. 1986;3:399-406.

³¹ FDA Memo, p. 17.

A Chinese meta-analysis published in 2013 reviewed 205 English- and Chinese-language studies using total daily doses primarily from 200 to 400 milligrams (mg)/day.³² Lower and higher doses were included as well. The meta-analysis included randomized controlled trials, cohort studies, and case series. The rate of ketoconazole-associated hepatotoxicity was 3.4 percent of all patients, using an intention-to-treat analysis in randomized control trials, and 3.6-4.2 percent of patients across all study types. However, neither the diagnostic criteria nor the severity of the liver injuries was discussed, and a dose- or duration-dependent relationship with hepatotoxicity was not found.

c. Adverse Event Reporting System data

The OSE review team searched the FDA's Adverse Event Reporting System (AERS) for cases of serious liver injury associated with ketoconazole use from 1980 through 2011.³³ A total of 42 cases of serious hepatotoxicity temporally associated with oral ketoconazole use in U.S. patients were found. Two-thirds (28) of these patients had no history of liver disease or malignancy. The median dose of ketoconazole was 200 mg/day, consistent with the FDA's dosing recommendations of 200-400 mg/day, and the median duration of use before hepatotoxicity was identified was 51 days.

Ninety percent of the patients were hospitalized, almost one-quarter of the patients required liver transplantation, and half died. There was one positive rechallenge, in which a 22-year-old female discontinued ketoconazole after developing jaundice, with elevated bilirubin and transaminase levels, and subsequently developed fulminant liver failure requiring transplant only two weeks after ketoconazole was restarted.

After assessing for potential alternative causes and applying causality criteria to the 42 cases, Dr. Leonard Seeff, one of the two hepatologists on the OSE review team, categorized 19 of the 42 (45 percent) "as probable or more likely to be causally related to ketoconazole therapy." Sixteen of these 19 cases (84 percent) resulted in death or liver transplantation.

d. United Network for Organ Sharing data

According to the OSE reviewers, the United Network for Organ Sharing (UNOS) database is thought to contain records of "essentially all" liver transplants that are performed in the U.S.³⁴ UNOS provided the FDA with records of all transplants attributed to ketoconazole, itraconazole, and fluconazole liver injury performed between October 1, 1987, and April 30, 2012, in addition to counts of patients placed on waiting lists between April 1, 1994, and April 30, 2012.³⁵

Ketoconazole was responsible for 10 liver transplants performed during this period and three additional cases of liver failure awaiting transplant since 1994, compared with none attributed to

³² Yan JY, Nie XL, Tao QM, Zhan SY, Zhang YD. Ketoconazole associated hepatotoxicity: A systematic review and meta-analysis. *Biomed Environ Sci.* 2013;26(7):605-610.

³³ FDA Memo, p. 7. Results of AERS search presented on p. 12-14.

³⁴ FDA Memo, p. 19.

³⁵ FDA Memo, p. 8-9.

either itraconazole or fluconazole.³⁶ Since 1991, ketoconazole led to approximately one transplant per 2 million prescriptions.³⁷ Were the other antifungals as hepatotoxic as ketoconazole, fluconazole would have led to 80 transplants and itraconazole 6 based on usage.³⁸

e. MiniSentinel analysis

OSE reviewers also analyzed the FDA's MiniSentinel database, which contains health care claims data from academic institutions, health insurance companies, and health maintenance organizations around the country, for rates of liver injury associated with several antifungals between January 2000 and September 2011.³⁹ While rates of liver injury with ketoconazole did not differ substantially from those with other antifungals (except voriconazole, which exhibited a much higher rate of hepatic events than any other antifungal, perhaps due to a sicker patient population treated with the drug), the reviewers noted that the data came with many limitations, most notably a potential underestimate of the true hepatic event rates due to a restrictive case definition (only primary discharge diagnoses of acute and subacute necrosis of the liver and "hepatitis unspecified" were assessed).

f. Estimated frequency of ketoconazole-associated hepatotoxicity in 2014

The primary study on which the OSE reviewers relied was that by Garcia-Rodriguez et al. of a cohort of 69,830 patients in the GPRD.⁴⁰ In this study, the estimated incidence of ketoconazole-associated hepatotoxicity, defined as symptomatic acute liver injury necessitating referral to a hospital or specialist, was 134.1 per 100,000 person-months of exposure. This is approximately equal to one case per 750 person-months of exposure. Of note, 90 percent of all prescriptions in this study were for less than one month and the study included only subjects with no history of hepatic disease or liver injury in the previous five years.

According to data obtained from IMS Health, 462,000 ketoconazole prescriptions were dispensed in 2014.⁴¹ The most conservative estimate of the number of new ketoconazole-associated liver injury cases resulting from prescriptions dispensed in 2014 would assume that all of these prescriptions were for only one month of therapy. Thus, extrapolating the Garcia-Rodriguez incidence of liver injuries per person-month of exposure, ketoconazole use in 2014

³⁶ FDA Memo, p. 21. Data as reported by UNOS to the FDA on July 17, 2012. There were slight discrepancies between the data provided by UNOS to the FDA in 2012 and those reported in two separate publications: 1) Russo MW, Galanko JA, Shrestha R, et al. Liver transplantation for acute liver failure from drug induced liver injury in the United States. *Liver Transpl.* 2004;10:1018-1023; and 2) Mindikoglu AL, Magder LS, Regev A. Outcome of liver transplantation for drug-induced acute liver failure in the United States: Analysis of the United Network for Organ Sharing database. *Liver Transpl.* 2009;15:719-729. The OSE review team was unable to determine the cause of these discrepancies, however, they did not substantively affect the differences in the rates between ketoconazole-induced liver transplants and those induced by itraconazole or fluconazole.

³⁷ FDA Memo, p. 22.

³⁸ FDA Memo, p. 21.

³⁹ FDA Memo, p. 9. Results presented on p. 19-21.

⁴⁰ FDA Memo, p. 15; Garcia-Rodriguez LA, Duque A, Castellsague J, Perez-Gutthann S, Stricker BH. A cohort study on the risk of acute liver injury among users of ketoconazole and other antifungal drugs. *Br J Clin Pharmacol.* 1999;48(6):847-852.

⁴¹ IMS Health data. Obtained on January 30, 2015.

may potentially have resulted in 616 cases of symptomatic acute liver injury necessitating hospitalization or specialist referral.

2. Drug interactions, including with statins leading to potentially fatal rhabdomyolysis

A variety of factors make ketoconazole a more frequent culprit in drug interactions than all other azole antifungal drugs. Among the azole class of antifungal drugs, it is the most potent inhibitor of hepatic enzyme CYP3A4, which is responsible for the metabolism of numerous drugs and, due to its lipophilicity, concentrates in the liver in high amounts, furthering the inhibition of the enzyme.⁴² After analyzing the MicroMedex 2.0 drug information database from Truven Health Analytics, OSE reviewers concluded that ketoconazole is known to interact with substantially more drugs than either itraconazole or fluconazole, including those causing the most dangerous drug interactions.⁴³

OSE reviewers analyzed the AERS database for cases of myopathy reported in patients treated with ketoconazole. A total of 32 cases of myopathy were reported with ketoconazole use, 28 of which were rhabdomyolysis.⁴⁴ In 26 of the 32 cases, ketoconazole was taken along with a statin drug for dyslipidemia, with simvastatin the most commonly implicated (18 cases). Myopathy resulted in acute renal failure and/or dialysis in 10 of the 32 cases,⁴⁵ with two deaths attributed to rhabdomyolysis-induced kidney failure secondary to a ketoconazole-statin drug interaction.⁴⁶

Ketoconazole's potent CYP3A4 enzymatic inhibitory effects have made it a drug of choice in drug interaction studies conducted in the pre-approval clinical testing stage of new drugs.⁴⁷ However, on October 16, 2013, the FDA recommended that drug companies and researchers avoid using ketoconazole in drug interaction studies to prevent the exposure of otherwise healthy subjects to its hepatotoxic and adrenal effects.⁴⁸

3. Adrenal effects

a. Physiology

Ketoconazole's mechanism of action is the inhibition of the synthesis of ergosterol, part of the cell walls in fungi.⁴⁹ It does so by impairing the function of cytochrome P450. As a result, ketoconazole can stop endogenous steroid production by adrenal glands and testicles. Consequently, the therapeutic potential of this mechanism has been explored.

⁴² FDA Memo, p. 25.

⁴³ FDA Memo, p. 26.

⁴⁴ FDA Memo, p. 22.

⁴⁵ FDA Memo, p. 23.

⁴⁶ FDA Memo, p. 24-25.

⁴⁷ FDA Memo, p. 25.

⁴⁸ Food and Drug Administration. FDA advises against using oral ketoconazole in drug interaction studies due to serious potential side effects. October 16, 2013. <http://www.fda.gov/Drugs/DrugSafety/ucm371017.htm>. Accessed January 13, 2015.

⁴⁹ FDA Memo, p. 6.

b. Cushing's syndrome

Cushing's syndrome is an extremely rare condition involving abnormally high levels of cortisol. The prevalence of Cushing's syndrome is estimated at 90 per million people in Europe, with the annual incidence of its most common, pituitary-related variant, Cushing's disease, estimated at 1.2-2.4 cases per million people.⁵⁰ However, only some of these patients require medical therapy, with a significant number of cases successfully treated with surgery or radiotherapy.

For Cushing's disease, the most common cause of Cushing's syndrome, transsphenoidal microsurgery has a remission rate of 65-90 percent.⁵¹ However, 20 percent of patients eventually present with recurrent disease and, while repeat surgery is possible, it results in lower remission rates than the primary surgery.⁵² Other options for treatment are radiotherapy and radiosurgery, which have reported remission rates of 50-60 percent, although responses occur over a 3-5 year period.⁵³ Pharmacologic therapy is indicated when other therapies fail or are contraindicated.

Because of its inhibition of steroid synthesis, ketoconazole has been used as medical therapy in Cushing's syndrome.⁵⁴ Such use is considered off-label.⁵⁵ A 2014 study of 200 patients with Cushing's syndrome who were treated with ketoconazole showed 49 percent achieving normal urinary free cortisol levels after an average of 28 months of treatment, while 25 percent had levels that did not change following an average of 10 months of treatment.⁵⁶

The EMA did initially ban all use of ketoconazole but subsequently allowed the use of ketoconazole for Cushing's syndrome.⁵⁷ The approval was based not on any controlled clinical trial data, but on the submission by the manufacturer of a systematic review of the published literature on the use of ketoconazole in patients with Cushing's syndrome.⁵⁸ Of the 28 studies involving 748 subjects cited in the manufacturer's submission, though, only one was prospective, and none were controlled clinical trials.

⁵⁰ European Medicines Agency. Assessment report: Ketoconazole HRA. September 25, 2014. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003906/WC500181493.pdf. Accessed February 2, 2015.

⁵¹ Biller BMK, Grossman AB, Stewart PM, et al. Treatment of Adrenocorticotropin-Dependent Cushing's Syndrome: A Consensus Statement. *The Journal of Clinical Endocrinology & Metabolism*. 2008;93(7):2454-2462.

⁵² Rutkowski MJ, Flanigan PM, Aghi MK. Update on the management of recurrent Cushing's disease. *Neurosurgical Focus*. 2015;38(2):E16.

⁵³ Biller BMK, Grossman AB, Stewart PM, et al. Treatment of Adrenocorticotropin-Dependent Cushing's Syndrome: A Consensus Statement. *The Journal of Clinical Endocrinology & Metabolism*. 2008;93(7):2454-2462.

⁵⁴ Fleseriu, Maria. "Recent Advances in the Medical Treatment of Cushing's Disease." *F1000Prime Reports* 6 (March 3, 2014).

⁵⁵ FDA Memo, p. 3

⁵⁶ Castinetti F, Guignat L, Giraud P, et al. Ketoconazole in Cushing's disease: is it worth a try? *J Clin Endocrinol Metab*. 2014;99(5):1623-1630.

⁵⁷ European Medicines Agency. Ketoconazole HRA recommended for approval in Cushing's syndrome. September 26, 2014. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/09/news_detail_002174.jsp&mid=WC0b01ac058004d5c1. Accessed January 20, 2015.

⁵⁸ European Medicines Agency. Assessment report: Ketoconazole HRA. September 25, 2014. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003906/WC500181493.pdf. Accessed February 2, 2015.

c. Prostate cancer

Given its anti-androgen affect, ketoconazole has been studied for use in conjunction with androgen deprivation therapy in prostate cancer.⁵⁹ This use remains off-label and, to the best of our knowledge, a new drug application for this use had not been submitted to the FDA as of February 1, 2015. The American Society of Clinical Oncology in 2014 noted that ketoconazole has biologic activity against prostate cancer but that its survival and quality-of-life benefits remain unknown. The society also highlighted multiple therapies that do have survival and quality of life benefits.⁶⁰

C. Other, safer antifungals render ketoconazole non-essential for remaining FDA-approved indications

As discussed above, in contrast with the EMA, the FDA decided to keep ketoconazole on the U.S. market for the (non-first-line) treatment of five systemic mycoses: blastomycosis, histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, and chromomycosis. These five infections are very rare, with the incidence of histoplasmosis, coccidioidomycosis, and blastomycosis estimated at 3.4, 3.2, and 0.7 per 100,000 person-years in older Medicare beneficiaries.⁶¹ Paracoccidioidomycosis is not endemic to the U.S. and is instead found mostly in Latin America.⁶² Chromomycosis mostly occurs in subtropical and tropical regions, although cases have been reported in the U.S.⁶³

Table 1 (page 11) lists these five remaining indications for ketoconazole, along with other antifungals that have been: (1) approved by the FDA for the infections; or (2) recommended by the Infectious Diseases Society of America (IDSA) and/or have evidence indicating their effectiveness for the infections.

⁵⁹ FDA Memo p. 4.

⁶⁰ Basch E, Loblaw D, Oliver T, et al. Systemic therapy in men with metastatic castration-resistant prostate cancer: American Society of Clinical Oncology and Cancer Care Ontario clinical practice guideline. *Journal of Clinical Oncology*. 2014;32(30):3436-3448.

⁶¹ Baddley JW, Winthrop KL, Patkar NM, et al. Geographic distribution of endemic fungal infections among older persons, United States. *Emerg Infect Dis*. [serial on the Internet]. September 2011. Accessed February 2, 2015. <http://dx.doi.org/10.3201/eid1709.101987>

⁶² Bellissimo-Rodrigues F, Machado AA, Martinez R. Paracoccidioidomycosis epidemiological features of a 1,000-cases series from a hyperendemic area on the southeast of Brazil. *American Journal of Tropical Medicine and Hygiene*. 2011;85(3):546-550.

⁶³ Garnica M, Nucci M, Queiroz-Telles F. Difficult mycoses of the skin: Advances in the epidemiology and management of eumycetoma, phaeohyphomycosis and chromoblastomycosis. *Current Opinion in Infectious Diseases*. 2009;22(6):559-563.

Table 1. Remaining FDA-Approved Indications for Oral Ketoconazole.

	Other Antifungals Approved for Infection	Antifungals (Other Than Ketoconazole) That Are IDSA-Recommended and/or Have Data Supporting Effectiveness for Condition*
Blastomycosis	Itraconazole	Amphotericin B Itraconazole Fluconazole Voriconazole
Histoplasmosis	Itraconazole	Amphotericin B Itraconazole Posaconazole Voriconazole Fluconazole
Coccidioidomycosis	None	Fluconazole Itraconazole Posaconazole Voriconazole Amphotericin B
Paracoccidioidomycosis	None	Itraconazole Voriconazole Amphotericin B
Chromomycosis	None	Itraconazole Posaconazole

* Recommended in one or more IDSA guideline documents and/or shown to be efficacious in at least one clinical study.

Potential arguments for the continued use of ketoconazole for systemic mycoses are that it:

- (1) Remains a possible treatment if another antifungal cannot be used, or is ineffective, for therapy; and
- (2) Is the only approved treatment for three invasive mycotic infections.

These two arguments are addressed in the context of IDSA treatment recommendations and other evidence of efficacy of alternative antifungals, in addition to OSE reviewers' and the EMA's conclusions regarding the remaining need for ketoconazole as an oral antifungal agent.

1. IDSA recommendations and evidence of efficacy for antifungals other than ketoconazole

IDSA has developed treatment guidelines for three of ketoconazole's five remaining indications: blastomycosis, histoplasmosis, and coccidioidomycosis. For all three, IDSA has not recommended ketoconazole as a first-line therapy, due to the drug's unfavorable adverse-effect profile when compared to other antifungals. Although the FDA has similarly removed ketoconazole's approval as a first-line medication, IDSA's decision – and underlying rationale –

not to confer first-line status on ketoconazole for any of these systemic mycoses are nevertheless worth reviewing.

- For blastomycosis, IDSA recommends treatment with either itraconazole or amphotericin B depending on disease severity.⁶⁴ In its 2008 recommendation, the society noted that itraconazole has replaced ketoconazole as first-line therapy due to better antimycotic activity and an improved side-effect profile. Fluconazole and ketoconazole are recommended as second-line therapies. Voriconazole and posaconazole were listed as demonstrating *in vitro* activity against blastomycosis, and voriconazole has been used as an alternative agent in central nervous system infections.
- For histoplasmosis, IDSA (2007) recommends treatment with itraconazole or amphotericin B as first-line agents.⁶⁵ It notes that the other available azoles — fluconazole, ketoconazole, voriconazole, and posaconazole — are options for second-line treatment.
- For coccidioidomycosis, IDSA (2005) recommends using azole antifungals for initial treatment.⁶⁶ Itraconazole and fluconazole are recommended with amphotericin B as needed depending on disease location and severity. Ketoconazole remains a treatment option as well. Voriconazole has been used as treatment successfully in cases.⁶⁷ Additionally, posaconazole has been shown to be effective in two small open-label trials.⁶⁸⁻⁶⁹

For the remaining two indications, paracoccidioidomycosis and chromomycosis, IDSA has not developed treatment guidelines, but there is some evidence of efficacy for antifungals other than ketoconazole:

- In the case of paracoccidioidomycosis, itraconazole was shown to be effective in one open-label trial.⁷⁰ In another open-label trial, itraconazole and voriconazole demonstrated

⁶⁴ Infectious Disease Society of America. Clinical practice guidelines for the management of blastomycosis. Updated 2008.

⁶⁵ Infectious Diseases Society of America. Clinical practice guidelines for the management of patients with histoplasmosis. Updated 2007.

⁶⁶ Galgiani JN, Ampel NM, Blair JE, et al. Coccidioidomycosis. *Clinical Infectious Diseases*. 2005;41(9):1217-1223.

⁶⁷ Kim MM, Vikram HR, Kusne S, Seville MT, Blair JE. Treatment of refractory coccidioidomycosis with voriconazole or posaconazole. *Clin Infect Dis*. 2011;53(11):1060-1066.

⁶⁸ Catanzaro A, Cloud GA, Stevens DA, et al. Safety, tolerance, and efficacy of posaconazole therapy in patients with nonmeningeal disseminated or chronic pulmonary coccidioidomycosis. *Clin Infect Dis*. 2007;45(5):562-568.

⁶⁹ Stevens DA, Rendon A, Gaona-Flores V, et al. Posaconazole therapy for chronic refractory coccidioidomycosis. *Chest*. 2007;132(3):952-958.

⁷⁰ Naranjo MS, Trujillo M, Munera MI, Restrepo P, Gomez I, Restrepo A. Treatment of paracoccidioidomycosis with itraconazole. *J Med Vet Mycol*. 1990;28(1):67-76.

similar efficacy.⁷¹ A Cochrane review concluded there were not enough studies of good quality to assess the most effective treatment.⁷²

- Chromomycosis has not been as extensively studied as the other systemic fungal infections. However, studies with small numbers of patients do show the efficacy of itraconazole and posaconazole in treatment.^{73, 74, 75}

2. OSE review team's conclusions on alternative therapies for systemic mycoses

The OSE review team noted that ketoconazole was first approved in 1981 using single-arm, open-label trials, along with case series and reports, with studies being small and noncomparative in nature.⁷⁶ While acknowledging that the data for other antifungals were also limited to varying degrees, OSE reviewers nevertheless determined that newer and safer antifungals, primarily itraconazole and fluconazole, obviated any need for ketoconazole.

For two of ketoconazole's five remaining indications, blastomycosis and histoplasmosis, another medication, itraconazole, has been approved by the FDA for the treatment of the infection.⁷⁷ With respect to these two infections, in addition to histoplasmosis, The OSE review team concluded that itraconazole exhibits "comparable-to-enhanced efficacy in the treatment of non-meningeal coccidioidomycosis with comparable-to-lower relapse rates in coccidioidomycosis, blastomycosis, and histoplasmosis compared to oral ketoconazole."⁷⁸

As far as the relative efficacy of ketoconazole and other antifungals for paracoccidioidomycosis, OSE reviewers concluded that for ketoconazole, itraconazole, and fluconazole, "the three drugs appear to have similar efficacy in treating paracoccidioidomycosis."⁷⁹ For chromomycosis, OSE reviewers did not conduct a review of treatment efficacy due to the lack of published studies examining this issue.⁸⁰

3. OSE reviewers' and EMA's conclusions on the need of ketoconazole for fungal infections resistant to other therapies

⁷¹ Queiroz-Telles F, Goldani LZ, Schlamm HT, Goodrich JM, Espinel-Ingroff A, Shikanai-Yasuda MA. An open-label comparative pilot study of oral voriconazole and itraconazole for long-term treatment of paracoccidioidomycosis. *Clin Infect Dis*. 2007;45(11):1462-1469.

⁷² Menezes VM, Soares BGO, Fontes CJF. Drugs for treating paracoccidioidomycosis. *Cochrane Database Syst Rev*. 2006;(2):CD004967.

⁷³ Queiroz-Telles F, Purim K, Fillus J, et al. Itraconazole in the treatment of chromoblastomycosis due to *Fonsecaea pedrosoi*. *Int J Dermatol*. 1992;31(11):805-812.

⁷⁴ Restrepo A, Gonzalez A, Gomez I, Arango M, de Bedout C. Treatment of chromoblastomycosis with itraconazole. *Ann N Y Acad Sci*. 1988;544:504-516.

⁷⁵ Keating GM. Posaconazole. *Drugs*. 2005;65(11):1553-67; discussion 1568-69.

⁷⁶ FDA Memo, p. 28.

⁷⁷ Food and Drug Administration. Itraconazole (SPORANOX). FDA-approved label (June 2014 version). <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>. Accessed January 20, 2015.

⁷⁸ FDA Memo, p. 46.

⁷⁹ FDA Memo, p. 35.

⁸⁰ FDA Memo, p. 31.

Another possible argument for keeping ketoconazole on the market might be the potential resistance of invasive mycoses to select agents, thus requiring the use of alternative agents.⁸¹ However, although increasing, data on azole resistance are limited, especially with regard to the systemic mycoses for which ketoconazole is still indicated in the U.S. There is some evidence of cross-resistance and individual drug resistance mechanisms for the clinically used azoles, but these data come from studies of candida and aspergillus infections.^{82,83} In cases of cross-resistance, the use of ketoconazole as a last-line drug would be negligible, as other azoles have the same mechanism of action.⁸⁴ Additionally, given the number of azole drugs available for each of ketoconazole's five remaining indications (see Table 1, page 11), another, safer treatment option would likely be available should there be resistance to one drug.

In its memo, the OSE review team noted that for many patients treated for blastomycosis, histoplasmosis, and coccidioidomycosis who failed ketoconazole therapy, treatment with itraconazole and fluconazole was successful.⁸⁵ The OSE reviewers presented their final conclusions on the remaining medical need for ketoconazole for fungal infections in a table titled "Unmet Medical Needs Assessment" (see Table 2). In the table, they concluded that there were alternative treatments available for all of the fungal infections for which ketoconazole was indicated. The OSE reviewers concluded unequivocally that the drug "offer[s] [no] enhanced efficacy in a special population such that the risk for serious hepatic injury would be tolerable" for any of its former or current indications for fungal infections.

Table 2. Unmet Medical Need Assessment (taken as-is from Table 14 of the same name from the OSE reviewers' memo)⁸⁶

	Dermatophyte Infections	Chronic Mucocutaneous Candidiasis	Systemic Fungal Infections
Are there unique beneficial characteristics of the drug compared to exiting alternative treatments? Pharmacology Formulation Compliance Penetration into the cerebrospinal fluid	No	No	No
Are there alternative treatments for the same indications with comparable or improved efficacy or improved safety?	Yes	Yes	Yes
Does the drug offer enhanced efficacy in a special population such that the risk for serious hepatic injury would be tolerable?	No	No	No

⁸¹ FDA Memo, p. 33.

⁸² Rodriguez-Tudela, Juan Luis, Laura Alcazar-Fuoli, Emilia Mellado, Ana Alastruey-Izquierdo, Araceli Monzon, and Manuel Cuenca-Estrella. Epidemiological cutoffs and cross-resistance to azole drugs in aspergillus fumigatus." *Antimicrobial Agents and Chemotherapy*. 2008;52(7): 2468-2472.

⁸³ FDA Memo, p. 33.

⁸⁴ *Ibid.*

⁸⁵ FDA Memo, p. 46.

⁸⁶ FDA Memo, p. 40.

The EMA concluded in its July 2013 assessment of ketoconazole for fungal infections that there was “no direct comparison [between ketoconazole and] other azoles that could substantiate assumption of a potential superiority [of ketoconazole] over existing azoles to expect a treatment response when others would have failed.”⁸⁷ We agree with the assessments of both the OSE review team and the EMA that the purported benefit of ketoconazole for resistant infections remains largely hypothetical and certainly does not outweigh the drug’s unique, life-threatening risks.

D. Conclusion: Ketoconazole offers no unique benefits, only unique risks compared with other, safer antifungals

The FDA’s decision to keep ketoconazole on the market for five systemic fungal infections (blastomycosis, histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, and chromomycosis) as a last resort if other antifungals fail or are not tolerated, and only in those without pre-existing liver disease, ran counter to the exhaustive risk-benefit analyses conducted by its own OSE reviewers. The OSE review team concluded that the evidence on the efficacy and safety of ketoconazole for these remaining indications was a far cry from the quality and rigor that would be required in a new drug application today. Its 1981 approval was based on single-arm, noncomparative studies and individual case reports.⁸⁸ The OSE review team could not even review the evidence base for ketoconazole’s chromomycosis indication “due to the paucity of published studies and case reports/series.”⁸⁹

While acknowledging that the data for other antifungals was similarly limited, OSE reviewers nevertheless concluded that other antifungals, primarily itraconazole and fluconazole, demonstrated “comparable-to-enhanced efficacy and better safety profiles” than ketoconazole in the treatment of these systemic mycoses.⁹⁰ The OSE review team, therefore, “was unable to view the risk of serious potentially life-threatening hepatic injury as tolerable for the potential benefit of ketoconazole treatment.”⁹¹

It is important to note that the FDA’s restriction of ketoconazole to those without a prior history of liver disease is patently insufficient as a means of preventing serious liver injury: OSE reviewers noted that ketoconazole hepatotoxicity is “idiosyncratic”⁹² and therefore “unpredictable.”⁹³ Two-thirds of the AERS cases of ketoconazole-related hepatotoxicity analyzed by the OSE review team involved patients with no prior history of liver disease, with some of these patients dying from fulminant liver failure.⁹⁴ Regular monitoring for hepatic injury will similarly fail to prevent all cases of severe liver failure, as ketoconazole-induced liver injury

⁸⁷ European Medicines Agency. Assessment report for ketoconazole containing medicinal products. July 25, 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Ketoconazole-containing_medicines/WC500168346.pdf. Accessed January 13, 2015.

⁸⁸ Wu TC. On the development of antifungal agents: Perspective of the U.S. Food and Drug Administration. *Clin Infect Dis.* 1994;19 Suppl 1:S54-58.

⁸⁹ FDA Memo, p. 31.

⁹⁰ FDA Memo, p. 48.

⁹¹ *Ibid.*

⁹² FDA Memo, p. 5.

⁹³ FDA Memo, p. 46.

⁹⁴ FDA Memo, p. 12-13.

is often rapid in onset (as early as one week after beginning therapy) and exhibits no decipherable relationship to dose, duration, or therapeutic indication.⁹⁵

The FDA's decision also conflicts with that made by the EMA, relying on the same evidence (including the study by Garcia-Rodriguez et al.⁹⁶) to which the FDA was privy at the time, to ban ketoconazole as a systemic antifungal drug. Like the OSE reviewers, the EMA concluded that "the risk of liver injury is greater than the benefits in treating [any] fungal infections."⁹⁷ The EMA continues to stand by its decision more than a year and a half later. (As mentioned above, the EMA's decision last year to approve ketoconazole for Cushing's syndrome is irrelevant to the U.S. context, as the FDA has never approved the drug for this condition.)

Furthermore, oral ketoconazole prescribing data in the year following the FDA's July 2013 safety communication demonstrate the futility of the FDA's efforts to restrict the use of the drug to rare, last-resort, systemic infections. In its safety communication, the FDA reported that 609,000 prescriptions of ketoconazole tablets were dispensed in 2012, with nonsystemic fungal infections treated in outpatient clinics representing the most common use of the drug.⁹⁸ Despite the FDA's removal of this most common use as an approved indication, however, 462,000 oral ketoconazole prescriptions were still dispensed in 2014,⁹⁹ representing only a 24 percent decline from 2012 sales.

Extrapolating, conservatively, the incidence of ketoconazole-associated liver injury from Garcia-Rodriguez et al. of one per 750 person-months of exposure, oral ketoconazole use in 2014 may potentially have resulted in at least 616 cases of symptomatic acute liver injury necessitating hospitalization or specialist referral (see "Estimated frequency of ketoconazole-associated hepatotoxicity in 2014" on p. 7-8).

We agree with both the OSE review team and the EMA that ketoconazole's risks of severe liver injury, extensive drug interactions, and adrenal suppression outweigh any of its limited benefits as an antifungal treatment. Because oral ketoconazole is approved only for the treatment of fungal infections, we believe they should be removed from the market. Unless the FDA bans oral ketoconazole, its continued marketing will result in hundreds of preventable cases of serious liver damage a year.

⁹⁵ FDA Memo, p. 47.

⁹⁶ Garcia-Rodriguez LA, Duque A, Castellsague J, Perez-Gutthann S, Stricker BH. A cohort study on the risk of acute liver injury among users of ketoconazole and other antifungal drugs. *Br J Clin Pharmacol.* 1999;48(6):847-852.

⁹⁷ European Medicines Agency. European Medicines Agency recommends suspension of marketing authorisations for oral ketoconazole. July 26, 2013.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/07/news_detail_001855.jsp. Accessed January 13, 2015.

⁹⁸ Food and Drug Administration. 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. July 26, 2013. <http://www.fda.gov/Drugs/DrugSafety/ucm362415.htm>. Accessed January 13, 2015.

⁹⁹ IMS Health data. Obtained on January 30, 2015.

II. SUMMARY OF PETITION REQUESTS

For the reasons stated above, we hereby petition the FDA, pursuant to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(e), , and 21 C.F.R. §§ 10.30, to immediately ban all versions of oral ketoconazole.

III. ENVIRONMENTAL IMPACT STATEMENT

Nothing requested in this petition will have an impact on the environment.

IV. CERTIFICATION

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,

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Enclosure

**CDER Regulatory Briefing
January 4, 2013**

Benefit-Risk Assessment of Oral Ketoconazole Tablets

Background Document

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1 SUMMARY OF THE ISSUE

On July 11, 2011, the French Health Agency (AFSSAPS) suspended the French Marketing Authorization for ketoconazole tablets due to safety concerns and an unfavorable benefit/risk assessment of efficacy and safety. This decision was based on published clinical studies and on France's post-marketing data (not currently available to us), which showed a more frequent and severe risk of hepatotoxicity associated with ketoconazole as compared with that of other available azole antifungals for the same indications. AFSSAPS acknowledged the off-label use of ketoconazole for adrenocorticotrophic hormone (ACTH)-dependent Cushing syndrome; however, the French agency considered that this use should not interfere with the benefit/risk evaluation of ketoconazole as an antifungal agent. EMA's final decision is now expected to take place in March 2013. In the EU, Janssen is only seeking to retain ketoconazole as second line therapy for the following three indications: *Malassezia* folliculitis, *Tinea capitis*, and chronic mucocutaneous candidiasis.

In December 2011, the Office of Surveillance and Epidemiology (OSE) initiated a benefit-risk assessment of oral ketoconazole. OSE's ongoing safety review and benefit-risk assessment will be finalized by January 2013. This briefing document outlines the benefit-risk assessment of the OSE review team.

The Applicant (Janssen Pharmaceuticals) for NDA 18-533 (Nizoral), the reference listed drug, has requested withdrawal of this NDA for commercial reasons. Currently, six generic formulations of oral ketoconazole are available in the US market. The Division's response to the withdrawal request is pending the ongoing safety review and benefit/risk assessment.

2 QUESTIONS FOR THE REGULATORY BRIEFING PANEL

Question 1: Does the benefit-risk profile of oral ketoconazole tablets support continued marketing in the United States?

- For all indications?
- For some indications?
- For none of the approved indications?

Question 2: If yes and in addition to updating the label with safety information, what are your regulatory recommendations?

- Remove labeled indications where the risks clearly outweigh the benefits
- Develop risk mitigation strategies for the drug

3 KETOCONAZOLE BACKGROUND INFORMATION

Ketoconazole is an azole antifungal drug available as an oral tablet and in topical formulations. Oral ketoconazole is approved for the treatment of the following systemic fungal infections:

Candidiasis, chronic mucocutaneous candidiasis, oral thrush, candiduria, blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. Ketoconazole tablets are also indicated for the treatment of patients with severe recalcitrant cutaneous dermatophyte infections who have not responded to topical therapy or oral griseofulvin, or who are unable to take griseofulvin.

Ketoconazole is not a first line treatment option for most fungal infections (IDSA 2009, ECIL-3, 2009) considering its risk profile and the existence of other therapeutic options. While other antifungal drugs are approved for the treatment of candida infections and aspergillosis, itraconazole and ketoconazole are the only two antifungal drugs approved for the treatment of histoplasmosis and blastomycosis. Ketoconazole is the only antifungal drug approved for the treatment of coccidioidomycosis, paracoccidioidomycosis, chromomycosis and chronic mucocutaneous candidiasis.

All approved members of the azole class of antifungal drugs (fluconazole, itraconazole, voriconazole, and posaconazole) are associated with hepatotoxicity. The product labeling for each of the products has a warning regarding risk of hepatotoxicity, including fatalities.

3.1 CURRENT REGULATORY STATUS OF KETOCONAZOLE IN THE UNITED STATES

Oral ketoconazole was approved in 1981 for the treatment of several fungal infections. In 1983, FDA added a boxed warning about fatal hepatotoxicity. The last labeling update occurred in 2002. From 2003-2006 several communications took place with the Sponsor to update the labeling (liver transplantation, multiple drug-drug interactions and contraindications). Most changes were agreed upon by the Division and Sponsor, however a few outstanding issues regarding drug interactions of ketoconazole remained to be resolved. DAIP is currently working with the Sponsor to update the labeling. In 2008, the sponsor requested withdrawal of the NDA for commercial reasons. The last batch was manufactured on June 13, 2005 and expired in June 2007. The FDA response to the withdrawal request is still pending, awaiting the conclusion of the ongoing safety review and benefit/risk assessment.

Currently, six generic formulations of oral ketoconazole are available in the US market.

3.2 KETOCONAZOLE USE FOR NON-LABELED INDICATIONS

Ketoconazole has been used for the treatment of ACTH-dependent Cushing syndrome, particularly in inoperable cases and in failures after surgery. Ketoconazole acts on several of the P450 enzymes, including the first step in cortisol synthesis, cholesterol side-chain cleavage, and conversion of 11-deoxycortisol to cortisol. The use of ketoconazole in the treatment of androgen-dependent prostate cancer is based on its ability to inhibit androgen synthesis to near castration levels, which has been studied in a rat model. Several clinical studies have been conducted to explore ketoconazole use in Cushing

syndrome and prostate cancer. A total of 28 active and completed clinical studies are registered in the [clinicaltrials.gov](http://www.clinicaltrials.gov) database for use in prostate cancer: <http://www.clinicaltrials.gov/ct2/results?term=ketoconazole+prostate+cancer>. There is no current NDA submission for any of these indications.

4 KETOCONAZOLE SAFETY CONCERNS

4.1 HEPATOTOXICITY

The clinical manifestations of hepatotoxicity attributed to ketoconazole can range from asymptomatic elevations in hepatic enzymes that may resolve despite continued therapy to serious, fulminant, acute liver failure requiring liver transplantation to avert death. Asymptomatic transient elevations in serum alanine aminotransferase levels frequently occur during treatment with ketoconazole. Janssen and Symoens¹ noted >1,000 patients in their investigation who experienced transient liver enzyme elevations that were not associated with clinical symptoms. In those patients, the liver enzyme elevations normalized despite continued ketoconazole therapy in some cases, while others had improvement in liver enzymes following discontinuation of the drug. The resolution of liver enzyme elevations despite continued ketoconazole therapy has not been well-explained. One proposed pathophysiologic mechanism is a Herxheimer-like reaction in which there is transient release of hepatic mycotoxins into the systemic circulation from fungal organisms following initiation of ketoconazole therapy.^{1,2}

Janssen and Symoens¹ also noted an 11 week median time to onset of anicteric reactions; the median time to onset of jaundice was 6 weeks, but was variable and could develop as early as 1-2 weeks following initiation on the drug. Additionally, the authors cited one fatality in which there was continued exposure to the drug despite onset of jaundice, which may have contributed to the fatal outcome in that case.

The liver injury induced by ketoconazole is primarily hepatocellular and characterized by elevation in alanine aminotransferase.³ Cholestatic and mixed hepatocellular-cholestatic patterns of injury have also been reported.⁴ Acute liver injury characterized by hepatic necrosis resulting in death or necessitating life-saving liver transplantation has also been reported. Lewis and colleagues identified female gender and age >40 years as factors possibly associated with an increased risk for hepatic injury from the drug, and they also

¹ Janssen P, Symoens J. Hepatic Reactions during Ketoconazole Therapy. *Am J Med* 1983; 74 (1B):80-85.

² Stricker B, Blok A, Bronkhorst F, Van Parys G, Desmet V. Ketoconazole-associated Hepatic Injury. *J Hepatol* 1986; 3:399-406.

³ Hussaini SH, Farrington EA. Idiosyncratic Drug-induced Liver injury: An Overview. *Expert Opin Drug Saf* 2007; 6(6):673-684.

⁴ Song JC, Deresinski S. Hepatotoxicity of Antifungal Agents. *Curr Opin Invest Drugs* 2005; 6(2):170-177.

noted a widely variable time period of exposure (1.5 to 24 weeks) prior to the onset of jaundice associated with ketoconazole-induced liver injury.⁵

The mechanism of ketoconazole-induced liver injury has not been fully elucidated but some preclinical investigations suggest that N-deacetyl ketoconazole, a major metabolite, is further biotransformed into a reactive metabolite N-deacetyl-N-hydroxyketoconazole, that can undergo further metabolism to metabolites that are toxic to liver cells^{6,7}. Cellular targets within the liver include inhibition of mitochondrial function⁸ and DNA fragmentation⁹ data investigating a mechanism exist. To date, there are no reliable pharmacogenomic markers to predict the at-risk population; hepatic injury appears to be idiosyncratic.

4.2 DRUG-DRUG INTERACTIONS

Ketoconazole is a competitive inhibitor of the cytochrome P450 3A4 isoenzyme (CYP3A4), which is involved in the metabolism and elimination of approximately one-half of all prescribed drugs today. Among the azole antifungals, ketoconazole is the most potent CYP3A4 inhibitor.¹⁰ In addition, recent data indicates that ketoconazole can adversely affect the metabolism of drugs through pathways other than through CYP3A4 inhibition; ketoconazole antagonizes pregnane X receptor, which regulates the transcription of drug-metabolizing enzymes, and glucocorticoid receptor, which normally upregulates pregnane X receptor.¹¹ Ketoconazole is a substrate and an inhibitor of P-glycoprotein (P-gp), a membrane transporter (efflux pump) protein encoded by the ABCB1/MDR1 gene that is expressed on kidney, liver, bowel, and cells of the blood-brain barrier; it affects the biliary, renal, and intestinal excretion/absorption of drugs and protects the brain from harmful substances.¹²

⁵ Lewis JH, Zimmerman HJ, Benson GD, Ishak KG. Hepatic Injury associated with Ketoconazole Therapy. *Gastroenterology* 1984; 86:503-513.

⁶ Rodriguez RJ, Acosta D. N-Deacetyl Ketoconazole-induced Hepatotoxicity in a Primary Culture System of Rat Hepatocytes. *Toxicology* 1997; 117:123-131.

⁷ Rodriguez RJ, Buckholtz CJ. Hepatotoxicity of Ketoconazole in Sprague-Dawley Rats: Glutathione Depletion, Flavin-containing Monooxygenases-mediated Bioactivation and Hepatic Covalent Binding. *Xenobiotica* 2003; 33(4):429-441

⁸ Rodriguez RJ, Acosta D. Inhibition of Mitochondrial Function in Isolated Rat Liver Mitochondria by Azole Antifungals. *J Biochem Toxicology* 1996; 11(3):127-131.

⁹ Amin A, Hamza AA. Oxidative Stress Mediates Drug-induced Hepatotoxicity in Rats: A Possible Role of DNA Fragmentation. *Toxicology* 2005; 208:367-375.

¹⁰ Albengres E, Le Louet H, Tillement J-P. Systemic Antifungal Agents: Drug Interactions of Clinical Significance. *Drug Saf* 1998; 18(2):83-97.

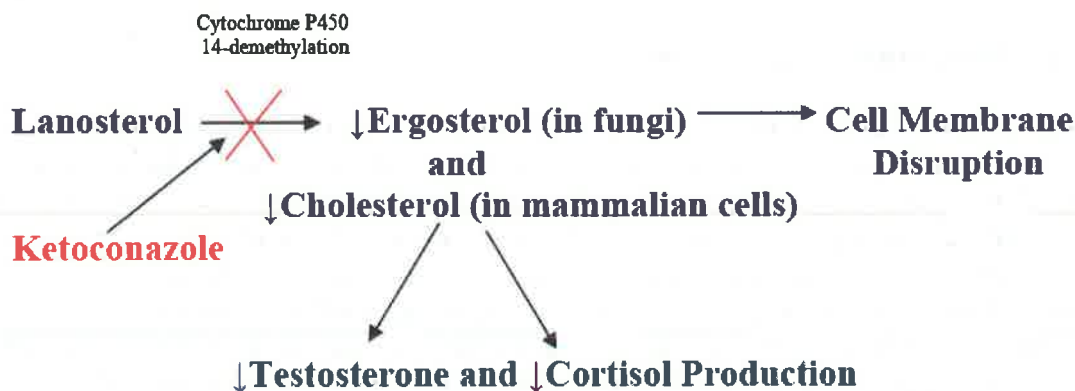
¹¹ Dvorak Z. Drug-Drug Interactions by Azole Antifungals: Beyond a dogma of CYP3A4 enzyme activity inhibition. *Toxicol Let* 2011; 202:129-132.

¹² Zhou S-F. Structure, function, and regulation of P-glycoprotein and its clinical relevance in drug disposition. *Xenobiotica* 2008; 38(7-8):802-832.

4.3 INHIBITION OF ENDOCRINE HORMONE SYNTHESIS

Ketoconazole exerts its action by impairing the synthesis of ergosterol, a component of fungal cell walls, from lanosterol by inhibiting the cytochrome P450 isoenzyme 14- α -demethylase.¹³ Ketoconazole can block adrenal and testicular steroid production, particularly at high dosages, through its inhibition of the cytochrome P450 isoenzyme system.¹⁴ To our knowledge, this property is unique to ketoconazole as an antifungal. Figure 1 below is a schematic of the mechanism by which ketoconazole is believed to suppressed steroid synthesis.

Figure 1. Ketoconazole Mechanism of Adrenal and Testicular Steroid Suppression



5 METHODOLOGY AND DATA SOURCES

All of the information presented in this background document represent data collated and interpreted by OSE reviewers within the Division of Pharmacovigilance and the Division of Epidemiology.

5.1 PHARMACOVIGILANCE METHODS

5.1.1 AERS Search Strategies

OSE focused on serious hepatic injury as a ketoconazole-induced event in response to the French regulatory action. Our myopathy focus was the result of a disproportionate Empiric Bayes Geometric Mean (EBGM) datamining score of 3.356 (90% CI 2.701-4.134) for the MedDRA High Level Term 'Myopathies'. Therefore OSE conducted two AERS searches:

¹³ Friedlander TW, Ryan CJ. *Adrenal Androgen Synthesis Inhibitor Therapies in Castration-Resistant Prostate Cancer*. In: Figg WD, Chau CH, Small EJ, eds. *Drug Management of Prostate Cancer*. New York: Springer; 2010:91-97.

¹⁴ Pont A, Williams PL, Loose DS, Feldman D, Reitz RE, Bochra C, Stevens DA. Ketoconazole Blocks Adrenal Steroid Synthesis. *Ann Intern Med* 1982; 97(3):370-372.

- **Liver injury:** AERS search for US and serious cases of Nizoral® (ketoconazole) reports coded with any MedDRA preferred term within the “Drug Related Hepatic Disorders Severe Events Only (Broad-Standardized MedDRA Query) submitted to FDA between January 1, 1980 and December 1, 2011.
- **Myopathy:** AERS search for Nizoral® (ketoconazole) reports coded with any MedDRA preferred term within the “Myopathies” High Level Term hierarchy submitted to FDA between January 1, 1980 and December 1, 2011.

We retrieved and reviewed ketoconazole-associated myopathy cases and determined the majority of these were attributed to a drug interaction between ketoconazole and an HMG-CoA reductase inhibitor.

5.1.2 Ketoconazole Induced Liver Injury

Liver toxicity is a well established adverse event for oral ketoconazole. This toxicity ranges from asymptomatic elevations in liver function tests to fulminant hepatic failure or necrosis resulting in hepatic transplant or death. Since ketoconazole induced liver injury is not a newly established adverse event, OSE selected AERS search criteria to retrieve only the most serious of hepatotoxicity cases originating within the US to determine if FDA continues to receive serious US-based reports of liver injury and further describe the clinical characteristics of these cases. In screening crude AERS reports, we used a Drug Induced Liver Injury Network (DILIN) adapted case definition (Table 1).

Table 1. Hepatotoxicity AERS Case Definition

Case Definition
Temporal relationship with oral ketoconazole use and onset of liver injury (e.g. diagnosis or abnormal laboratory marker (serum liver biochemistries) and dysfunction
AND either criterion below
Elevation in serum ALT and/or alkaline phosphatase levels and total bilirubin ≥ 2.5 mg/dl and at least one of the following: 1) Hepatic failure (INR ≥ 1.5, ascites or encephalopathy) 2) Other organ failure due to the DILI event
OR
Diagnosis of liver failure or death/liver transplant due to liver event

Each report that met the case definition was included as a case. Where available in an AERS submission reporting a hepatic adverse event, the following information was collected: demographic data (age, sex, received date, event date), suspect drug information (indication, dose, dosage form and duration), medical and medication history, reported clinical manifestations (such as the presence of jaundice, encephalopathy, liver necrosis, liver failure, pale stool, dark urine, ascites), laboratory markers for hepatic injury [aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), total bilirubin (Tbili), International Normalized Ratio (INR)], outcome (hospitalization, liver transplantation), and cases of rechallenge.

In addition to safety evaluator review of these cases, they were further adjudicated by an OSE hepatologist (Dr. Leonard Seeff). The hepatologist reviewed each case and assessed causality using a modified likelihood scale developed by the National Institutes of Health-Drug Induced Liver Injury Network (DILIN) study group.

5.1.3 Myopathy

Our objective in reviewing myopathy as an adverse event was to investigate an AERS datamining signal. All AERS cases were reviewed and assessed for potential ketoconazole-induced causes of myopathy. We collected information on demographics, outcome, indication for use and suspect interacting drug, characterized the data and provided a descriptive analysis.

5.1.4 Efficacy and Safety Literature Search Strategy

We conducted an internet-based search of the English-language scientific literature using Embase, PubMed, and Web of Science to retrieve articles describing the safety, hepatotoxicity, and drug-drug interactions associated with oral ketoconazole, including published data from clinical specialty networks on drug-related acute liver injury resulting in fatalities or requiring liver transplantation. Relevant articles cross-referenced in the retrieved reports were included. We also searched for clinical studies that assessed the efficacy and safety of ketoconazole with respect to its labeled indications, and sought comparable data with respect to two other within- class azole antifungals - itraconazole and fluconazole.

Relevant Medical Subject Headings (MeSH terms) for PubMed indexing included: alanine transaminase/blood, drug-induced liver injury/blood, ketoconazole/adverse effects, ketoconazole/pharmacology, liver failure/acute, liver failure, acute/therapy, liver transplantation, prospective studies, antifungal agents/adverse effects, drug-induced liver injury/complications, drug interactions, clinical trial, and comparative study.

5.2 PHARMACOEPIDEMIOLOGY METHODS

5.2.1 Literature Search for Analytic Studies

We conducted a focused literature search to assess publications providing quantitative estimates of hepatotoxicity with ketoconazole use. The identified studies were summarized and drug utilization data were used to provide exposure denominators for selected published reports.

5.2.2 Liver Transplants from Antifungal Hepatotoxicity

We queried the United Network for Organ Sharing (UNOS) to obtain counts of patients who received liver transplants or were placed on the waiting list for a liver transplant in the U.S. because of hepatotoxicity from azole antifungals (ketoconazole, fluconazole, itraconazole). These counts included actual liver transplants performed between October

1, 1987 and April 30, 2012, plus counts of patients placed on the waiting list due to hepatotoxicity during the period April 1, 1994 to April 30, 2012. These nationwide counts were related to prescription drug utilization data for azole antifungals during a corresponding period of time.

5.2.3 MiniSentinel Methods

The objective of this analysis was to quantify the frequency of serious hepatic disorders following prescription of ketoconazole and selected other oral antifungal drugs. As part of the evaluation of ketoconazole hepatotoxicity, we queried the MiniSentinel database regarding diagnoses of hepatic disease following use of oral antifungal drugs.

This was a retrospective health care claims data analysis of cohorts of antifungal drug users. The data source was the MiniSentinel database, comprising data from 17 Data Partners, with academic, health insurance company, and health maintenance organization (HMO) sites contributing data on a mix of publicly and privately covered individuals. As of December 2011, the database included data from 2000-2011 on 126 million individuals, and included inpatient data from 88 hospitals. Under the distributed data model, analytic programs are provided to each data partner, and the data partners run the programs and report their results, which are then compiled. In this way the confidentiality of each site's databases are protected. The base population for this analysis was all covered individuals with no age restrictions. The time frame was January 1, 2000 to September 30, 2011. The cohorts were new users of oral antifungal drugs (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole, terbinafine, and griseofulvin). Only oral use was considered. New users were defined as individuals dispensed a drug of interest with no prior prescriptions for any drug of interest within 183 days. Exposure episodes were considered to have a duration equal to the total days supply of all prescriptions for the drug of interest when not separated by a gap of more than 30 days. The risk window, during which outcomes were determined, was the exposure episode plus 30 days of follow-up time (MiniSentinel requires the allowed in-between-prescription gap to equal the post-treatment follow up period).

We adapted the outcome definition from the team working on an algorithm to identify severe liver injury in Medicare data. Primary hospital discharge diagnoses of acute and subacute necrosis of the liver (ICD9 570.xx) or hepatitis unspecified (ICD9 573.3) (including toxic, noninfectious hepatitis) were considered as outcomes. In addition, outcomes were analyzed for the presence of one or more severity indicators; namely, death (as a hospital discharge status or disposition), hepatic coma (572.2x), liver transplant (50.5x), liver allotransplantation orthotopic (CPT 47135), liver allotransplantation heterotopic (CPT 47136), hepatorenal syndrome (572.4), jaundice other than newborn (782.4), or hematemesis (578.0). Records were examined for severity indicators for 14 days prior to admission and 14 days after discharge; the rationale was to capture events or procedures occurring in different hospitals.

Patients with hepatic disorder diagnosis during the baseline period were excluded. To exclude off-label users of ketoconazole, patients with diagnoses of malignancy or Cushing's syndrome up to 1 year before the antifungal prescription were ineligible.

Similarly, because ketoconazole is used off-label to treat malignancies, patients with procedure codes for chemotherapy or radiation therapy during this time were excluded, as were patients with the outcome diagnoses. A sensitivity analysis used a 6-month rather than a 12-month exclusionary period.

5.3 BENEFIT-RISK FRAMEWORK

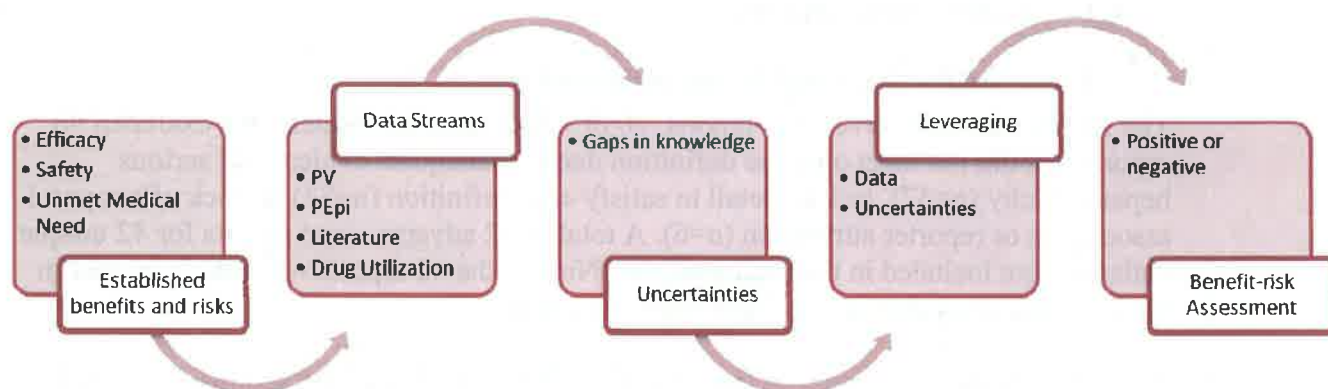
Staff from CDER's Office of Planning and Analysis (OPA) have developed a framework for benefit-risk considerations within the Center. OPA developed this framework in response to a 2006 Institute of Medicine (IOM) report which highlighted a lack of formal, systematic benefit-risk assessment. This framework has been piloted in the pre-marketing assessment of new drugs but it has not been used to weigh benefits and risks in the post-marketing setting. To our knowledge, this application of the CDER benefit-risk framework is the first use of this model in the post-marketing evaluation of an approved drug.

The CDER Benefit-Risk Framework includes five decision factors (Analysis of Condition, Unmet Medical Need, Clinical Benefit, Risk, and Risk Management) incorporated into a structured assessment process as follows:

- (1) Information on the Therapeutic Area, including analysis of condition and unmet medical need, which provide a clinical context for weighing benefits and risks
- (2) Product-specific information, including consideration of clinical benefit, risks, and risk management.
- (3) Evidence and Uncertainties, which involves differentiating facts from gaps and uncertainties in the data
- (4) Conclusions and Reasons, which involves analyzing information, weighing the data and its uncertainties, and drawing conclusions within each key consideration.
- (5) Benefit-risk summary assessment, which involves a balanced analysis of factors and trade-offs with resulting regulatory recommendation(s).

In conducting this benefit-risk assessment, the OSE Review Team was challenged with organizing and structuring our analytical thought processes due to the diverse data streams accessed, marked complexity of the data, varied methodological limitations and sources of uncertainty, and the multiple labeled indications under review. The OSE review devised an algorithmic approach that incorporated the five decision factors from the CDER Benefit-Risk Framework while preserving the Framework's emphasis on leveraging the facts, data, and analysis with uncertainties guided by clinical judgment, in order to provide a structured, balanced, and scientifically sound assessment. Figure 2 (below) depicts the algorithm used by the OSE Review Team in arriving at a benefit-risk assessment for this product.

Figure 2 Integrating the CDER Benefit-Risk Assessment Framework into the OSE Review Team's Analytical Thinking: an Algorithmic Approach



The five steps in our algorithmic approach are as follows:

1. Established benefits and risks: refers to the major benefits and risk drivers as generally acknowledged in the scientific literature and reflected in the product label. Analysis of Condition and Current Therapeutic Options, two decision factors from the CDER Benefit-Risk Framework, would be considered in this step.
2. Data Streams: refers to the various data sources accessed and analyzed to inform us about the safety, efficacy, pharmacology, chemistry, toxicology, and contemporary use patterns for the drug and whether it fulfills an unmet medical need in the contemporary clinical armamentarium of drug therapies for fungal infections. In this step, we integrated Benefits and Risks, two additional decision factors from the CDER Benefit-Risk Framework.
3. Uncertainties: refers to the gaps in our knowledge that reflect upon the limitations and biases identified upon analysis of each data stream, including methodological deficiencies in the design, conduct, and statistical analysis of published studies and clinical trials, and variable quality of reporting of safety and efficacy results.
4. Leveraging: refers to the use of clinical judgment to weigh the strengths and limitations of the data with respect to efficacy, safety, and unmet medical need, in order to identify important attributes of the drug that best inform us in making an overall benefit-risk assessment. In this step, we integrate the Evidence and Uncertainties as per the CDER Benefit-Risk Framework, in order to provide a scientific rationale supportive of our conclusions.
5. Benefit-risk assessment: refers to the overall conclusions (as well as with respect to one or more of a drug's labeled indications) based on consideration of all the component

steps described in the algorithm. Potential options for regulatory action, including Risk Management strategies - the fifth decision factor in the CDER Benefit-Risk Framework, are also considered in the context of this step.

6 MAJOR SAFETY CONCERNS ACROSS INDICATIONS

6.1 SERIOUS LIVER INJURY

6.1.1 AERS Cases and Hepatologist review

The AERS search retrieved 154 reports, 16 of which were duplicates. We excluded 96 reports that did not meet our case definition due to inadequate evidence of serious hepatotoxicity (n=57), lack of detail to satisfy case definition (n=33), or lack of temporal association or reporter attribution (n=6). A total of 42 adverse event reports for 42 unique patients were included in the final analysis. Nine of the 42 reports were also reported in the literature or as abstracts for professional meetings.

Table 2 contains aggregate data from the 42 AERS cases describing serious, US-based cases of hepatotoxicity, all of which were temporally associated with oral ketoconazole use. None of the cases were linked to a topical ketoconazole product. These data show that case patients received a median dose of 200mg/day. This dose is consistent with FDA approved dosage recommendations for labeled indications, which is generally 200-400 mg daily, depending on the severity of infection. The median duration of exposure leading up to the hepatic events was 51 days (range varied considerably from 8.5 to 180 days), and was driven largely by a high proportion of onychomycosis cases (20/42; 48%), an unlabeled use, requiring protracted treatment courses. The remaining uses were for candidiasis (21%), dermatophytosis (14%), and prostate cancer (2%). Three of the cases were categorized as 'Other' and included two cases of histoplasmosis, and a case of furunculosis. Three-fourths of the cases were female.

As a measure of pre-existing health status of these cases, we assessed each for a history of liver disease and malignancy. Twenty-eight (67%) of the cases had neither history, six (14%) cases documented a history of liver disease, another six (14%) reported a history of malignancy and two (5%) cases report a history of both. Among the cases with history suggestive of liver disease were reports documenting an alkaline phosphatase elevation, small bile duct necrosis, presence of multiple liver cysts, chronic liver disease with alcohol use, viral hepatitis infection, hepatomegaly, and cholecystectomy. Cases which reported a pre-existing malignancy, included leukemias, adenocarcinoma, Kaposi's sarcoma and cancers of the rectum, lip, prostate and thyroid.

We sought to identify the most serious liver injury cases associated with ketoconazole; therefore, we collected data, where available, on various clinical and laboratory findings that may reflect on liver injury severity. These data show significantly elevated median aminotransaminase enzymes (>10x upper the limit of normal), mildly elevated median

alkaline phosphatase and median total bilirubin (>20x upper limit of normal); however, the range of values for those laboratory test parameters were widely variable (30-3500 IU/L for AST, 71-3811 IU/L for ALT, 0.9-51 mg/dl for Tbili) and included values that would be considered within the normal range for the test. A significant proportion of cases provide histologic evidence of necrotic liver (43%), jaundice (62%) and other clinical or laboratory manifestations of liver failure, such as elevated prothrombin time (41%) and encephalopathy (26%). The reportable event required hospitalization in nearly all (90%) of the cases, one-half of the cases died, and the severity of the liver injury led to ten liver transplantations. One of the ten transplant recipients died after the procedure.

Table 2. Selected Demographic and Clinical Characteristics Serious, US-based AERS Cases of Hepatotoxicity Temporally Associated with Oral Ketoconazole Use from January 1, 1980 through December 1, 2011

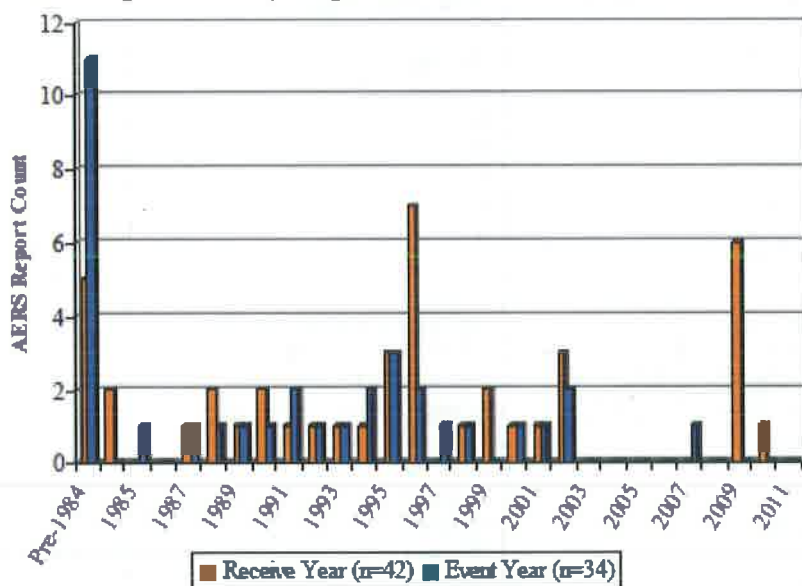
Demographic or Clinical Characteristic	Cases (N=42)
Age	(n=38)
Median (Range)	52 years (17-76)
Gender	(n=41)
Male	10 cases
Female	31
Ketoconazole Daily Dose	(n=37)
Median (Range)	200 mg (200-600)
Ketoconazole Duration Leading up to Hepatic Event	(n=33)
Median (Range)	51 days (8.5-180)
Ketoconazole Indication	
Onychomycosis	20 cases
Candidiasis	9
Dermatophytosis	6
Histoplasmosis	2
Furunculosis	1
Prostate Cancer	1
Not Reported	3
Characteristics of the Hepatotoxicity	
Peak Laboratory Markers ^a	
AST [Median (range)] [normal 0-35 IU/L]	419 IU/L (30-3500) (n=29)
ALT [Median (range)] [normal 0-35 IU/L]	633 IU/L (71-3811) (n=26)
ALP [Median (range)] [normal 30-120 IU/L]	270 IU/L (69-800) (n=19)
Tbili [Median (range)] [normal 0.3-1.0 mg/dl]	20 mg/dl (0.9-51) (n= 31)
INR/PT Elevated (Yes)	17 cases
Jaundice (Yes)	26 cases
Encephalopathy (Yes)	11 cases
Evidence of Liver Necrosis (Yes)	18 cases
Liver Failure (Yes)	35 cases
Hospitalization Required (Yes)	38 cases
Outcome	
Death	20 cases
Liver Transplant	9
Death and liver transplant	1
Improvement following drug cessation	9
Not reported	3

^aNormal laboratory values were taken from Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Laboratory reference values. NEJM 2004; 351: 1548-63. AST=aspartate aminotransferase ALT=alanine aminotransferase, ALP=alkaline phosphatase, Tbili=total bilirubin, INR=international normalized ratio, PT=prothrombin time.

Out of the 42 cases, there was one case of a positive rechallenge. This case report (ISR 1728520) describes a 22 year old female treated with oral ketoconazole for onychomycosis of the toes. After two months of oral ketoconazole, she became jaundiced and anorexic. She had hyperbilirubinemia and elevated liver transaminases. Ketoconazole tablets were discontinued and restarted when the symptoms resolved. Two weeks after restarting the drug, she developed icterus, elevated liver enzymes, light-colored stools and was in fulminant liver failure. She was placed on a liver transplant list.

Figure 3 represents the AERS reporting trend of adverse events for the 42 cases over the entire postmarketing period, stratified by event and report date. All but one case actually occurred before 2003; a 36 year old female who received the drug for tinea versicolor and required a liver transplant as reported by the Acute Liver Failure Study Group (ALFSG) registry. There were a total of six cases reported in 2009 and 2010 that described events that occurred before 1984. These data demonstrate that serious, US-based cases of ketoconazole-associated liver injury are events that have been primarily reported and have occurred prior to 2003. The largest proportion of reports were submitted to FDA in the three years after approval (1981-1984), soon after hepatotoxicity became a recognized concern with the drug and the Boxed Warning was added to the product label.

Figure 3. AERS Reporting Trend by FDA Received and Event Date for Serious, US-based Hepatotoxicity Reports from January 1, 1980 through December 1, 2011



In addition to safety evaluator review, each case was subject to expert review by an OSE hepatologist. The purpose of the hepatology review was to assess each case for known confounders and assign a categorical causality score, ranging from highly likely to insufficient data to determine. The expert screened cases for temporality, latency of onset, hepatitis serology, concurrent malignancy, chronic alcohol use and evidence of co-administered hepatotoxic drugs in assigning a causality score. The hepatologist determined that 45% (19/42) of the cases were categorized as probable or more likely to be causally related to ketoconazole therapy. Moreover, death or liver transplantation was an outcome in 84% (16/19) of these cases.

6.1.2 Comparative Quantitative Risk Estimates

This section focuses on selected publications providing some level of quantification of the risk of ketoconazole hepatotoxicity, and on the analysis from the MiniSentinel project.

Garcia Rodriguez et al.¹⁵

This observational study of hepatotoxicity with antifungal drugs used the UK General Practice Research Database (GPRD) and was published in 1999. As this was one of the primary references cited by the EMA, we examine it here in detail.

The aim of the study was to determine the risk of acute liver injury among users of several different oral antifungal compounds. This was an observational retrospective cohort study comparing the frequency of acute liver injury among users of oral antifungal drugs. All data were obtained from the GPRD, which is a well-known resource for pharmacoepidemiological studies. GPRD comprises a network of general practitioners who use a particular software product for an electronic medical record (EMR), and enter relevant clinical data on the patients in their practice, as part of providing clinical care. Data are then collected from the EMR system and uploaded into a research database. Information collected from these participating physicians include demographic information, diagnoses, prescriptions, laboratory results, and details of referrals for specialist or inpatient care.

The time period for this study was January 1, 1991 through September 30, 1996. The study cohort included patients aged 20-79 years who had received one or more prescriptions for an oral form of one of the study drugs (fluconazole, griseofulvin, itraconazole, ketoconazole, terbinafine) during the study time period. Patients were excluded from the cohort if in the past five years they had a history of cancer, liver disease, gallbladder disease, pancreatic disease, heart failure, HIV, alcohol abuse, certain autoimmune disorders, or inflammatory bowel disease.

Cases were identified from diagnostic codes for a broad set of hepatic-related conditions, reproduced below from the publication. (OXMIS was the diagnostic coding system in the GPRD at the time of this study.)

Three of the authors reviewed the medical records of patients with a condition of interest, to ascertain “acute liver injury,” defined as follows: one or more clinical symptoms of hepatic injury (nausea, vomiting, abdominal pain, jaundice), plus referral to a specialist or admission for inpatient care, plus one of the following: (1) ALT $\geq$ twice the upper limit of normal (ULN), or (2) AST, ALT, and ALP all $>$ ULN with one of the three $\geq$ twice ULN, and no evidence of an exclusionary condition.

¹⁵ Garcia-Rodriguez LA, Duque A, Castellsague J, Perez-Gutthann S, Stricker BH. A Cohort Study on the Risk of Acute Liver Injury Among Users of Ketoconazole and other Antifungal Drugs. *Br J Clin Pharmacol* 1999; 48(6):847-852.

Patients were followed from the date of the first prescription for a study drug until the end of the study period, or until one of the following: a diagnosis from the list above, a diagnosis of an exclusionary disorder, 80th birthday, or death. Patients were observed both during and after exposure to the antifungal drug, under the following categories: “current use” was defined as days prescribed plus 14, “past use” was defined as the 90 days following “current use,” and “nonuse” was defined as all time after “past use.”

Incidence rates during current use were calculated for these events and compared to the incidence rates for nonuse.

The sample included a total of 69,830 subjects who received one of the study drugs. Table 3 below shows the number of patients stratified by drug. The samples for fluconazole, itraconazole and ketoconazole had a preponderance of younger females, which the authors attributed to the most frequent indication for those particular drugs being candidiasis, versus onychomycosis for griseofulvin and terbinafine. Consistent with this, since vaginal candidiasis may be treated with a one-day therapy regimen using fluconazole or itraconazole, the authors reported that roughly three-fourths of fluconazole users and one-half of itraconazole users had a one-day duration of treatment.

A total of 73 patients had a diagnostic code included in the outcome definition. Medical charts were obtained for 66 of these, and after review by the authors (with the antifungal drug masked), 16 cases (or roughly one-quarter) were deemed to meet the case definition. Of these, 5 were with current antifungal use (all within the first month), 1 occurred during a past use period, and 10 during a nonuse period.

The table below is adapted from the publication and displays the results. Adjustments to the relative risks for age and gender could not be made because of the sparseness of the data.

Table 3. Acute Liver Injury in GPRD Among Current Users of Antifungal Therapies (Garcia Rodriguez et al. 1999)

Antifungal	Patients	Person-months	Person-months per pt (avg)	Acute liver injury cases	Incidence rate (95% CI) per 10,000 patients	Incidence rate (95% CI) per 100,000 person-mos	Incidence rate ratio versus nonuse (95% CI)
Fluconazole	35,833	29,701	0.8	0	0.0 (0.0, 1.0)	0.0 (0.0, 12.9)	0.0 (0.0, 20.0)
Griseofulvin	6,731	35,841	5.3	0	0.0 (0.0, 5.5)	0.0 (0.0, 10.7)	0.0 (0.0, 16.5)
Itraconazole	19,488	19,168	1.0	2	1.0 (0.1, 3.7)	10.4 (2.9, 38.1)	17.7 (2.6, 72.6)
Ketoconazole	1,052	1,492	1.4	2	19.0 (2.3, 68.7)	134.1 (36.8, 488.0)	228.0 (33.9, 933.0)
Terbinafine	13,430	40,638	3.0	1	0.7 (0.02, 4.2)	2.5 (0.4, 13.9)	4.2 (0.2, 24.9)

The authors point out that these data indicate a number-needed-to-harm for ketoconazole of around 500; i.e., one out of every 500 patients treated can be expected to develop acute liver injury, which they suggest is comparable to isoniazid.

For comparison, another GPRD study of itraconazole and fluconazole (ketoconazole was not included) found 1 case of asymptomatic liver enzyme elevation associated with 31,722 itraconazole prescriptions, and one case of obstructive jaundice requiring hospitalization with 68,994 fluconazole prescriptions.¹⁶

Chien et al.¹⁷

This study from Taiwan describes a randomized clinical trial to assess hepatic reactions to ketoconazole, in comparison to griseofulvin. A total of 211 patients with onychomycosis and no laboratory evidence of liver disease were randomized in a 2:1 ratio to treatment with ketoconazole 200 mg/day or griseofulvin 500 mg/day; treatment was continued as long as clinically indicated. Four patients out of 137 had to discontinue ketoconazole for clinical hepatitis (defined by jaundice or other symptoms); all 4 recovered. There were no such cases among 74 griseofulvin-treated patients. Asymptomatic transaminase elevations were present in 18% of ketoconazole recipients but were absent in griseofulvin recipients. This study showed a risk of frank hepatitis with ketoconazole treatment of 3%, which would support ketoconazole being uniquely hepatotoxic, not merely among antifungal drugs, but among marketed drugs in general. However, a 3% risk seems inordinately high compared to other clinical trial data; in the proposed Nizoral[®] product labeling, under Adverse Reactions, the incidence of hepatic dysfunction in clinical trials is given as <1%.

Janssen and Symoens¹

This widely-cited paper from the manufacturer was published early in ketoconazole's marketing history (1983) and attempted to estimate the risk of symptomatic hepatitis with ketoconazole treatment from spontaneous postmarketing reports. The author's case definition for symptomatic liver reactions was not precisely stated, but included both icteric reactions (involving jaundice, dark urine, or pale stools) and anicteric reactions (involving fever, fatigue, weakness, malaise, anorexia, nausea, vomiting). From 1979 through March 15, 1982, the manufacturer had received reports of 31 cases of symptomatic liver reactions; older females, and patients with previous hepatitis, griseofulvin use, or "idiosyncrasy to other drugs" appeared to be over-represented in this case series. The median duration of exposure was 8 weeks. One of the 31 cases progressed to fatal hepatic necrosis. Based on an estimated total cumulative tablets distributed of 17.9 million through December 31, 1981, and assuming an average of 60 days of treatment per patient, the authors estimated that 300,000 patients worldwide had been treated with ketoconazole, and concluded that the "estimated incidence of reported symptomatic hepatic reactions" was 1:10,000. An update to this analysis reportedly revised this estimate to 1:15,000 (though the primary reference could not be located).¹⁸

¹⁶ Bradbury BD, Jick SS. Itraconazole and fluconazole and certain rare, serious adverse events. *Pharmacotherapy*. 2002;22:697-700

¹⁷ Chien R-N, Yang L-J, Lin P-Y, Liaw Y-F. Hepatic Injury during Ketoconazole Therapy in Patients with Onychomycosis: A Controlled Cohort Study. *Hepatology* 1997; 25:103-107.

¹⁸ Janssen PAJ, Cauwenbergh G, Symoens J. Hepatic Reactions During Ketoconazole Treatment: A 1 Year Update. Beerse, Belgium: Janssen Pharmaceutica, 1983. [As reported in Lewis JH, Zimmerman J, Benson GD, et al: Hepatic Injury Associated with Ketoconazole Therapy. *Gastroenterology* 86:503-513, 1984]

Details of how this risk estimate was calculated are unclear in the publication. The authors appear to have included both premarketing and postmarketing reports in the numerator, since some of the cases evidently predated the launch of ketoconazole, particularly the two listed from 1979, in view of the “international birth date” for ketoconazole of June 1, 1980.¹⁹ Generally speaking, it is not desirable to pool premarketing and postmarketing data when calculating such risk estimates, since there is considerably more uncertainty for both numerators and denominators in the postmarketing environment.

These estimates of 1 in 10,000 or 1 in 15,000 ketoconazole exposures leading to symptomatic hepatotoxicity have been cited by other authors.^{4,20,21} However, from the description in the paper, these figures are more properly regarded as spontaneous reporting rates than incidences, even though the authors failed to clarify the distinction. Stricker and colleagues² correctly pointed out that these calculations did not account for under-reporting of events during postmarketing surveillance. They suggested that if a reporting rate equal to 1 in 10,000 exposures is adjusted for under-reporting, it could be consistent with an actual risk of 1:1,000 or even higher. This could make the actual risk comparable to the risk of approximately 1 in 500 observed in the aforementioned GPRD study.

Publications on Liver Transplantation for Drug Induced Liver Injury

Russo and colleagues²² reported a study using the national United Network for Organ Sharing (UNOS) database to ascertain the numbers of patients receiving liver transplants as a consequence of drug-induced hepatotoxicity. They surveyed the UNOS database during the period January 1, 1990 to October 31, 2002, and found that drug hepatotoxicity was the reason for roughly 15% of all liver transplants, with acetaminophen toxicity accounting for about half of the drug hepatotoxicity transplant cases. With respect to antifungal drugs, during the study period there were 6 transplants due to ketoconazole hepatotoxicity and 1 for itraconazole hepatotoxicity.

A similar analysis of UNOS data was subsequently published by Mindikoglu and colleagues and included data from the period October 1, 1987 through December 31, 2006.²³ This analysis found that among antifungal drugs during this period, ketoconazole

¹⁹ Rapporteur Reports EMA shared with FDA based on a confidentially agreement. Archived within OSE at the following location: L:\DRUG FILES\K\Ketoconazole\Ketoconazole OSE Review 2012.

²⁰ Bercoff E, Bernuau J, Degott C, Kalis B, Lemaire A, Tilly H, Rueff B, Benhamou JP. Ketoconazole-induced Fulminant Hepatitis. *Gut* 1985; 26:636-638.

²¹ Lake-Bakaar G, Scheurer PJ, Sherlock S. Hepatic Reactions associated with Ketoconazole in the United States. *Br Med J* 1987; 294:419-422.

²² Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver Transplantation for Acute Liver Failure from Drug Induced Liver Injury in the United States. *Liver Transpl* 2004; 10:1018-1023.

²³ Mindikoglu AL, Magder LS, Regev A. Outcome of Liver Transplantation for Drug-Induced Acute Liver Failure in the United States: Analysis of the United Network for Organ Sharing Database. *Liver Transpl* 2009; 15:719-729.

was implicated as the cause of liver injury leading to eight transplants, two with terbinafine and one with itraconazole. There was an additional case attributed to acetaminophen for which fluconazole was a concomitant drug.

Because the UNOS database is thought to capture essentially all the liver transplants performed in the U.S., it is reasonable to relate these data to the amount of antifungal drugs prescribed in the U.S. during roughly the same period. Table 4 presents these data. Unfortunately for the present purpose, prescription data are not available prior to the 1990s, so this table includes the Russo et al. data (1990-2002) but not the Mindikoglu et al. data (1987-2006). Among the antifungals of interest, ketoconazole had the highest number of hepatotoxicity-related liver transplants, but the second lowest number of prescriptions over approximately the same period. These data suggest that liver transplantation attributed to ketoconazole-induced liver injury, when considering prescription volume, is disproportionately higher compared to other antifungals.

Table 4. Liver Transplants Due to Hepatotoxicity from Antifungals, U.S., 1990-2002

Antifungal drug implicated	UNOS liver transplants, 1/1/90 – 10/31/2002	Total estimated U.S. prescriptions, oral formulations only, 1991-2002*
Fluconazole	0	64,447,283
Griseofulvin	0	13,647,288
Itraconazole	1	9,250,269
Ketoconazole	6	10,758,495
Terbinafine	0	12,585,245

*SOURCE: IMS Health, Vector One®; National extracted Jan 2012

– NOTE DATA NOT AVAILABLE FOR 1990.

MiniSentinel: Hepatic Disease Diagnoses with Oral Antifungal Drugs

Table 5 summarizes the results overall. Fluconazole was the most prescribed oral antifungal assessed and had the highest number of events (n=24); by site, Data Partner 008 had the most fluconazole events (n=10), though Data Partner 015 had the most fluconazole users (45% of the total). Only raw data on the demographic characteristics and no data on clinical characteristics of the antifungal drug users were available. The highest frequency of hepatic events was observed with voriconazole, which is used chiefly in immunocompromised patients with severe fungal infections. The majority of events had no severity indicators associated with them.

Table 5. MiniSentinel Analysis of Hepatic Events (see definition) Following Use of Selected Oral Antifungal Drugs, 1-1-2000 to 9-30-2011

Antifungal drug	Users*	Events during risk period**	Events per 1M Risk Period Days**	Unique pts with events	Unique events with severity indicators	Unique events per 100,000 users	Unique events with severity indicators per 100,000 users
Fluconazole	2,476,781	38	0.39	37	8	1.5	0.3
Griseofulvin	224,259	2	0.13	2	0	0.9	0
Itraconazole	32,288	1	0.37	1	0	3.1	0
Ketoconazole	203,363	8	0.76	8	1	3.9	0.5
Posaconazole	448	0	0	0	0	0	0
Terbinafine	335,183	4	0.12	4	1	1.2	0.3
Voriconazole	3,898	7	16.22	6	1	153.9	25.7

*183 day event washout period for pre-existing diagnoses, and no malignancy or Cushing's syndrome exclusions

**1M=1 million and data are through 30 days past last prescription

The MiniSentinel analysis has a number of limitations that should be borne in mind. No adjustment for confounding variables was performed and the events were not adjudicated by chart review. The prescribed dose was not available, which might have distinguished higher-dose off-label uses of ketoconazole from its use to treat fungal infections. Our case definition required a primary discharge diagnosis to define an outcome of liver injury, but the patient's primary discharge diagnosis is not consistently indicated throughout all data sources in the MiniSentinel database. Thus, an unknown but possibly non-negligible proportion of events were excluded for lacking an indicator that the diagnosis was the primary discharge diagnosis. Speculatively, this might account for the event rates being lower than reported in the literature. Despite this limitation, the event rate observed with voriconazole still exceeded 1 per 1000 users (under the less stringent exclusion criteria). Voriconazole is indicated only for serious, systemic fungal infections, so its elevated event rate may be reflecting use in a more medically ill population. Another factor may be that voriconazole may be relatively more hepatotoxic than ketoconazole. Voriconazole's label warns that serious (even fatal) hepatic events occurred during clinical trials, and recommends liver enzyme monitoring. Also, one observational study reported a higher frequency of hepatic dysfunction (as evidenced by clinical laboratory findings) with voriconazole than fluconazole or amphotericin.²⁴ A

²⁴ Riedel A, Choe L, Inciardi J, Yuen C, Martin T, Guglielmo BJ. Antifungal prophylaxis in chemotherapy-associated neutropenia: a retrospective, observational study. BMC Infect Dis. 2007; 7: 70.

strength of the analysis include the large number of antifungal users in the samples for the more widely used drugs.

On balance, the MiniSentinel data did not implicate ketoconazole as being uniquely hepatotoxic in the class of oral antifungal drugs, but the aforementioned limitations must be borne in mind, particularly with event rates below those reported in the literature. The highest observed frequency of events was with voriconazole, based on a smaller sample and most likely a different patient population than that taking ketoconazole or other oral antifungals.

United Network for Organ Sharing (UNOS) Data

These data were provided to Dr. Leonard Seeff on July 17, 2012 by Sarah Taranto, Data Request Manager/SAS Analyst II, UNOS. As shown, of the three azole antifungal drugs included in the search, only ketoconazole was associated with liver transplants.

Table 6. Liver Transplants Attributed to Fluconazole, Ketoconazole, or Itraconazole Hepatotoxicity in the UNOS Database, 10/1/1987 to 4/30/2012.

Azole antifungal drug	Liver transplants in which it was implicated*
Fluconazole	0**
Ketoconazole	10
Itraconazole	0

*Based on OPTN data as of July 13, 2012

**One ketoconazole-related transplant was initially attributed to fluconazole toxicity

The earliest of these transplants was in 1989 and the most recent was in 2003. In addition, three patients were placed on the UNOS waiting list for a liver transplant between April 1, 1994 and April 30, 2012 without receiving transplants, the most recent in 2005; of these, one died, one improved without a transplant, and one was lost to follow-up. In all three cases, the suspected hepatotoxin was ketoconazole. Note that there are slight discrepancies with the published data in the Mindikoglu et al. and Russo et al. papers, both of which listed one itraconazole case during the time frame; and in addition, the Mindikoglu et al. paper listed 8 transplants (rather than 10) with ketoconazole from October 1, 1987 to December 31, 2006. There was no obvious explanation for these slight discrepancies.

For context, it is possible to relate these data from UNOS to the prescription use data, as shown in the following table. This shows that the number of transplants attributed to ketoconazole hepatotoxicity was disproportionate to prescriptions; if the ratio to prescriptions had been the same, there would have been roughly 80 liver transplants attributed to fluconazole and 6 to itraconazole during this time (p-value = 0.02 for itraconazole vs. ketoconazole, Fisher's exact).

Table 7. UNOS Liver Transplants for Azole Antifungal Drugs, 1991-2010

Azole antifungal drug	Liver transplants in which it was implicated*	Total U.S. prescriptions for oral formulations, 1991-2010**
Fluconazole	0	162,807,473
Itraconazole	0	11,546,818
Ketoconazole	8	16,073,930

* Based on OPTN data as of July 13, 2012

**SOURCE: IMS Health, Vector One® National. Extracted Jan 2012

6.2 KETOCONAZOLE DRUG INTERACTIONS

6.2.1 Myopathy Attributed to a Ketoconazole-Statin Drug Interaction

The AERS search retrieved 63 reports, 31 of which were identified as duplicates. The remaining 32 cases were included in the case series of myopathy reported with ketoconazole use.

Table 8 below summarizes the 32 cases of myopathy reported with ketoconazole use for this case series. The reporter classified 28 of these cases as rhabdomyolysis. One case involved a patient receiving topical ketoconazole, all remaining cases involved patients receiving ketoconazole tablets. The average age was 68.9 years with a range from 29 to 84 years. There was a gender imbalance with 26 cases reported in males and 6 cases reported in females, which was largely driven by the predominant off-label use of ketoconazole in the treatment of prostate cancer. Prostate cancer (17/32) and fungal skin infections (6/32) were the leading indications in this case series. Based on twenty reports that provided ketoconazole dosages, the median dose was 600mg daily (range 200-1200mg). Of the 32 cases, the event year was reported in 18 cases. While this drug has been approved since 1981, 14 out of 18 cases reported an event date during or after 2007 (Figure 4). The United States was the leading report country of origin (24/32 cases). Eighteen of 32 cases involved a drug-drug interaction with simvastatin and ketoconazole. Four reports cited lovastatin as the interacting drug. An additional four cases involved other HMGCoA reductase inhibitors (i.e., atorvastatin, pravastatin, rosuvastatin, cerivastatin).

Three cases report myopathy with ketoconazole monotherapy. This included one case of ketoconazole monotherapy in an avid weight lifter who was treated with intravenous fluids, transferred to another facility and lost to follow up. Another case report of ketoconazole monotherapy provided limited information to assess causality (no time to onset, creatine kinase values, confounding disease states, or concomitant medications) and provided a dosing regimen (400 mg three times daily) that suggests off-label use. The third case complained of muscle pain while on simvastatin and topical ketoconazole without supporting laboratory values or clinical details to support a diagnosis of rhabdomyolysis attributed to a ketoconazole drug interaction.

Table 8. Select Characteristics of AERS Ketoconazole-Myopathy Received by FDA from January 1, 1980 through December 1, 2011

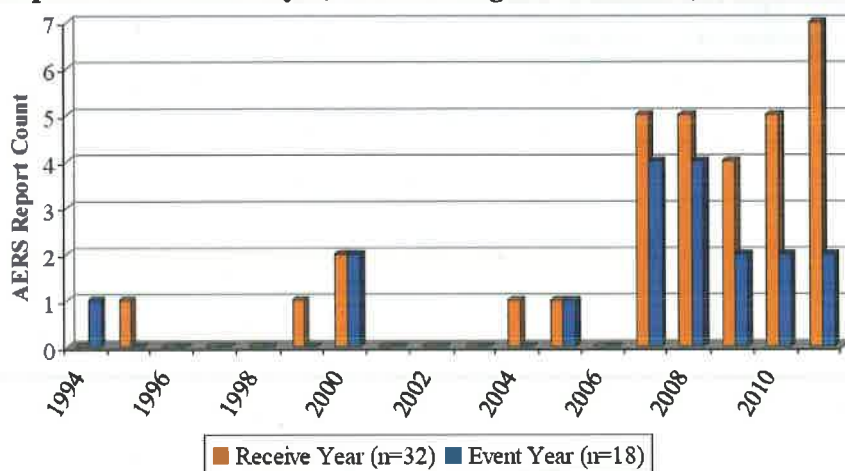
Demographic or Clinical Characteristic	Cases (N=32)
Age	(n=32)
Median (Range)	73 years (29-84)
Gender	(n=32)
Male/Female	26/6 cases
Ketoconazole Daily Dose	(n=20)
Median (Range)	600 mg (200-1200)
Ketoconazole Indication	
Prostate malignancy	17 cases
Fungal skin infections	6
Pituitary adenoma	1
Not reported	8
Markers of Myopathy Severity	
Dialysis required or diagnosis of ARF	10 cases
Myoglobinuria documented	8 cases
Rhabdomyolysis diagnosed	28 cases
Creatine kinase [median (range) IU/L]: [normal 60-400 IU/L male] ^a [normal 40-150 IU/L female] ^a	39,784 (2,274-1,277,288) (n=26) ^b
Co-suspected Drug in Ketoconazole-Drug Interaction	
HMG-CoA reductase inhibitors (n=26)	Simvastatin: n=18 Rosuvastatin: n=1 Lovastatin: n=4 Cerivastatin: n=1 Pravastatin: n=1 Atorvastatin: n=1
Others (n=6)	Ketoconazole monotherapy: n=3 Hydrocortisone: n=2 Atripla ^c : n=1
Outcome	
Death	2 cases
Hospitalization	12
Disability	0
Life-threatening	3
Other serious	14
Required intervention	1

^a Normal laboratory values were taken from Kratz A, Ferraro M, Sloss PM, Lewandrowski KB. Laboratory reference values. NEJM 2004; 351: 1548-63.

^b Creatine kinase (CK) was elevated in 28 cases, two of which did not provide CK laboratory values to base an estimate.

^c Atripla is a combination drug product containing the following drugs: efavirenz, emtricitabine, tenofovir.

Figure 4. AERS Reporting Trend by FDA Received and Event Date for Myopathy Reports from January 1, 1980 through December 1, 2011



Two reports with an outcome of death were reported due to HMGCoA reductase inhibitor-ketoconazole interaction. The indication for use of ketoconazole was prostate cancer in one case (ISR # 5939705) and pituitary adenoma (ISR # 5323667) in another case. Both of these cases required treatment with dialysis to treat the adverse event of rhabdomyolysis. Vignettes of these two cases are provided below and are identified by ISR number, county of report, and event date.

- ISR # 5939705/United States/June 2008: A 74 year old male was prescribed ketoconazole for prostate cancer and was on concomitant lovastatin therapy for an unreported indication. He experienced weakness and fatigue, but this was attributed to advanced age. The patient lost mobility in his legs, suffered from kidney failure, and required hospitalization for rhabdomyolysis. Dialysis was performed for 4 hours every other day and the patient died 2 months after hospital admission. The reporter attribution for loss of mobility in legs and kidney failure was the drug-drug interaction with ketoconazole and lovastatin.
- ISR # 5323667/United States/March 2007: A 59 year old male experienced a drug-drug interaction with simvastatin 80mg and ketoconazole 400mg daily which led to rhabdomyolysis. He was prescribed simvastatin for dyslipidemia and ketoconazole for pituitary adenoma. Approximately one month after adding ketoconazole therapy to simvastatin, the patient experienced weakness with a 2 week history of diarrhea

and flatus and was found to have acute renal failure (BUN/SCr: 134/5.9). He was transferred to a larger institution for urgent daily dialysis. He went into cardiac arrest and died approximately 1 week after hospital transfer. Past medical history included: diabetes, hyperlipidemia, hypertension, stasis dermatitis, Cushing's syndrome with underlying pituitary adenoma, congestive heart failure, chronic obstructive pulmonary disease requiring home oxygen and chronic renal insufficiency. The reporter attributed the rhabdomyolysis to the drug-drug interaction with simvastatin and ketoconazole.

6.2.2 Azole-Drug Interaction Comparative Quantitative Risk Estimates

In our review, we assessed myopathy as an outcome caused by a clinically significant drug interaction between ketoconazole and select HMG-CoA reductase inhibitors. Drug interactions are a significant safety concern for all azole antifungal drugs.²⁵ Our myopathy assessment prompted us to consider the breadth and severity of all ketoconazole drug interactions compared to other azole-drug interactions, as part of our benefit risk evaluation.

We considered the relative potency by which each azole inhibits CYP3A4, each drug's lipophilicity and extrahepatic pathways for azole-drug interactions as measures of the relative extent of azole-drug interaction potential. Available data demonstrate that ketoconazole is the most potent CYP3A4 inhibitor among the azoles^{26,27} This feature is often exploited as ketoconazole is frequently used as the index inhibitor of human cytochrome P450-3A isoforms in drug-drug interaction studies.²⁸ Itraconazole is a less potent inhibitor than ketoconazole and fluconazole even more so.^{26,27,29} Fluconazole's inhibitory potency is substantially lower than ketoconazole and itraconazole resulting in a reduction of well documented fluconazole mediated drug interactions.²⁷ When these interactions occur, they tend to occur at higher fluconazole doses that result in saturation of isoform binding. This differential binding affinity for CYP3A4 would suggest that ketoconazole has the potential to induce more clinically meaningful drug-drug interactions compared to itraconazole or fluconazole.

Ketoconazole and itraconazole are highly lipophilic, relative to fluconazole, which predisposes both drugs to concentrate in the liver and exert comparable CYP3A4 inhibition. As fluconazole is more water soluble than ketoconazole and itraconazole, it

²⁵ Bruggemann RJM, Alffenaar JWC, Blijlevens NMA, Billaud EM, Kosterink JGW, Verweij PE, Burger DM. Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents. *Clinical Infectious Diseases*. 2009; 48: 1441-1458.

²⁶ Niwa T, Shiraga T, Takagi A. Drug-drug interaction of antifungal drugs. *Yakugaku Zasshi* (Japanese-abstract available in English) 2005; 125(10): 795-805.

²⁷ Venkatakrishnan K, von Moltke LL, Greenblatt DJ. Effects of the antifungal agents on oxidative drug metabolism. *Clin Pharmacokinet*. 2000; 38(2): 111-180.

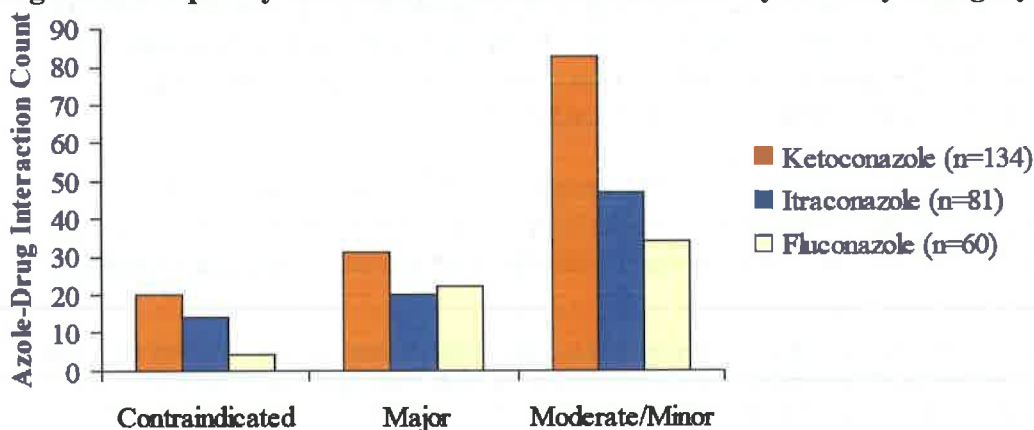
²⁸ Greenblatt DJ, Zhao Y, Venkatakrishnan K, et al. Mechanism of cytochrome P450-3A inhibition by ketoconazole. *Journal of Pharmacy and Pharmacology*. 2011; 63: 214-221.

²⁹ Ervine CM, Matthew DE, Brennan B, Houston JB. Comparison of ketoconazole and fluconazole as cytochrome P450 inhibitors. *Drug Metabolism and Disposition*. 1996; 24(2): 211-215.

undergoes less biotransformation than other azoles and less likely to induce a clinically relevant drug interaction. Additionally, ketoconazole and itraconazole, but not fluconazole, are substrates for the drug transporter protein (Pgp),³⁰ which is another mechanism by which these drugs may cause clinically meaningful drug interactions. Together, these data suggest that ketoconazole and itraconazole would have greater propensity to induce drug interactions than fluconazole.

In our comparative assessment of azole-drug interactions, we consulted a reputable drug information data source (MicroMedex 2.0) to count the number of azole-drug interactions for ketoconazole, itraconazole and fluconazole that are supported by confirmatory drug interaction studies and well documented case reports. We considered this analysis as a practical measure of the relative extent of azole-drug interactions that may be encountered in clinical practice. These data are summarized in Figure 5 below by severity category. Contraindicated reactions are the most severe, followed by major interactions and the moderate-minor interactions are the least worrisome. Among drug interactions with good supportive evidence, the absolute number of drugs that ketoconazole is known to interact is substantially greater than either itraconazole or fluconazole, and this difference is consistent across severity categories. The most clinically significant of these interactions (e.g. contraindicated reactions) are more likely to be encountered with ketoconazole than either itraconazole or fluconazole. We acknowledge that these data may be biased towards ketoconazole because this drug is likely more extensively studied as an index inhibitor in drug interaction studies, but we would also point out that these data are consistent with relative CYP3A4 inhibition potencies and could very well reflect real differences.

Figure 5. Frequency of Established Azole Interactions by Severity Category



6.3 KETOCONAZOLE DOSE-DEPENDENT ENDOCRINE EFFECTS

Ketoconazole can block adrenal and testicular steroid production, particularly at high dosages ($\geq 400\text{mg}$ daily), through its inhibition of the cytochrome P450 isoenzyme

³⁰ Shakeri K, Stahlmann R. Drug interactions during therapy with three major groups of antimicrobial agents. *Expert Opin Pharmacother.* 2006; 7(6): 639-651.

system.³¹ By virtue of this property, the drug has been used therapeutically in treating hormone-dependent illnesses, such as prostate cancer and Cushing's syndrome, which are off-label indications in the US. Androgen receptor signaling permits growth of prostate tumors in castrated patients; ketoconazole, an androgen synthesis blocker, has been studied in multiple clinical trials due to its ability to interfere with androgen production.³² Ketoconazole also enhances the activity of some chemotherapeutic agents, including docetaxel, which is the main therapeutic agent used for castration-resistant prostate cancer.³³

We believe dose-dependent endocrine effects may represent a dose-limiting toxicity that limits the utility of the drug in the treatment of systemic fungal infections. Serious infections may require higher ketoconazole doses for protracted treatment intervals to achieve and sustain a clinical response. In contrast, itraconazole and fluconazole do not appear to have these properties at clinically useful doses and would be preferable to avoid these toxicities in the treatment of systemic fungal infections.

7 BENEFIT-RISK ASSESSMENT BY INDICATION

Search of the English-Language Medical Literature

We conducted an internet-based search of the English-language scientific literature using Embase, PubMed, and Web of Science to retrieve articles describing clinical studies that assessed the efficacy and safety of ketoconazole with respect to its labeled indications. We also sought comparable data with respect to two other within-class azole antifungals - itraconazole and fluconazole.

Statistical Methodology:

In reviewing the retrieved non-randomized observational studies and randomized clinical trials, we restricted our analysis to the evaluable populations for efficacy and safety as identified in the publications. We acknowledge that the findings based on these populations may be biased, because the original randomization may have been compromised and, therefore, underpin serious limitations in interpretation; however, in many articles, the intent-to-treat populations were not clearly delineated, whereas only the evaluable populations were reported. Findings based on evaluable populations can be biased due to post-randomization factors.

³¹ Pont A, Williams PL, Loose DS, Feldman D, Reitz RE, Bochra C, Stevens DA. Ketoconazole Blocks Adrenal Steroid Synthesis. *Ann Intern Med* 1982; 97(3):370-372.

³² Molina A, Beldegrun A. Novel Therapeutic Strategies for Castration Resistant Prostate Cancer: Inhibition of Persistent Androgen Production and Androgen Receptor Mediated Signaling. *J Urol* 2011; 185:787-794.

³³ Figg WD, Woo S, Zhu W, Chen X, Seun Ajiboye A, Steinberg SM, Price DK, Wright JJ, Parnes HL, Arlen PM, Gulley JL, Dahut WL. A Phase 1 Clinical Study of High Dose Ketoconazole plus Weekly Docetaxel for Metastatic Castration Resistant Prostate Cancer. *J Urol* 2010; 183:2219-2226.

In attempting to analyze the efficacy data for ketoconazole and the other azoles in the treatment of dermatophyte infections due to *T capitis*, *T cruris*, *T corporis*, *T pedis*, *T manuum*, and *T barbae*, the retrieved studies were too disparate in terms of study design and conduct, and there were too many methodological issues to permit statistical analyses. However, as we retrieved multiple randomized clinical efficacy trials comparing ketoconazole with fluconazole in the treatment of *T versicolor*, we conducted a meta-analysis to assess comparative efficacy. In relation to treatment effect of the antifungal drugs in patients with chronic mucocutaneous candidiasis, we opted not to perform any statistical analyses due to the preponderance of observational studies and lack of randomized clinical trials as well as the sparse quantity of data relevant to itraconazole and fluconazole in the context of this therapeutic area.

In the absence of placebo-controlled superiority studies in the context of the labeled indications for the systemic fungal infections, we estimated the treatment effect of ketoconazole, itraconazole, and fluconazole as therapy for blastomycosis, coccidioidomycosis, and histoplasmosis based on weighted estimates derived predominantly from single arm observational studies, which comprised the only source of efficacy data. For paracoccidioidomycosis, one randomized clinical trial and two single arm observational studies were used. Our weighted estimates were based on efficacy data for 400 mg/day regimens for blastomycosis, coccidioidomycosis, and histoplasmosis and on data for 200 mg/day for paracoccidioidomycosis, as those dosing regimens represented the preponderance of the data. The efficacy findings could be biased due to differences in the characteristics of the patient populations and the clinical syndromes under treatment. For oropharyngeal and esophageal candidiasis, we conducted a meta-analysis involving multiple retrieved randomized clinical efficacy trials comparing ketoconazole with fluconazole.

Comprehensive Meta-Analysis Software was used for all meta-analyses and weighted analyses for this review. A random effects model was preferred in order to account for heterogeneity and variability across the selected studies.

Efficacy and Safety of Ketoconazole across its FDA-approved indications

Historically, ketoconazole was approved in 1981 on the basis of open, non-comparative studies buttressed by case reports and case series.³⁴ In evaluating the clinical studies retrieved from the English-language medical literature related to ketoconazole's labeled indications, it was apparent that many reported studies were single arm and non-comparative involving small patient populations (generally less than 60 patients); some early studies did not report safety experience. Non-randomized observational studies and clinical studies relevant to the same indications for itraconazole and fluconazole had similar limitations. Other limitations related to heterogeneity across the studies in terms of study design, enrollment criteria, efficacy endpoints, dosing regimen, duration of treatment, variability of clinical syndromes, heterogeneity of underlying diseases, approach to assessing therapeutic response to antifungal therapy, and provisions for dose escalation.

³⁴ Wu T. On the development of antifungal agents: Perspective of the US Food and Drug Administration. Clin Infect Dis 1994; 19 (suppl 1):S54-S58.

Labeled Indication for Dermatophyte Infections: *For the treatment of patients with severe recalcitrant cutaneous dermatophyte infections who have not responded to topical therapy or oral griseofulvin, or who are unable to take griseofulvin.*

A total of 33 clinical studies and case series were retrieved related to the treatment of dermatophyte infections due to *Tinea corporis*, *T. cruris*, *T. capitis*, *T. manuum*, and *T. barbae*. Evaluation of the studies was limited by small study populations that were not statistically powered to demonstrate a difference across subgroups, poor documentation of statistical methodology, lack of randomized active controlled comparative studies involving other within-class azoles, inadequate reporting of safety data, differences in endpoint definitions, and use of non-fixed treatment schedules.

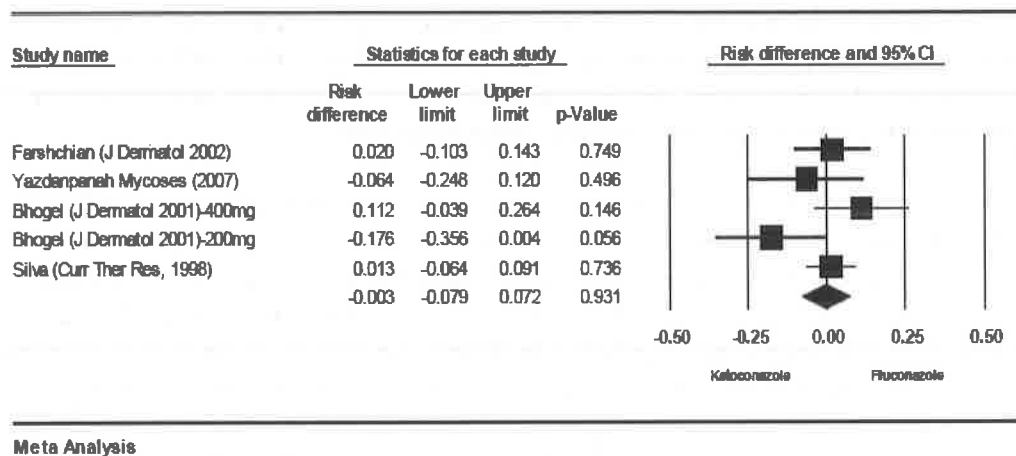
Griseofulvin was most frequently cited comparator agent in published randomized clinical trials related to this indication including nine ketoconazole studies, two itraconazole studies, and one fluconazole study. The three azole antifungals exhibited comparable efficacy to griseofulvin in the published trials. Only one comparative clinical trial involving multiple azole antifungals was retrieved; the results of the trial evidenced similar efficacy for ketoconazole and fluconazole (response rates of 63% and 64%, respectively). Thus, overall, notwithstanding the limitations and the lack of multiple comparative azole-azole trials, the clinical data demonstrated comparable efficacy for ketoconazole, itraconazole, and fluconazole in the treatment of dermatophyte infections.

In terms of safety, asymptomatic elevations in hepatic transaminases were reported following exposure to all three drugs. Discontinuations due to drug-related adverse events included two cases of serious drug-related hepatic injury reported in patients treated with ketoconazole. One case involved a 68 year old female with recalcitrant dermatophytosis of her feet and toenails who developed focal liver parenchymal necrosis despite monitoring blood tests (LFTs) every 3 weeks. Her symptoms and LFT abnormalities resolved following discontinuation of ketoconazole; however, she exhibited a positive rechallenge when the drug was restarted 17 weeks later. The second case involved a 48 year old male treated for fingernail onychomycosis in an open-label dermatophytosis study. He developed fatigue, nausea, and icterus in association with marked LFT elevations after 81 days of ketoconazole; his symptoms and lab abnormalities resolved two months following discontinuation of the drug. A liver biopsy was not performed. Overall, there were no deaths or liver transplantations among the ketoconazole-, itraconazole-, and fluconazole-treated patients.

Other Fungal Skin Infections: Pityriasis versicolor (*T. versicolor*):

We retrieved three comparative randomized clinical trials comparing ketoconazole to fluconazole and one trial comparing ketoconazole, itraconazole, and fluconazole in the treatment of *T. versicolor*. We performed a meta-analysis of the efficacy data relevant to the multiple trials in which ketoconazole and fluconazole were compared using a random effects model to account for heterogeneity across the studies. As depicted in the figure below, ketoconazole and fluconazole exhibited similar efficacy in the treatment of this infection.

Figure 6: Comparative Efficacy of Ketoconazole and Fluconazole in the Treatment of *T. versicolor*: Meta-analysis



Labeled Indication: Chronic mucocutaneous candidiasis

We retrieved a total of 12 publications; there were eight case series/ observational studies and two placebo-controlled studies involving ketoconazole therapy, whereas only two small case series were retrieved relevant to itraconazole and fluconazole. In general, ketoconazole was administered as continuous daily dosing for this indication. All three drugs were reported as providing successful treatment; however, due to methodological deficiencies, no statistical analyses could be performed.

In terms of safety, there was one patient who was discontinued from ketoconazole due to serious hepatic injury (biopsy-confirmed hepatitis) and another with asymptomatic elevation in liver function tests. No patients given itraconazole or fluconazole were discontinued. Additionally, relapses were reported frequently among ketoconazole recipients, including one report of two relapses involving ketoconazole-resistant isolates. There were nine deaths reported in the ketoconazole subgroup (none considered drug-related). No deaths or liver transplantations were reported in patients given itraconazole or fluconazole.

Labeled Indication for Systemic Fungal Infections: candidiasis, blastomycosis, coccidioidomycosis, histoplasmosis, and paracoccidioidomycosis

In terms of systemic fungal infections, ketoconazole (Nizoral®) tablets is labeled for the treatment of candidiasis (including oral thrush and candiduria), chromomycosis, and endemic mycoses, including blastomycosis, histoplasmosis, coccidioidomycosis, and

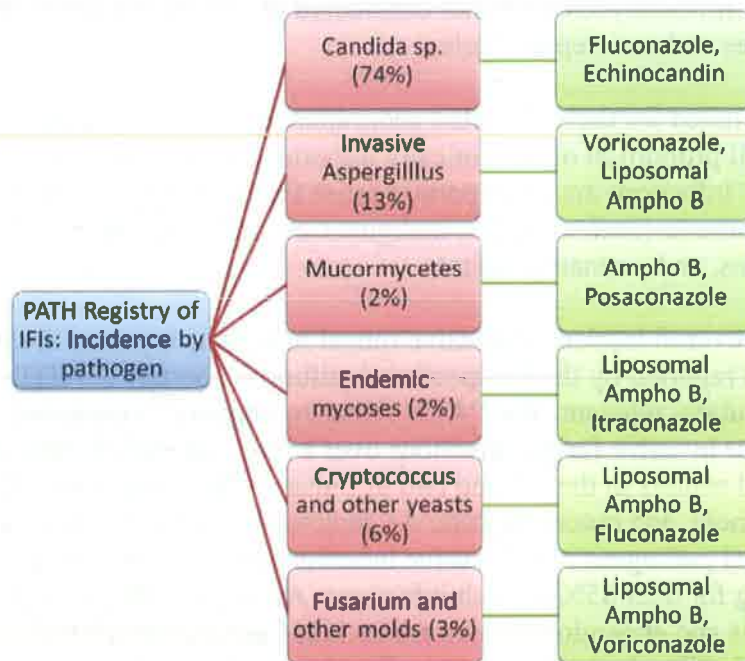
paracoccidioidomycosis. Chromomycosis was not considered in this review due to the paucity of published studies and case reports/series.

The endemic mycoses are noted for their restricted geographic distribution; however, they constitute only a small proportion of all clinically important invasive fungal infections. Invasive fungal infections are an important cause for morbidity and mortality in immunocompromised patients (such as AIDS, malignancies, organ and stem cell transplants), elderly patients, and premature infants.

In order to understand the overall burden of invasive fungal infections reported in the country currently, the data reported by the Prospective Antifungal Therapy (PATH) Alliance Registry is particularly relevant. The PATH Alliance Registry³⁵ conducted prospective surveillance for invasive fungal infections over a five year period from 2004-2008 at 23 tertiary medical centers in the US and two in Canada. The registry provides current surveillance, treatment, and outcomes data. As depicted in Figure 7 below, there is an extensive list of fungal pathogens with invasive infections due to *Candida spp.* and *Aspergillus spp* accounting for over 85% of such infections. Among the six pathogen categories, only candidiasis and endemic mycoses are included among the labeled indications for ketoconazole. The drug exhibits virtually no meaningful *in vitro* activity against many of the other pathogen groups. However, despite the labeled indications, oral ketoconazole was not reported as being used for the treatment of any patient in the registry. Triazole antifungals or amphotericin B were the most frequently used drugs.

Figure 7: Invasive fungal infections by pathogen based on culture data from PATH Alliance Registry with the two most frequently prescribed antifungal drug therapies (N=6,807 patients)

³⁵ Azie N, Neofytos D, Pfaller M, et al. The PATH (Prospective Antifungal Therapy) Alliance registry and invasive fungal infections: update 2012. *Diagn Micro Inf Dis* 2012; 73:293-300.



Comparative Microbiologic Spectrum of Activity of the Various Systemic Antifungals

In addition to the burden of invasive fungal infections, the comparative *in vitro* activities of the major systemic antifungal agents against clinically important groups of pathogenic fungi should be considered. The table on the slide illustrates (in general terms) the comparative semiquantitative *in vitro* activities of ketoconazole, itraconazole, and fluconazole against various fungal pathogens. Ketoconazole has limited activity against *Candida* species as well as the causative fungi for *Blastomycosis*, *Histoplasmosis*, and *Coccidioidomycosis* compared to the more reliable activity of itraconazole. Fluconazole has more reliable activity than ketoconazole against *Coccidioidomycosis* and *Candidiasis*. In addition, itraconazole and fluconazole exhibit a broader spectrum activity against other clinically important fungal pathogens compared to ketoconazole; itraconazole has activity against *Aspergillus spp.* and *Sporothrix schenckii*, whereas fluconazole has expanded activity against *cryptococcal infections*. Ketoconazole exhibits no microbiologic activity against *Aspergillus spp.*, *Fusarium spp.*, and *Mucor/Zygomycetes*, which are important causes of invasive fungal infections in immunocompromised patients.

Table 9: Comparative Microbiologic Activity of Various Systemic Antifungals

TABLE 2 Spectrum and extent of activity of commonly used systemic antifungal agents^a

Organism	Activity ^b of antifungal agent:				
	Amphotericin B	Ketoconazole	Fluconazole	Itraconazole	Caspofungin
<i>Aspergillus</i> spp.	+++	0	0	+++	++
<i>B. dermatitidis</i>	+++	++	+	+++	++
<i>C. immitis</i>	+++	++	+++	+++	++
<i>C. neoformans</i>	+++	+	+++	++	0
<i>Candida</i> spp.					
<i>C. albicans</i>	+++	++	+++	+++	+++
<i>C. glabrata</i>	++	+	++	++	+++
<i>C. guilliermondii</i>	++	+	+++	+++	++
<i>C. krusei</i>	++	+	0	++	+++
<i>C. lusitanae</i>	++	++	+++	+++	+++
<i>C. parapsilosis</i>	+++	++	+++	+++	++
<i>C. tropicalis</i>	+++	++	+++	+++	+++
<i>Fusarium</i> spp.	++	0	0	+	0
<i>H. capsulatum</i>	+++	++	++	+++	++
<i>Mucor</i> , <i>Rhizopus</i> , and other fungi belonging to class Zygomycetes	+++	0	0	0	+
<i>P. brasiliensis</i>	+++	+++	++	+++	++

^a This table is a general overview for comparison of the activity of some systemic drugs against various fungi. Readers are recommended to refer to the text for more detailed information or data at the species or strain level.

^b In some cases, the meaning of reduced *in vitro* susceptibility is far from certain (e.g., the echinocandins). 0, no meaningful activity; +, occasional activity; ++, moderate activity but resistance is noted; +++, reliable activity with occasional resistance.

From: Manual of Clinical Microbiology, 8th Ed. 2003

Molecular Mechanisms of Azole Resistance

Clinically important antifungal resistance may adversely affect the response of a fungal infection to treatment with a particular drug product. Resistance to azole antifungals was first noted in the literature in patients having prolonged use of oral ketoconazole for chronic mucocutaneous candidiasis and in HIV-infected patients receiving fluconazole for the treatment of oropharyngeal or esophageal candidiasis.³⁶ Minimum inhibitory concentration (MIC) interpretative breakpoints for *in vitro* antifungal susceptibility testing have been established for *Candida* species for amphotericin B, 5-flucytosine, fluconazole, itraconazole, voriconazole, and the echinocandins³⁷; however, MIC breakpoints have not been established for ketoconazole. Additionally, appropriate methods have not yet been established for *in vitro* antifungal susceptibility testing for the endemic mycoses.

As a class, the azole antifungals all act at the same target in the sterol synthesis pathway as described previously in this report. In the case of *Candida* species, resistance to one azole antifungal frequently is associated with cross-resistance to other members of the azole class. Molecular mechanisms of azole resistance have been best characterized in *Candida albicans*. Four major molecular mechanisms of azole resistance have been characterized in *Candida albicans* as follows:³⁸

(1) Decreased drug concentration: due to upregulation of efflux pump transporter genes, CDR1, CDR2, and MDR1, which decrease drug concentrations within fungal cells.

³⁶ White T. *Mechanisms of Resistance to Antifungal Agents*. In: Murray P, Baron EJ, Jorgensen J, Landry ML, Pfaller MA, eds. *Manual of Clinical Microbiology*. Washington, DC: ASM Press; 2007:1961-1968.

³⁷ Pfaller MA. Antifungal Drug Resistance: Mechanisms, Epidemiology, and Consequences for Treatment. *Am J Med* 2012; 125:S3-S13.

³⁸ Kanafani Z, Perfect J. Resistance to Antifungal Agents: Mechanisms and Clinical Impact. *Clin Infect Dis* 2008; 46:120-128.

Upregulation of the CDR genes confers broad resistance to almost all azole antifungals, whereas upregulation of the MDR1 gene encoded pumps confers resistance limited to fluconazole.

(2) Altered target site: The ERG11 gene encodes for the target enzyme, lanosterol 14 α demethylase, involved in formation of ergosterol, a major fungal cell component. Mutations that alter the gene affect the target enzyme by reducing binding affinity to the azole antifungal drugs.

(3) Upregulation of the target enzyme: There are excessive concentrations of the target enzyme in fungal cells, such that azole antifungal drugs imported into the fungal cells are overwhelmed by target and cannot inhibit ergosterol synthesis.

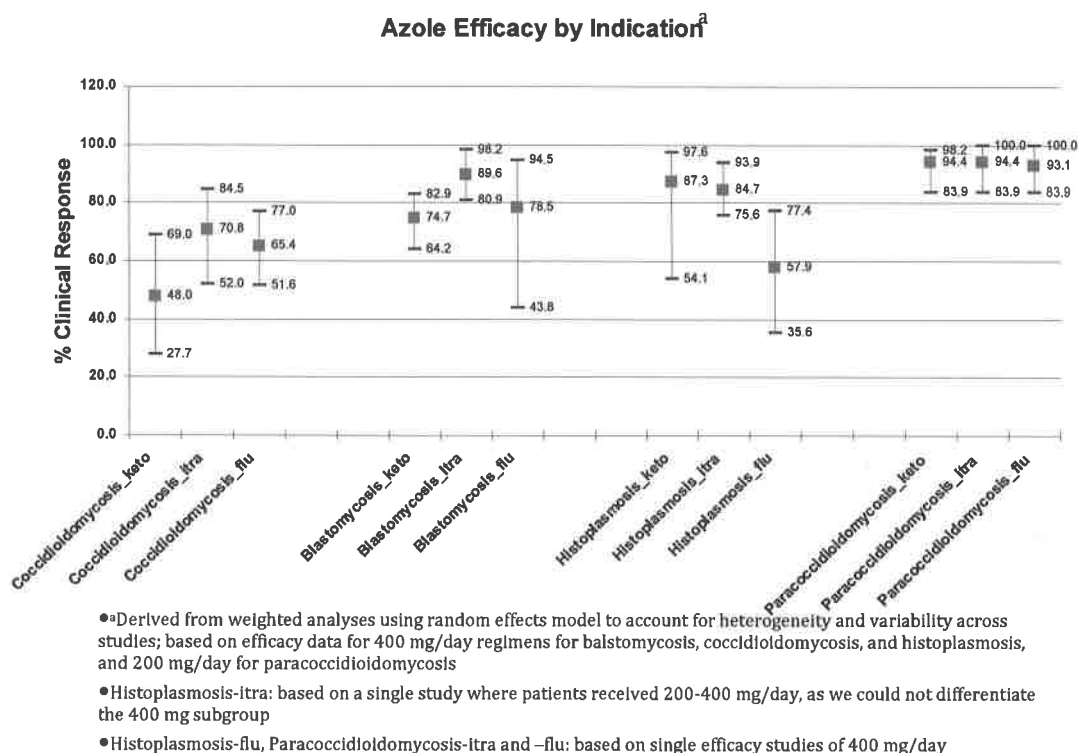
(4) Bypass pathways: Mutations in ERG3 gene prevents the formation of toxic products that normally result from ergosterol depletion in the fungal cell membrane, thereby negating the action of the azoles intended to inhibit fungal cell viability.

Azole Efficacy in the Treatment of Systemic Fungal Infections: Blastomycosis, Histoplasmosis, Coccidioidomycosis, and Paracoccidioidomycosis

Due to the lack of randomized comparative clinical trials to assess the efficacy of ketoconazole in the treatment of the endemic mycoses, we performed weighted analyses using a random effects model based on efficacy data (primarily from single-arm non-randomized observational studies) to arrive at estimates of the treatment effect (clinical response) of ketoconazole, itraconazole, and fluconazole in the systemic fungal infections. We chose clinical response as the efficacy endpoint of interest, because there was considerable heterogeneity across the studies in the manner in which therapeutic response to antifungal therapy was assessed. For coccidioidomycosis, blastomycosis, and histoplasmosis, we focused on efficacy data relevant to a 400 mg/day dose regimen; for paracoccidioidomycosis, we focused on efficacy data relevant to a 200 mg/day dose regimen. The figure below depicts the point estimates (with 95% confidence intervals) for the clinical response rates for the drugs stratified by type of endemic mycosis.

Figure 8: Comparative Efficacy of Systemic Antifungals in the Treatment of Systemic Fungal Infections: Weighted Analyses to estimate Treatment

Effect



In assessing the comparative efficacy data based on the weighted analyses, itraconazole and fluconazole may have improved efficacy compared to ketoconazole in the treatment of non-meningeal coccidioidomycosis (allowing for some overlap of the 95% CIs). Itraconazole may have slightly better efficacy than ketoconazole in the treatment of blastomycosis, whereas itraconazole and ketoconazole may have improved efficacy compared to fluconazole in treatment of histoplasmosis. The three drugs appear to have similar efficacy in treating paracoccidioidomycosis.

The comparative efficacy of the three drugs based on the weighted analyses should be interpreted with caution due to the following considerations:

- (1) Bias: due to reliance on data derived from non-randomized observational studies, which are subject to bias and confounding;
- (2) Lack of reliable 95% confidence intervals (CI): due to the small study populations and heterogeneity with respect to aspects such as patient characteristics, study design, and conduct issues, there is less precision in some of the estimates as reflected by broad ranges of plausible values (95% CI) for the true parameter;
- (3) Difficulties in excluding no difference between treatment arms due to the wide overlapping 95% CIs for the drugs.

The efficacy of ketoconazole in coccidioidal meningitis has been studied; doses ≤ 400 mg/day have generally been considered inadequate due to low cerebrospinal fluid concentrations. Higher doses (800 mg/day up to 2 grams/day) have been evaluated in

small case series.^{39,40} Graybill and colleagues³⁹ reported on 15 patients with coccidioidal meningitis of whom five received ketoconazole (in doses $\geq 1,200$ mg/day) as sole therapy; one was a clinical failure, one experienced hepatotoxicity necessitating discontinuation of the drug, and three experienced remissions (although one of the three patients later relapsed and needed retreatment). The remaining patients received ketoconazole plus intrathecal amphotericin B. A follow-up publication on the pharmacology and toxicology of such high doses of ketoconazole revealed that CSF penetration was poor despite doses >800 mg/day, and nausea and vomiting associated with such high ketoconazole doses limited tolerability.⁴¹

Candidiasis

In contrast to the clinical studies of ketoconazole for the other systemic fungal infections reviewed, the preponderance of comparative data on the efficacy and safety of the azoles for candidiasis is evidenced from six randomized comparative studies focused on oropharyngeal and esophageal candidiasis in immunocompromised patients (AIDS and malignancies): three with fluconazole as the comparator, two with itraconazole as the comparator, and one placebo-controlled study.

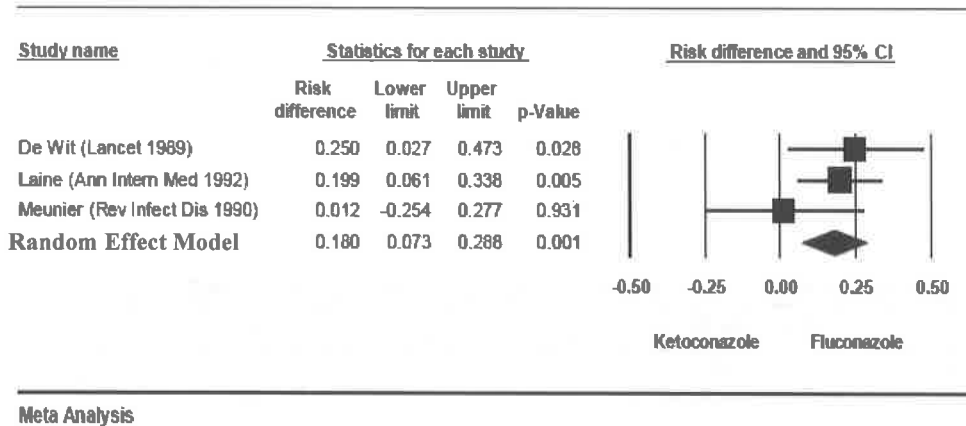
Overall, ketoconazole appears less efficacious than itraconazole and fluconazole in the treatment of oropharyngeal and esophageal candidiasis. We performed a meta-analysis of the pooled data from the three randomized clinical efficacy trials comparing ketoconazole and fluconazole in treating oropharyngeal and esophageal candidiasis in immunocompromised patients. The results of the meta-analysis are illustrated in the figure below, which shows that fluconazole exhibits superiority to ketoconazole in its efficacy in treating the disorder in this special population. (We were unable to perform a meta-analysis of the itraconazole efficacy data because one of the studies reported efficacy data stratified by oropharyngeal involvement versus esophageal involvement, whereas the other study provided only composite data.)

³⁹ Graybill J, Stevens D, Galgiani J, et al. Ketoconazole treatment of coccidioidal meningitis. *Annals New York Acad Sci* 1988; 544:488-496.

⁴⁰ Craven P, Graybill J, Jorgensen J, Dismukes W, Levine B. High-dose ketoconazole for treatment of fungal infections of the central nervous system. *Ann Intern Med* 1983; 98:160-167.

⁴¹ Sugar A, Alsip S, Galgiani J, et al. Pharmacology and toxicity of high dose ketoconazole. *Antimicrob Agents Chemother* 1987; 31(12):1874-1878.

Figure 9: Meta-Analysis of Randomized Clinical Trials of Ketoconazole vs Fluconazole for the Treatment of Oropharyngeal and Esophageal Candidiasis



In relation to efficacy in the treatment of candidemias and invasive candidiasis, we retrieved only four publications involving comparative clinical trials data. One clinical study evaluating ketoconazole compared to amphotericin B in treating fungal infections in neutropenic cancer patients demonstrated ketoconazole's efficacy in localized infections, but ketoconazole performed less effectively than amphotericin B in candidal pneumonia and fungemias (especially those infections due to *Candida tropicalis*).⁴² In contrast, published data support the efficacy of fluconazole in non-neutropenic patients with invasive candidiasis. In a randomized, prospective, comparative study of amphotericin B and fluconazole in patients with candidemia without neutropenia, fluconazole had similar efficacy to amphotericin B but with less side effects.⁴³ In a randomized, double blind, non-inferiority trial, anidulafungin was shown to be non-inferior to fluconazole in the treatment of candidemias and other invasive candidal infections (excluding endocarditis, osteomyelitis, and meningitis).⁴⁴ Additionally, in a randomized, double-blind controlled trial of fluconazole versus itraconazole in the treatment of candidemia in 43 pediatric intensive care unit patients, the cure rates for itraconazole and fluconazole were comparable (81% and 82%, respectively) demonstrating the effectiveness of both drugs in the treatment of invasive candidiasis.⁴⁵

Relapse rates following antifungal therapy

Relapse rates can represent both an efficacy and a safety concern, especially in patients with potentially life threatening systemic fungal infections. As depicted in the table

⁴² Fainstein V, Bodey G, Elting L, et al. Amphotericin B or ketoconazole therapy of fungal infections in neutropenic cancer patients. *Antimicrob Agents Chemother* 1987; 31(1): 11-15.

⁴³ Rex J, Bennett J, Sugar A, et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. *N Engl J Med* 1994; 331: 1325-1330.

⁴⁴ Reboli A, Rotstein C, Pappas P, et al. Anidulafungin versus fluconazole for invasive candidiasis. *N Engl J Med* 2007; 356:2472-2482.

⁴⁵ Mondal R, Singhi S, Chakrabarti A, et al. Randomized comparison between fluconazole and itraconazole for the treatment of candidemia in a pediatric intensive care unit: A preliminary study. *Pediatr Crit Care Med* 2004; 5:561-565.

below, itraconazole appears to have a low relapse rate across the listed systemic fungal infections. Ketoconazole has a high relapse rate in patients with non-meningeal coccidioidomycosis. The high relapse rate for ketoconazole in patients with Blastomycosis and Histoplasmosis given 800 mg/day regimens is partly related to dose-dependent adverse drug reactions that limit tolerability, such that some patients discontinued treatment without seeking alternative drug therapy and subsequently relapsed. The relapse rates for the three drugs were <10% in patients with paracoccidioidomycosis.

Table 10: Relapse Rates in the Treatment of Systemic Fungal Infections

	Ketoconazole	Itraconazole	Fluconazole
Blastomycosis and Histoplasmosis	12-14% (B); 4-6% at <400 mg and 30% at 800 mg doses (H)	<10% (B); 15% (H)	NR (B); 15% (H)
Coccidioidomycosis (non-meningeal)	38-58%	9-25%	28-37%
Paracoccidioidomycosis	<10%	<10%	<10%

Abbreviations: B = Blastomycosis; H = Histoplasmosis

Special Populations with Systemic Fungal Infections

In addition to the experience in oropharyngeal and esophageal candidiasis, several published observational trials reported outcomes for patients with AIDS and disseminated histoplasmosis who received ketoconazole, itraconazole, or fluconazole. The data relevant to clinical response for patients receiving each drug as initial therapy or as maintenance therapy to prevent relapse is summarized in the table below. Although the study populations were small, it is evident from the table that ketoconazole is relatively ineffective as initial therapy compared to itraconazole and fluconazole in the treatment of such infections in immunocompromised patients. Ketoconazole was also associated with unacceptably high relapse rate of 50% notwithstanding its intended use as maintenance therapy intended to prevent relapse.

Table 11: Comparative Efficacy in the Treatment of Disseminated Histoplasmosis in Patients with AIDS

		Ketoconazole	Itraconazole	Fluconazole
Initial Therapy	Dosage	Not reported	600 mg/d x 3 days, then 400 mg/d for 12 weeks	1600 mg Day 1, then 800 mg/d for 12 weeks
	Patients, N	15	59	49
	Clinical response (%)	1/14 (7%) ^a	50 (85%) ^c	36 (74%) ^d
	Action taken	Non-responders presumed changed to amphotericin B	6 treatment failure: 2 deaths, 4 survivors changed to amphotericin B	36 responders entered into maintenance
Maintenance Therapy to prevent relapse	Dosage	Not reported	Long-term maintenance was not assessed	400 mg/d for one year

	Patients, N	20	NA	36
	Clinical response (%)	Not reported	NA	15/36 (42%)
	Relapse	10/20 (50%) ^b	NA	11/36 (31%)

Abbreviations: NA = not applicable

Safety of Ketoconazole Tablets: Experience from the treatment of patients with systemic fungal infections enrolled in randomized clinical trials

In reviewing published safety data for ketoconazole, itraconazole, and fluconazole, it became evident that gastrointestinal adverse events (nausea, vomiting, diarrhea, abdominal pain) were associated with all three drugs, whereas dermatologic events (such as alopecia, dry skin, dry lips) were most commonly associated with fluconazole. The table below summarizes the safety experience for each drug from randomized clinical trials in the treatment of oropharyngeal and esophageal candidiasis. This data was felt to be most representative, since it was derived from randomized trials in contrast to the nonrandomized observational studies involving the other major fungal infections covered in this review. In reviewing the data in the table, it is evident that hepatic events were most frequently reported among ketoconazole-treated patients. No fatalities or hepatic events necessitating liver transplantation attributed to drug toxicity were reported for any of the azole antifungals evaluated in the trials.

Table 12: Comparative Safety of Systemic Antifungals based on Randomized Clinical Trials Data

	Drug	Daily Dose	N	Nausea/ vomiting	Diarrhea	Rash	Headache	Elevated liver enzymes
Oropharyngeal candidiasis	Ketoconazole	200 mg	19	0%	0%	0%	0%	21%
	Fluconazole	50 mg	18	6%	0%	0%	0%	6%
Esophageal candidiasis	Ketoconazole	200-400 mg	71	7%	6%	7%	0%	6%
	Fluconazole	100-200 mg	72	3%	5%	2%	0%	9%
Oropharyngeal candidiasis	Ketoconazole	400 mg	18	0%	0%	0%	0%	0%
	Fluconazole	100 mg	19	5%	0%	0%	0%	0%
Oropharyngeal and esophageal candidiasis	Ketoconazole	400 mg	52	4%	0%	2%	0%	4%*
	Itraconazole	200 mg	59	0%	0%	2%	0%	0%
Oropharyngeal and esophageal candidiasis	Ketoconazole	200 mg	52, 19	5%	4%	5%	3 %	2%
	Itraconazole	200 mg	46, 12	10%	0%	4%	9%	0%

Dose-dependent adverse events were reported only among ketoconazole-treated patients in the published studies on systemic fungal infections. In a prospective randomized study in which patients with Blastomycosis and Histoplasmosis were administered either 400 mg/day or 800 mg/day of ketoconazole (see table below), gastrointestinal and endocrine adverse events attributed to ketoconazole were reported more commonly in the 800

mg/day subgroup. Hepatic events, in contrast, did not appear to exhibit such a dose-dependent relationship. In addition, in the study, twice as many patients discontinued in the high dose subgroup compared to the low dose group due to adverse drug effects.

Table 13: Dose-dependent Adverse Effects of Ketoconazole

Adverse event	400 mg/day (N=71) ^a	800 mg/day (N=63) ^b
	n (%)	n (%)
Anorexia, nausea, or vomiting	12 (16.9)	27 (42.9)
Impotence/decreased libido	2 (3.6)	6 (14.3)
Gynecomastia (men)	1 (1.8)	6 (14.3)
Menstrual irregularities	1 (6.3)	4 (19.0)
Bilirubin >3 mg/dL	0 (0.0)	0 (0.0)
Increased AST (>3x ULN)	1 (1.4)	2 (3.2)
Increased alkaline phosphatase	0 (0.0)	1 (1.6)

^amale, female = 55, 16; ^bmale, female=42, 21;

*adapted from Ann Intern Med 1985; 103 (6 pt 1):861-872

Unmet Medical Need

Considerations assessed in determining whether ketoconazole fulfills an unmet medical need currently in the context of its labeled indications are summarized in the table below.

Table 14: Unmet Medical Need Assessment

	Dermatophyte Infections	Chronic Mucocutaneous Candidiasis	Systemic Fungal Infections
Are there unique beneficial characteristics of the drug compared to exiting alternative treatments? Pharmacology Formulation Compliance Penetration into the cerebrospinal fluid	No	No	No
Are there alternative treatments for the same indications with comparable or improved efficacy or improved safety?	Yes	Yes	Yes
Does the drug offer enhanced efficacy in a special population such that the risk for serious hepatic injury would be tolerable?	No	No	No

In relation to its pharmacologic features, oral ketoconazole is optimally absorbed in an acid stomach, which could be problematic considering many adults are taking prescription and over-the-counter antacids, proton-pump inhibitors, or H2-blockers for various gastric and ulcer-related disorders. Although itraconazole similarly requires stomach acidity for optimal absorption, fluconazole's absorption is not affected by stomach acidity or food. Oral ketoconazole tablet formulation for systemic use may be difficult for administration to pediatric populations; itraconazole and fluconazole are marketed in oral suspensions that would be more suitable and easily administered to small children. Single-dose, continuous daily, and intermittent weekly dosing regimens of ketoconazole, itraconazole, and fluconazole have been assessed in published studies; ketoconazole tablets does not appear to offer a distinct advantage compared to the other two drugs with regard to regimens that would minimize dosing frequency so as to enhance patient compliance in the treatment of various fungal infections. Of note, however, ketoconazole is not recommended for the treatment of meningeal fungal infections, because it does not achieve therapeutic levels in the cerebrospinal fluid; this characteristic of the drug is a distinct disadvantage compared to fluconazole, which has demonstrated efficacy in meningeal coccidioidomycosis. Additionally, ketoconazole exhibits dose-dependent endocrine hormonal side effects, which are not characteristic of itraconazole or fluconazole.

As discussed previously, itraconazole and fluconazole are existing alternative treatments for systemic fungal infections with comparable-to-improved efficacy and better safety profiles than ketoconazole. Additionally, in special populations of immunocompromised patients, ketoconazole exhibited poor efficacy and higher relapse rates compared to itraconazole and fluconazole. Finally, ketoconazole exhibits a narrower spectrum of fungal activity compared to the other two drugs; its efficacy in treating *Candida* infections can be limited by cross-resistance with the other azole antifungals, and the drug lacks meaningful *in vitro* activity against multiple pathogens associated with invasive fungal infections (such as Aspergillosis, Mucormycosis, Cryptococcosis, and *Fusarium* infections), which are susceptible to one or more of the other triazole antifungals.

Supplementary Exploratory Analysis: Number Needed to Harm

In order to gain additional insight in making a benefit-risk assessment for ketoconazole, we conducted a supplementary exploratory analysis based on pooled data from the retrieved literature studies. The table below summarizes information related to the safety and efficacy of ketoconazole, itraconazole, and fluconazole in relation to the labeled indications for oral ketoconazole based on pooled literature data. As depicted in the table, the pooled reports represent over 1,600 ketoconazole-exposed, 1,300 itraconazole-exposed, and 1,200 fluconazole-exposed patients in the evaluable population for efficacy. The information is stratified by ketoconazole labeled indication category to provide a broader perspective on differences in duration of treatment, comparators in published efficacy trials, special populations studies, and safety concerns. In the overall clinical experience, patients received ketoconazole for various indications from a few weeks duration for dermatophyte infections up to 32 months for coccidioidomycosis. Overall, there was a paucity of published randomized comparative azole-azole comparative trials

(except for the treatment of *T. versicolor* and candidiasis as previously discussed). Importantly, itraconazole and fluconazole have been employed successfully to treat patients who previously received ketoconazole and subsequently failed to respond, progressed, or relapsed. In terms of safety, serious drug-related hepatic injury was reported among three patients in total in the evaluable (non-AIDS) patient population for safety.

Table 15: Pooled Efficacy and Safety Data from Published Literature Studies

	Dermatophyte Infections	Chronic Mucocutaneous Candidiasis (CMCC)	Systemic Fungal Infections
# Ketoconazole-treated patients ^a	640 ^b	150 ^e	826 ^g
# Itraconazole-treated ^a	690 ^c	2 ^f	597 ^h
# Fluconazole-treated ^a	737 ^d	8 ^f	550 ⁱ
Treatment duration (range)	2-8 weeks (some longer durations)	up to 6 months (some did not pre-specify duration)	Weeks to months depending on indication
EFFICACY			
Comparative efficacy studies	Griseofulvin, terbinafine, fluconazole	Placebo	Fluconazole, itraconazole; dose-ranging studies
Special Populations	Children	CMCC	Malignancy, AIDS
Successful response to itraconazole or fluconazole for ketoconazole- treated patients who failed to respond, progressed, or relapsed	NR	Yes	Yes
SAFETY			
Relationship of AE Frequency to dosage	NR	NR	Ketoconazole: increased freq of gastrointestinal and endocrine events
Serious drug-related hepatic injury*: ketoconazole	2	1	0
Serious drug-related hepatic injury*: itraconazole, fluconazole, other comparators	0	0	0

Abbreviations: ^apooled evaluable patients for efficacy from published studies/case series; ^bderived from 15 published studies/case series; ^cderived from 13 published studies/case series; ^dderived from 5 published studies/case series; ^ederived from 10 published case series/studies; ^fderived from a single case series; ^gderived from 20 published studies; ^hderived from 14 published studies; ⁱderived from 13 published studies; NR = not reported; *non-AIDS patients with biopsy-confirmed liver necrosis or hepatitis, or evidence of clinical findings suggestive of hepatic dysfunction (such as jaundice).

The number needed to harm (NNH) is an epidemiologic measure of the number of patients who need to be exposed to a drug to cause harm in one patient who would otherwise not have experienced the event. It is calculated as the inverse of the risk difference. As shown in the following 2 x 2 table, the OSE Review Team limited our analysis to the pooled data on serious drug-related hepatic injury among the evaluable (non-AIDS) patients for safety for the dermatophyte and systemic fungal infection

indications; we excluded information relevant to Chronic Mucocutaneous Candidiasis due to the sparse data.

Table 16: Number Needed to Harm Determination (Based on Pooled Evaluable Patients for Safety)

	Ketoconazole exposed, n	Itraconazole and fluconazole exposed, n	Total, N
Serious hepatic injury/hepatitis	2	0	2
No serious hepatic injury	1050	2534	3584
Total	1052	2534	3586
Risk for serious hepatic injury	.0019011	0	.0005577

Based on the pooled data in Table 15, the risk difference (Ketoconazole – [Itraconazole + Fluconazole]) = 0.0019011 (95% CI: -0.00073, 0.00453); Fishers exact test: $p = 0.086$. Taking the inverse of the risk difference, the NNH (Number needed to harm) = 526.

Although the NNH estimate based on the pooled safety experience above was consistent with the NNH described in the context of the pharmacoepidemiologic GPRD data, the result should be interpreted with caution. There are important limitations to consider, including

- (1) Bias: due to reliance on data derived from non-randomized observational studies, which are subject to bias and confounding;
- (2) Lack of reliable 95% confidence intervals (CI): due to the small study populations and heterogeneity with respect to aspects such as patient characteristics, study design, and conduct issues among the pooled studies, there is less precision in the risk difference estimate as reflected by the range of plausible values (95% CI) for the true parameter;
- (3) Difficulties in excluding no difference in the risk of serious hepatic injury between ketoconazole-exposed compared to unexposed groups, because the 95% CI for the risk difference does not exclude zero.

Patients with AIDS who received ketoconazole, itraconazole, or fluconazole and who were discontinued from published studies due to hepatic events were not included in the supplementary NNH analysis above, because there was insufficient clinical and laboratory details to permit evaluation of a possible relationship to one of the antifungal drugs. Data regarding concomitant medications (including antiretroviral therapy) and concurrent opportunistic infections under treatment were also not provided in many publications.

Integrating the CDER Benefit-Risk Assessment Framework into the OSE Review Team’s analytical thinking: an algorithmic approach

Uncertainties in assessing data related to the efficacy of ketoconazole, itraconazole, and fluconazole in the context of ketoconazole's labeled indications

We identified four areas of uncertainty in assessing the various data streams relevant to the efficacy, safety, and utility of ketoconazole tablets in the context of the drug's therapeutic labeled indications:

- Identifying quantitative estimates of absolute risk and relative risk for ketoconazole-induced serious adverse drug reactions compared to those linked to other marketed oral systemic antifungals.
 - We did not retrieve any published citations that provided quantitative estimates for the absolute risk or relative risk of serious non-hepatic toxicities associated with ketoconazole, itraconazole, and fluconazole. For example, no pathophysiologic mechanism was identified in our literature search to explain the negative inotropic effect of itraconazole on the human heart, and there were no published estimates of the incidence of such drug-related cardiotoxicity.^{46,47} Thus, due to these uncertainties, we could not leverage the risks for serious hepatic versus non-hepatic toxicities on a quantitative basis in understanding the comparative safety profiles of the drugs.
 - We did not retrieve any published citations that provided comparative quantitative estimates of relative risk for specific drug-drug interactions for ketoconazole, itraconazole, and fluconazole.
- Methodological deficiencies and other limitations in the design and conduct of the published efficacy studies for ketoconazole tablets and the other azoles in the context of ketoconazole's labeled indications
 - Lack of large, randomized, adequate, and well-controlled clinical efficacy trials that would have substantiated the drug's effectiveness with respect to the labeled indications, particularly the endemic mycoses.
 - Various methodological deficiencies across the published case series, observational studies, and small clinical trials included:
 - a. Heterogeneity in study design, endpoint definitions, choice of dosing regimens, duration of therapy, assessment of therapeutic response to antifungal therapy, and characteristics of the enrolled patient populations, including concurrent medical conditions and diverse range of localized vs disseminated organ system involvement associated with the systemic fungal infections, (such as skin, bone, lung, soft tissue, CNS, lymph node, or other organ system involvement);
 - b. Inconsistencies in defining a 'response' or a 'success' across the studies;
 - c. Potential bias and confounding due to lack of randomization protection in the published case series and the nonrandomized, open label, observational studies;

⁴⁶ Slordal L, Spigset O. Heart failure induced by non-cardiac drugs. *Drug Saf* 2006; 29 (7):567-586.

⁴⁷ Maxwell C, Jenkins A. Drug-induced heart failure. *Am J Health Sys Pharm* 2011; 68:1791-1804.

- d. Some of the controlled studies were not statistically powered for the prespecified efficacy endpoints; none of the retrieved studies were sufficiently powered for a safety issue as the study's primary endpoint;
 - e. Dose escalation incorporated into some of the studies of the systemic fungal infections created difficulties in tracking patients across various dosing strata and was not supported by prespecified objective criteria to identify the clinical circumstances that warranted dose escalation;
 - f. the occurrence of adverse events in patients treated with the drug
- Variable quality of reporting and missing data
 - Spontaneous postmarket reports submitted to FAERS
 - Literature reports and published studies; some did not include any safety data
 - Specific limitations of the scientific evidence as described previously in this report regarding the weighted estimates of clinical response: bias, lack of reliable 95% CIs, and difficulties in excluding no difference
 - Assessment of the medical necessity of ketoconazole in the therapeutic areas of prostate cancer and Cushing's syndrome (unapproved uses)

In relation to the off-label use of the drug in the treatment of Cushing's syndrome and prostate cancer, the following table provides a brief overview summary:

Table 17: Overview Summary of the Use of Ketoconazole in Unapproved Therapeutic Areas

Unapproved area of use	Published contemporary clinical guidelines	Published Studies	Daily dosages administered (mg/day)	Safety issues
Cushing's syndrome	International consensus panel	Case series	600 - 800	No serious hepatic events
Castration-resistant prostate cancer	National Comprehensive Cancer Network (NCCN) clinical practice guidelines; European Society for Medical Oncology	Prospective observational studies, retrospective medical records reviews, phase 1 dose escalation study	600 – 1,200	Abnormalities in liver transaminases, bilirubin, or alkaline phosphatase; Grade 3/4 increases in LFTs managed by dose reduction or withdrawal; no fatalities/liver transplants

As depicted above, oral ketoconazole has been included in published consensus guidelines and practice guidelines in relation to use in the treatment of Cushing's syndrome and castration-resistant prostate cancer. The doses administered in published case reports and studies were higher than the labeled 200-400 mg/day range. No serious outcomes related to hepatic adverse events were reported.

Integrating the CDER Benefit-Risk Assessment Framework into the OSE Review Team's analytical thinking: an algorithmic approach:

Leveraging:

As described previously, leveraging refers to the use of clinical judgment to weigh the strengths and limitations of the data with respect to efficacy, safety, unmet medical need, and quantitative benefit risk methodologies in order to identify important attributes of the drug that best inform in making an overall benefit-risk assessment. The identified attributes may effectively ‘tip’ the balance between a positive and a negative benefit-risk assessment. In relation to ketoconazole tablets, we leveraged the strengths and limitations of the data in thinking about two main areas, comparative efficacy and comparative safety (both hepatic and non-hepatic adverse drug reactions).

Comparative efficacy assessment for ketoconazole tablets, itraconazole, and fluconazole: We viewed the following information as important attributes that were collectively considered as negative factors in the overall benefit-risk assessment for ketoconazole:

- Notwithstanding the limitations previously described, the weighted estimates of treatment effect for ketoconazole, itraconazole, and fluconazole reveal that itraconazole exhibits comparable-to-enhanced efficacy in the treatment of non-meningeal coccidioidomycosis with comparable-to-lower relapse rates in coccidioidomycosis, blastomycosis, and histoplasmosis compared to oral ketoconazole. The comparative clinical efficacy of the three drugs based on the weighted analyses is consistent with their comparative microbiologic activities against the pathogens (discussed previously in this document).
- Fluconazole has the advantage of efficacy for the treatment of meningeal fungal infections, a therapeutic area in which ketoconazole is ineffective due to poor penetration into the cerebrospinal fluid.
- Notwithstanding the limitations of cross-study comparisons, itraconazole and fluconazole have better efficacy than oral ketoconazole in the treatment of fungal infections in immunocompromised patients. Our meta-analysis of published randomized clinical trials indicated that fluconazole has superior efficacy compared to ketoconazole in the treatment of oropharyngeal and esophageal candidiasis in patients with HIV infection and those with malignancies.
- For patients with coccidioidomycosis, histoplasmosis, and blastomycosis who previously received a ketoconazole-containing regimen and failed to respond, relapsed, or experienced disease progression, itraconazole and fluconazole provided successful treatment in many cases.

Comparative safety assessment for ketoconazole tablets, itraconazole, and fluconazole in relation to serious hepatic injury: We viewed the following information as important attributes that were collectively considered as negative factors in the overall benefit-risk assessment for ketoconazole:

- The nature of hepatic injury attributed to ketoconazole tablets was considered unpredictable and potentially life-threatening. The

pharmacoepidemiologic analysis of the organ transplantation data from UNOS revealed that the number of liver transplants attributed to ketoconazole hepatotoxicity for the level of prescribing was disproportionately higher compared to itraconazole and fluconazole. This finding was considered consistent with the higher relative risk estimate for acute liver injury for ketoconazole compared to non-use as reported in the study by Garcia-Rodriguez and colleagues.

- Notwithstanding the uncertainties due to the limited size and lack of statistical power of the published observational and randomized clinical studies across its labeled indications, serious hepatic injury in ketoconazole-treated patients did not exhibit a dose-dependent relationship and did not exhibit a relationship to treatment duration or therapeutic indication.
- Based on retrieved literature, there is a wide range in the duration of oral ketoconazole therapy prior to onset of jaundice (reported as 1.5-24 weeks in the study of Lewis and colleagues and 1-20 weeks in the study by Janssen and Symoens), which illustrates the difficulties in defining a time period of safe use that would preclude the risk of fulminant hepatic injury.
- No pharmacogenomic marker has been identified for ketoconazole-induced liver injury.

Comparative safety assessment for ketoconazole tablets, itraconazole, and fluconazole in relation to serious non-hepatic adverse drug reactions and drug-drug interactions:

We viewed the following information as important attributes that were collectively considered as negative factors in the overall benefit-risk assessment for ketoconazole:

- The risk for serious and life-threatening drug-drug interactions attributed to ketoconazole tablets was considered greater and buttressed by stronger evidence compared to itraconazole and fluconazole based on the analysis of the information from Micromedex.
- There are multiple clinically-important pathways for drug-drug interactions involving ketoconazole. In terms of the pathway that is most frequently implicated with commonly prescribed drugs, the cytochrome P450 isoenzyme system, ketoconazole exhibits stronger potency as an inhibitor of CYP3A4 compared to itraconazole and fluconazole as demonstrated in published preclinical studies.
- Notwithstanding the limited size and statistical power of the published observational and randomized clinical efficacy trials for ketoconazole across its labeled indications, the tolerability of the drug at the high doses needed to treat systemic fungal infections was limited due to gynecomastia and menstrual irregularities; those adverse events developed as a consequence of ketoconazole's potent inhibition of the synthesis of adrenal steroids and testosterone. Although there were few comparative trials of ketoconazole with itraconazole and fluconazole, drug-induced adverse endocrine events were not reported for itraconazole and fluconazole in the reviewed studies and were not identified as safety findings that limited tolerability of those two drugs when administered at

high dosages to patients with systemic fungal infections in the observational studies. In addition, pharmacologic studies in animal models and healthy human volunteers indicate that itraconazole and fluconazole do not substantially affect the synthesis of adrenal steroids and testosterone.^{48,49}

- Serious non-hepatic adverse events associated with itraconazole and fluconazole, such as heart failure, torsades de pointe, and QT prolongation, were not reported in the clinical efficacy studies reviewed from the literature. Although we could not directly leverage the risk of serious non-hepatic toxicities of itraconazole and fluconazole compared to the hepatotoxicity of ketoconazole due to the lack of adequate and well controlled clinical trials and published estimates of relative risk, we noted the lack of cases of itraconazole-induced heart failure and fluconazole-induced QT prolongation in our integrated safety experience in contrast to the multiple cases of serious liver toxicity for ketoconazole-treated patients.

8 CONCLUSIONS

In consideration of the totality of the scientific evidence, having weighed the strengths and limitations of the data streams, the OSE Review Team are of the opinion that the overall benefit-risk assessment for ketoconazole (Nizoral[®]) tablets is negative in the context of all of the drug's labeled indications. In non-life-threatening conditions, such as dermatophyte infections and chronic mucocutaneous candidiasis, the OSE Review Team could not justify the risk of serious and potentially life-threatening hepatic injury for the potential benefit of therapy with this drug. In invasive candidiasis and endemic mycoses, considering the existence of alternative approved drug therapies (such as itraconazole and fluconazole) with comparable-to-enhanced efficacy and better safety profiles, the OSE Review Team was unable to view the risk of serious potentially life-threatening hepatic injury as tolerable for the potential benefit of ketoconazole treatment.

The OSE Review Team has included a completed CDER benefit-risk assessment template in Appendix 1 of this review to summarize our findings, concerns, analysis, and conclusions in the context of the framework.

⁴⁸ Hanger D, Jevons S, Shaw J. Fluconazole and testosterone: in vivo and in vitro studies. *Antimicrob Agents Chemother* 1988; 32(5): 646-648.

⁴⁹ Van Cauteren H, Heykants J, De Coster R, Cauwenbergh G. *Rev Infect Dis* 1987; 9 (suppl 1):S43-S46.