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Vikram Krishnasamy, M.D., M.P.H.
Resident, General Preventive Medicine
Johns Hopkins School of Public Health
615 N. Wolfe Street
Baltimore, MD 21205

Sammy Almashat, M.D., M.P.H.
Sidney Wolfe, M.D.
Michael Carome, M.D.
Public Citizen's Health Research Group
1600 20th Street, NW
Washington, DC 20009

Re: Docket No. FDA-2015-P-0578

Dear Petitioners:

This letter responds to your citizen petition received February 24, 2015 (Petition). The Petition asks the Food and Drug Administration (FDA or the Agency) to immediately require the removal of oral ketoconazole[1] from the market 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.[2] FDA has carefully reviewed the Petition and all relevant information available to the Agency concerning ketoconazole. Based on our review of this information and for the reasons described below, we deny your Petition. However, as with all FDA-approved products, the Agency will continue to monitor and review available safety information as it relates to ketoconazole and take any further action as appropriate.

I. BACKGROUND

A. Ketoconazole

In 1981, FDA approved a new drug application (NDA) for Nizoral (ketoconazole) (NDA 018-533).[3] The Nizoral NDA was held by Janssen Research & Development, Inc. (Janssen), and Nizoral was approved as an azole antifungal agent for the treatment of several fungal infections,

[1] The action requested in the Petition is limited to ketoconazole 200 milligram oral tablets and so this response is limited to that dosage form, and route of administration, and all references to ketoconazole, unless otherwise indicated, refer to this dosage form and route of administration (see Petition at 1).

[2] Petition at 1.

[3] Since that time FDA has approved a number of generic versions of ketoconazole. For the current list of approved products visit FDA's website at https://www.accessdata.fda.gov/scripts/cder/ob/.

both systemic and non-systemic.[4] All azole compounds interfere with the synthesis and permeability of fungal cell membranes. Ketoconazole blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14a-demethylase, which is responsible for conversion of lanosterol to ergosterol in the fungal cell membrane.[5] This results in an accumulation of methylated sterol precursors and a depletion of ergosterol within the cell membrane, thus weakening the structure and function of the fungal cell membrane.[6] The role of ketoconazole in the treatment of systemic fungal infections and severe recalcitrant dermatophyte infections diminished dramatically when FDA approved the newer azoles – fluconazole in early 1990 and itraconazole in late 1992.[7]

Since Nizoral was approved, there have been a number of labeling changes. According to the current labeling, ketoconazole should be used only when other effective antifungal therapy is not available or tolerated and the potential benefits are considered to outweigh the potential risks.[8] With those limitations, ketoconazole currently is indicated for the treatment of the following systemic fungal infections: blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis, collectively referred to in this response as the endemic mycoses.

FDA agrees with the Petition that the incidence of these infections across the entire United States is not common.[9] However, these infections occur more frequently in distinct geographic areas.[10] For example, the Centers for Disease Control and Prevention[11] provide recent incidence data based on geographic areas: (1) coccidioidomycosis occurs in 42.6 per 100,000 persons living in endemic areas that are reportable (Arizona, California, Nevada, New Mexico, and Utah); the highest rates are among persons aged 60-70, at 69.1 per 100,000 persons in highly endemic areas such as metropolitan Phoenix and Tucson, Arizona; and it is estimated to cause between 15 percent and 30 percent of community-acquired pneumonia cases in metropolitan areas of Arizona; (2) blastomycosis occurs in approximately 1-2 people per 100,000 per year in reportable states (Arkansas, Louisiana, Michigan, Minnesota and Wisconsin), and occurs in 10 to 40 people per 100,000 persons living in northern Wisconsin; and (3) histoplasmosis occurs in adults aged 65 and older throughout the U.S. in 3.4 cases per 100,000, with the highest rate, of 6 people per 100,000 in this population, living in the Midwestern region of the U.S. Exposure to

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[4] The NDA was held by Johnson & Johnson Pharmaceutical Research & Development LLC, now known as Janssen Research & Development, LLC.

[5] Nizoral labeling (2014), available on http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

[6] Id.

[7] Terrell, CL. "Antifungal Agents. Part II. The Azoles," *Mayo Clin Proc.* 74(1): 78-100 (1999), at 78.

[8] Nizoral labeling (2014).

[9] See Petition at 10.

[10] Chu JH, Feudtner C, Heydon K, Walsh TJ, Zaoutis, TE. "Hospitalizations for Endemic Mycoses: A Population-Based National Study," *Clin InfectDis* 42(6): 822-825 (2006).

[11] The Centers for Disease Control and Prevention describe statistical incidence data for fungal diseases endemic in the United States, which can be found at: https://www.cdc.gov/fungal/diseases/.

the *Histoplasma* fungus is estimated to occur in 60 percent to 90 percent of people living in the Ohio and Mississippi River valleys at some point during their lifetime.[12] Additionally, histoplasmosis is an important opportunistic infection among HIV-infected patients in endemic areas. In a small study in an underserved U.S. city endemic for histoplasmosis, it was reported as the AIDS-defining illness in 25 percent of patients.[13]

Overall, the endemic mycoses result in hospitalization of approximately 100,000 to 500,000 patients in the United States every year.[14] A retrospective cohort study using the 2002 Nationwide Inpatient Sample, a national database of hospital inpatient stays, described the incidence and epidemiology of endemic mycoses requiring hospitalization. As discussed in that study, the rate of all endemic mycoses requiring hospitalization was 22.5 cases per 1 million persons in the United States.[15] An estimated 332 pediatric and 6003 adult patients with endemic mycoses required hospitalization (4.6 and 28.7 cases per 1 million children and adults, respectively). As expected, patients who are hospitalized for treatment of an endemic mycosis are usually severely ill; however, there are also many more patients with less-severe illness who require outpatient antifungal treatment. The severity of the endemic mycoses is reflected in the all-cause mortality rates, which were 5 percent and 7 percent among children and adults, respectively. The majority (87 percent) of all persons who died were immunocompetent. These data reinforce the overall morbidity and mortality associated with these infections that occur in both immunocompromised as well as otherwise healthy individuals.[16]

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[12] Id., citing Baddley JW, Winthrop KL, Patkar NM, Delzell E, Beukelman T, Xie F, Chen L, Curtis, JR. "Geographic Distribution of Endemic Fungal Infections Among Older Persons, United States," *Emerg Infect Dis* 17(9): 1664-1669 (2011).

[13] Baddley JW, Sankara IR, Rodriquez JM, Pappas PG, Many WJ, Jr. "Histoplasmosis in HIV-infected Patients in a Southern Regional Medical Center: Poor Prognosis in the Era of Highly Active Antiretroviral Therapy," *Diagn Microbiol Infect Dis*. 62(2):151-156 (2008).

[14] See Hammerman KJ, Powell KE, Tosh FE. "The Incidence of Hospitalized Cases of Systemic Mycotic Infections," *Sabouradia* 12(1): 33-45 (1974). While there are no precise numbers, one estimate of the incidence rate was made using Medicare sample data, which calculated national, regional and state-based incidence rates and identified 776 cases (357 histoplasmosis, 345 coccidioidomycosis, and 74 blastomycosis). In 86 of these cases there was no patient exposure to a traditional disease-endemic area, which may make them more difficult to track. See Baddley JW, Winthrop KL, Patkar NM, Delzell E, Beukelman T, Xie F, Chen L, Curtis, JR. "Geographic Distribution of Endemic Fungal Infections Among Older Persons, United States," *Emerg Infect Dis* 17(9): 1664-1669 (2011). This study was based on data collected from 1999 to 2008 and acknowledged the following limitations: the conclusions may not represent all older Americans, recognition of endemic mycoses may vary by region, and the validity of using the International Classification of Diseases, 9th Revision, in claims data is uncertain.

[15] Chu JH, Feudtner C, Heydon K, Walsh TJ, Zaoutis TE. "Hospitalizations for Endemic Mycoses: A Population-Based National Study," *Clin Infect Dis* 42(6): 822–825 (2006). The study supported geographic distribution of the endemic mycoses: coccidioidomycosis mostly occurred in the southern and western regions of the country, and blastomycosis generally occurred in the southern and Midwestern states; histoplasmosis was largely found along the Ohio and Mississippi Rivers and occurred primarily in the Midwestern and southern regions of the country.

[16] Id. at 825.

B. The Petition

Your Petition asks FDA to withdraw approval of ketoconazole because the risk of fatal liver failure and adrenal insufficiency, and its numerous drug interactions, outweigh the benefits in treating fungal infections.[17] In support of your Petition, you rely primarily on a January 2013 assessment prepared by the FDA Office of Surveillance and Epidemiology (OSE) regarding the benefits and risks of ketoconazole (OSE January 2013 Assessment).[18] According to the Petition, there are no patients for whom the benefits of ketoconazole outweigh its risks and there are other effective, safer therapies for the treatment of the fungal infections for which ketoconazole is still used today.[19]

II. LEGAL AND REGULATORY FRAMEWORK

Section 505(e) of the Federal Food, Drug and Cosmetic Act (FD&C Act) establishes the circumstances under which the Agency will, after due notice and opportunity for a hearing, withdraw approval of an NDA or an abbreviated new drug application (ANDA) (21 U.S.C. 355(e)). With respect to safety concerns, the Agency will withdraw approval of a drug product if it finds either of the following:

> (1) [T]hat clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; or
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> (2) [T]hat new evidence of clinical experience, not contained in such application or not available to [FDA] until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the [FDA] when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved....

Section 505(e)(1) and (2) of the FD&C Act.

FDA regulations set forth the procedures for withdrawal of approval.[20]

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[17] Petition at 1.

[18] See Petition at 4 ("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.").

[19] Petition at 4.

[20] 21 CFR 314.150.

III. FDA REGULATORY ACTIONS REGARDING KETOCONAZOLE

In 2008, Janssen requested that FDA withdraw approval of the Nizoral NDA under 21 CFR 314.150(c)[21] because it was no longer being marketed.[22] However, before FDA acted on this request, the French medicine agency, the National Agency for the Safety of Medicine and Health Products, suspended marketing authorization for ketoconazole based on safety concerns regarding hepatotoxicity.[23] The actions of the French agency and its referral of the issue to the European Medicines Agency (EMA), along with Janssen's request to withdraw approval of Nizoral, prompted FDA to re-evaluate the safety of oral ketoconazole and its role as a systemic antifungal agent in the United States.

In December 2011, OSE initiated a benefit risk assessment of ketoconazole as part of this re-evaluation, which resulted in the OSE January 2013 Assessment cited in the Petition. In addition to that information, FDA considered opinions from other disciplines within the Center for Drug Evaluation and Research (CDER), including the Office of Surveillance and Epidemiology, the Division of Anti-Infective Products, the Division of Metabolism and Endocrinology Products, the Division of Oncology Products, the Office of Hematology and Oncology Products, and CDER senior management, as well as external experts in infectious diseases and hepatotoxicity, regarding the safety of ketoconazole.

In July 2013, FDA completed its comprehensive review of the safety and effectiveness of ketoconazole in the context of the drug's labeled indications for the treatment of superficial and

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[21] Under § 314.150(c), FDA will withdraw approval of a drug if an applicant requests its withdrawal because the drug is no longer being marketed and none of the conditions in paragraphs (a) and (b) apply to the drug. Section 314.150(a), in part, permits the agency to begin procedures for withdrawal if FDA finds that clinical or other experience, tests or other scientific data show that the drug is unsafe for use under the conditions of use upon the basis of which the drug was approved, or that new information together with the evidence available when the drug was approved show that there is a lack of substantial evidence from adequate and well controlled investigations that the drug will have the effect it is purported to have under the conditions of use prescribed, recommended, or suggested in the labeling. Section 314.150(b), in part, permits FDA to begin procedures for withdrawal if the applicant has failed to establish a system for maintaining required records, if FDA finds that, on the basis of new information evaluated together with the evidence available when the drug was approved, that the methods used in or the facilities and controls used for the manufacturing, processing and packing are inadequate to ensure and preserve the identity, strength and purity of the drug, or that the labeling is false and misleading, among other reasons. (§ 314.150(a) and (b)).

[22] FDA's notice that the Agency was withdrawing approval of Nizoral (NDA 018-533) was published in the *Federal Register* (80 FR 61426, Oct 13, 2015), and effective Nov 12, 2015.

[23] European legislation requires that there is a coordinated European approach when a member state takes regulatory action regarding a medicine that is authorized in more than one country. There were subsequent regulatory actions within the European Medicines Agency (EMA), the European equivalent to the FDA, regarding ketoconazole. In July 2013, EMA's Committee on Medicinal Products for Human Use recommended suspension of marketing authorization for ketoconazole throughout the European Union (See Petition at 3, footnote 13). Subsequently on Nov 19, 2014, EMA granted marketing authorization for ketoconazole in the treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12. See EMA Sept 25, 2014, Assessment Report (EMA/CHMP/534845/2014).

systemic fungal infections.[24] The Agency concluded that serious hepatic injury was the major toxicity for ketoconazole and that it was noted to be unrelated to dose, duration, or indication. The overall risk of ketoconazole-induced serious liver injury appeared higher than that associated with other azole antifungal drugs as assessed from pharmacoepidemiologic studies. However, in view of various methodological limitations, FDA concluded that there was uncertainty in quantifying precise estimates of the risk of acute liver injury for ketoconazole compared to other marketed oral azole antifungals. FDA also concluded that ketoconazole can produce adrenal insufficiency and that the co-administration of certain drugs could result in life-threatening drug interactions.[25]

The Agency took several steps to address these concerns, including withdrawing approval of certain approved indications (e.g., candida and dermatophyte infections) and limiting approval to specific endemic mycoses only when other effective antifungal therapy is not available or tolerated and the potential benefits are considered to outweigh the potential risks.[26] FDA concluded that because there are limited treatment options for patients who have endemic mycoses, the benefits outweighed the potential risks in using ketoconazole for these systemic fungal infections for patients who did not have alternative treatment options. In addition to requiring safety labeling changes that reflected this decision, FDA required a Medication Guide and released a Drug Safety Communication (DSC) to inform the public of these changes.[27] Because a generic drug must have the same labeling as its reference listed drug, with certain exceptions, generic versions of Nizoral also were required to change their labeling.[28]

In October 2013, FDA recommended that drug companies and researchers avoid using ketoconazole in drug interaction studies due to serious potential side effects and issued another DSC on ketoconazole to communicate this decision.[29]

FDA continued to review reported safety information regarding ketoconazole after 2013, and expanded the scope of that review after it received your Petition. During that review, FDA found that oral ketoconazole continued to be prescribed for treatment of skin and nail infections, indications that had been removed from ketoconazole labeling.[30] This conclusion was based on

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[24] See FDA July 26, 2013 Drug Safety Communication (DSC): FDA limits usage of Nizoral (ketoconazole) oral tablets due to potentially fatal liver injury and risk of drug interactions and adrenal gland problems, available at http://www.fda.gov/drugs/drugsafety/ucm362415.htm.

[25] Id.

[26] Id.

[27] Id.

[28] Section 505(j)(2)(A)(v) of the FD&C Act.

[29] See FDA Oct 16, 2013, DSC: FDA advises against using oral ketoconazole in drug interaction studies due to serious potential side effects, available at http://www.fda.gov/Drugs/DrugSafety/ucm371017.htm.

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

information from the FDA Adverse Event Reporting System (FAERS) database and recent drug utilization data on ketoconazole. Based on that information, on May 19, 2016, FDA issued another DSC, warning health care professionals to avoid prescribing ketoconazole for these indications because use of the medication carries the risk of serious liver damage, adrenal gland problems, and harmful interactions with other medications; risks that outweigh the benefits in treating these indications.[31]

IV. DISCUSSION

In the Petition, you request that FDA remove ketoconazole from the market.[32] You argue that 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.[33] We disagree. The OSE January 2013 Assessment, which is the basis for much of your Petition, was not the ultimate conclusion of the agency with respect to approval of ketoconazole.[34] Moreover, since 2013 FDA has continued to review all new sources of information on the safety of ketoconazole and has conducted a substantial literature search and analysis of pharmacoepidemiologic data on hepatotoxicity and ketoconazole.[35] Additionally, FDA has compiled and evaluated current drug utilization data for ketoconazole. Based on available information, FDA concludes that ketoconazole should remain on the market for the limited indications for which it is approved.

Systemic mycoses are serious and life threatening conditions that have limited approved treatment options. While there are other preferred treatment options for these infections, FDA's updated analyses support the Agency's conclusion that the risks and benefits of ketoconazole remain favorable for treatment of patients with these systemic infections when other effective antifungal therapy is not available or tolerated. The removal of ketoconazole from the market would eliminate oral therapy available to the small patient population with endemic mycoses who either have a contraindication to or are intolerant to alternative fungal medications. Ketoconazole is the only oral antifungal agent approved for coccidiomycosis and it shares labeled indications for oral treatment with itraconazole for blastomycosis and histoplasmosis.[36] No other oral antifungal agent is approved by FDA for all of these indications. Neither the

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[31] Id. FDA recognizes the limitations of FAERS data, which are often under-reported and cannot be used to quantify a level of risk nor can these data be used to quantify the risk among drugs.

[32] Petition at 1. We understand your request to be that FDA withdraw approval of ketoconazole under section 505(e) of the FD&C Act.

[33] Petition at 4.

[34] See Petition at 4 (stating that the Petition is "relying mainly on OSE reviewers' recent analysis").

[35] Since the 2013 labeling change, one patient death has been reported to FDA due to liver failure associated with oral ketoconazole prescribed to treat a fungal infection of the nails. See FDA May 19, 2016 DSC available at http://www.fda.gov/Drugs/DrugSafety/ucm500597.htm.

[36] As noted in the Petition at 11, ketoconazole is also the only approved treatment for paracoccidioidomycosis and chromomycosis, which are primarily encountered by U.S. patients returning from foreign travel.

information identified in the Petition nor FDA's analysis of other available information supports a finding that ketoconazole is unsafe for the limited conditions of use for which it is approved, as required by section 505(e) of the FD&C Act.

Although ketoconazole will remain on the market for its limited indications of use, FDA is requiring Safety Labeling Changes under section 505(o)(4) of the FD&C Act in order to provide adequate safety warnings to prescribers regarding the risks of ketoconazole. Specifically, FDA has concluded that the analysis of the information from FAERS, published literature and drug utilization information is "new safety information" as defined by Section 505-1(b)(3) of the FD&C Act.[37] FDA is requiring holders of approved applications for oral ketoconazole to make labeling changes that address this new safety information.[38]

A. Recent Observational Pharmacoepidemiologic Studies Do Not Establish That Ketoconazole's Risks Outweigh the Benefits in Treatment of Endemic Mycoses

FDA conducted a literature review of observational pharmacoepidemiologic studies of ketoconazole published since the 2013 OSE Assessment. Based on prior analysis and this more current review, FDA identified three relevant pharmacoepidemiologic studies that analyze acute drug-induced liver injury (DILI) from use of antifungal treatment. The 1999 Garcia Rodriguez study estimated the risk of clinical acute liver injury among users of antifungals (ketoconazole, griseofulvin, itraconazole, terbinafine, and fluconazole) in the general population.[39] The conclusion reached by Garcia Rodriguez was that ketoconazole and itraconazole were the two antifungals associated with a marked increase in cases of clinical acute liver injury.[40] FDA

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[37] Section 505(o)(2)(C) defines new safety information to have the meaning given that term under Section 505-1(b) of the FD&C Act. (21 USC 355(o)(2)(C)). Section 505-1(b)(3) (21 U.S.C. 355-1(b)(3)) states:

> The term 'new safety information', with respect to a drug, means information derived from a clinical trial, an adverse event report, a post approval study (including a study under section 505(o)(3)) or peer reviewed biomedical literature; data derived from the post market risk identification and analysis system under section 505(k); or other scientific data deemed appropriate by the [FDA] about --
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> (A) a serious risk or an unexpected serious risk associated with use of the drug that the [FDA] has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since the risk evaluation and mitigation strategy was required, or since the last assessment of the approved risk evaluation and mitigation strategy for the drug; or
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> (B) the effectiveness of the approved risk evaluation and mitigation strategy for the drug obtained since the last assessment of such a strategy.

[38] If the Secretary becomes aware of new safety information that the Secretary believes should be included in the labeling of the drug, the Secretary shall promptly notify the responsible person or, if the same drug approved under section 505(b) is not currently marketed, the holder of an approved application under 505(j). 21 U.S.C. 355(o)(4)(A).

[39] The Petition concedes that the Garcia Rodriguez study was "the most rigorous study" reviewed by OSE in 2013, and therefore it is the most rigorous study relied on by the Petitioner. (See Petition at 5). Garcia Rodriguez LA, Duque A, Castellsague J, Perez-Gutthann S, Stricker BHC. "A Cohort Study on the Risk of Acute Liver Injury Among Users of Ketoconazole and Other Antifungal Drugs," *Br J Clin Pharmacol* 48(6): 847-852 (1999).

[40] Garcia Rodriguez at 847. The study also concluded that the risk associated with ketoconazole should be taken into account when prescribing it as initial treatment for uncomplicated fungal infections; something that FDA did when it completed its 2013 review.

reviewed that study and other information related to ketoconazole-induced liver injury as part of its 2013 safety review of ketoconazole. At that time, FDA concluded that there were various methodological limitations in that and other studies that created uncertainty in quantifying precise estimates of the risk of acute liver injury among the azole antifungals considered.[41] In part, based on this uncertainty, in July 2013 FDA limited the approved indications for ketoconazole rather than removing it from the market.[42]

The two new epidemiologic studies reviewed by FDA that report the incidence rate or frequency of acute liver injury among users of azole antifungals are an improvement over the Garcia Rodriguez study to the extent they include higher numbers of ketoconazole users and outcome events. The first study was a U.S. study based on Kaiser Permanente Northern California data by Lo Re, which evaluated the incidence rate of acute liver injury among new initiators of different azoles.[43] The second study was a Taiwanese study based on Taiwan's National Health Insurance Database by Kao, and it evaluated the risk of drug induced liver injury caused by oral antifungal medication.[44] However, the two new studies reported conflicting trends in the risk of acute liver injury among azole users. Therefore, rather than resolving the uncertainty of earlier studies, the trends identified in these new reports raise additional questions as to whether ketoconazole is associated with a higher risk of acute liver injury than other azole antifungals.

Overall the Lo Re study did not find that the risks of liver injury with ketoconazole use were significantly greater than the risks with other azole antifungals. The study concluded that the rates of acute liver injury were similarly low for fluconazole, ketoconazole and itraconazole.[45] This conclusion was based on the comparative incidence of two adverse liver events -- severe

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[41] The Garcia Rodriguez study has limited ability to provide a robust and precise risk estimate of ketoconazole-associated hepatotoxicity due to the sparseness of the outcome events and the limited information on potential confounders such as patient age.

[42] See Footnote 24 (July 2013 DSC).

[43] Lo Re V III, Carbonari DM, Lewis JD, Forde KA, Goldberg DS, Reddy KR, Haynes K, Roy JA, Sha D, Marks AR, Schneider JL, Strom BL, Corley DA. "Oral Azole Antifungal Medications and Risk of Acute Liver Injury, Overall and by Chronic Liver Disease Status," *Am J Med*, 129(3): 283-291.e5 (2016). The Lo Re study was conducted in years 2004-2010.

[44] Kao WY, Su C-W, Huang Y-S, Chou Y-C, Chen Y-C, Chung W-H, Hou M-C, Lin H-C, Lee F-Y, Wu J-C. "Risk of Oral Antifungal Agent-Induced Liver Injury in Taiwanese," *Br J Clin Pharmacol* 77(1): 180-189 (2014).

[45] Footnote 43 at 287. The analysis was from 195,334 azole initiators (178,879 fluconazole; 14,296 ketoconazole; 1653 itraconazole, incidence rate (events/1000 person-years) (95% confidence intervals) of liver aminotransferases >200 U/L. Specifically, the Lo Re study observed 265 severe liver aminotransferase elevations among fluconazole initiators (1 of 675 users; 13 events per 1000 person-years), 40 among ketoconazole initiators (1 of 357 users; 19.3 events per 1000 person-years), and 8 among itraconazole initiators (1 of 207 users; 24.5 events per 1000 person-years). It also observed 41 severe acute liver injury events among fluconazole initiators (1 of 4363 users; 2.0 events per 1000 person-years) 6 among ketoconazole initiators (1 of 2383 users; 2.9 events per 1000 person-years, 0 among itraconazole initiators (0 events per 1000 person-years), 2 among voriconazole initiators (1 of 239 users; 16.7 events per 1000 person-years), and 1 among posaconazole initiators (1 of 28 users; 93.4 events per 1000 person-years).

liver aminotransferase elevations and severe acute liver injury[46] -- among users of the studied azoles.[47] In a subset of this study that compared acute liver injury risk in patients with and without liver disease, the Lo Re study found that in the subgroup without chronic liver disease, there was a non-statistically significant increase in the risk of severe acute liver injury for ketoconazole users, compared to fluconazole users, after accounting for the observed baseline patient characteristics.[48] However, as with earlier studies, there is uncertainty about this trend because the study was not powered to evaluate the risk stratified by liver disease status. Moreover, even though the Lo Re and Garcia Rodriguez studies reported similar trends (i.e., the risk estimate of ketoconazole was the highest among all antifungals), the magnitude of the absolute risk estimates differed substantially between the two studies—the incidence rate of acute liver injury among ketoconazole users was about five times higher in the Garcia Rodriquez study than in the Lo Re study. This inconsistency, along with the overall conclusion of the study, emphasizes the uncertainty and difficulty in evaluating the absolute risk for ketoconazole.

The Kao study concluded generally that oral antifungal agents are associated with low incidence of acute liver injury, but that the risk may be fatal. Kao concluded that fluconazole had the highest liver toxicity rate among azole users, followed by ketoconazole, griseofulvin, itraconazole and terbinafine.[49] The Kao study reviewed drug-induced liver injury identified by diagnostic code within 5 to 90 days of antifungal use. The results showed the incidence rates of drug induced liver injury per 10,000 persons were 31.6, 4.9, 4.3, 3.6, and 1.6 for fluconazole, ketoconazole, griseofulvin, itraconazole and terbinafine, respectively. Of note, the Kao study did not provide adjusted estimates for the relative risk of drug induced liver injury among different azoles. Drug specific risks were presented as crude proportions and did not account for any differences in baseline patient characteristics that could impact the risk of drug induced liver injury.[50]

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[46] Id. at 284, 285. Development of severe liver aminotransferase elevations were defined as an inpatient or outpatient alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >200 U/L. Severe acute liver injury was defined by an inpatient or outpatient international normalized ratio (INR) $\geq$ 1.5 and total bilirubin > 2 times the upper limit of normal within 30 days of each other.

[47] Id. at 285, 287. The Lo Re study also examined risks of acute liver failure among azole users, which was confirmed if a patient was hospitalized and had (1) no chronic liver disease, (2) coagulopathy (INR$\geq$ 1.5) without anticoagulation therapy, and (3) either hepatic encephalopathy or liver transplantation for acute liver failure. Among 187,703 azole users without chronic liver disease, acute liver failure was confirmed in 1 ketoconazole patient, emphasizing the rarity of this result.

[48] The analyses accounted for differences in the following baseline characteristics: age, gender, race/ethnicity, body mass index, presence of diabetes mellitus, cancer, heart failure, history of alcohol dependence/abuse, HIV infection and indication for antifungal use.

[49] The labeling in terbinafine, griseofulvin, fluconazole, voriconazole and itraconazole all have warnings about hepatic liver injury, recognizing that these drugs can cause serious hepatic toxicities, and warning or precaution against drug interactions.

[50] For example, the proportion of patients older than 60 years of age was significantly higher among fluconazole users than all other antifungals studied (47.8% in fluconazole users, 8.1% in ketoconazole users; 17 to 24% among users of the other azoles.) The significantly larger proportion of elderly patients might explain why fluconazole has the highest observed risk of DILI in the Kao study. In the Kao study, there was a total 90,847 patients using oral antifungals during the time period 2002-2008, griseofulvin (N= 18,677), terbinafine (N=12,376), ketoconazole (N= 57,321), fluconazole (N=3,793) and itraconazole (N=8,368).

In addition to the concerns mentioned, the ability to compare the results of the three studies is limited by a number of factors, including the following: the three studies were conducted in different time frames (i.e. early 1990s (Garcia Rodriguez) and 2000s (Kao and Lo Re)); different countries (i.e. U.S. (Lo Re), Taiwan (Kao), and the United Kingdom (Garcia Rodriguez)); and in slightly different populations.[51] These factors might contribute to some, but not likely all of the variations in the observed acute liver injury risk. A more fundamental difference among the studies was in their operational definitions of acute liver injury, which would have affected the study findings -- Lo Re defined acute liver injury using a combination of laboratory test results, whereas Garcia Rodriguez and Kao used diagnosis codes that indicated acute liver injury, with or without adjudication, based on clinical records.[52] When all of these issues are considered, the results of the three studies are inconclusive regarding the absolute or relative risk of ketoconazole-associated liver injury.

B. Drug Utilization Data Support FDA's Decision Not To Withdraw Approval of Ketoconazole

Because ketoconazole can cause serious hepatotoxicity, FDA conducted analyses to characterize the utilization of ketoconazole using both proprietary drug utilization databases available to the Agency and the Sentinel System. These databases provide epidemiologists sets of data from which experienced scientists can analyze and draw conclusions on trends and patterns of drug utilization. FDA analyzed the data on ketoconazole to assess the extent to which ketoconazole is being prescribed and for what reasons in the outpatient setting. From the data retrieved, FDA has identified patterns of use of ketoconazole that are relevant to the Agency's safety analysis.

Analysis of data from IMS Health, Total Patient Tracker,[53] a proprietary drug utilization

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[51] The ketoconazole users in the Lo Re study were mainly male (61%) while they were mainly female in the Kao and the Garcia Rodriguez studies (67% versus 59%, respectively); the Lo Re study was restricted to new users of antifungal drugs, while the others included pre-existing users.

[52] Specifically, it is possible that not all of the acute liver injury cases identified in the Garcia Rodriguez and Kao studies had the adverse event, because diagnosis codes have been shown to have low positive predictive value (<55%) to capture acute liver injury. See Lo Re V, III, Haynes K, Goldberg D, Forde, KA, Carbonari, DM, Leidl KBF, Hennessy S, Reddy, KR, Pawloski PA, Daniel GW, Cheetham, TC, Iyer A, Coughlin, KO, Toh S, Boudreau DM, Selvam N, Cooper WO, Selvan MS, VanWormer JJ, Avigan MI, Houstoun, M, Zornberg GL, Racoosin, JA, Shoaibi A. "Validity of Diagnostic Codes to Identify Cases of Severe Acute Liver Injury in the U.S. Food and Drug Administration's Mini-Sentinel Distributed Database," *Pharmacoepidemiol Drug Saf* 22(8): 861-872 (2013). Using laboratory test results to identify acute liver injury, as Lo Re did in the comparative azole study, can reduce false-positive error; however, it introduces bias when comparing the acute liver injury risk across antifungal users as physicians might monitor patients' liver function differently, depending on which antifungal therapy they received. A group of users who received more frequent liver function monitoring would appear to be at higher risk for liver adverse events, because the event would be more likely to be observed.

[53] IMS Health: Total Patient Tracker. Extracted Feb 2016. IMS, Vector One Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. Total Patient Tracker derives its data from the Vector One database which integrates prescription activity from a sample received from payers, switches and other software systems that may arbitrage prescriptions at various points in the sales cycle. Data from these sources are extrapolated to provide

database providing national estimates of drug utilization, showed that based on dispensed prescription claims data, outpatient utilization of oral ketoconazole has decreased since July 2013. The nationally estimated number of patients who were dispensed prescriptions for oral ketoconazole from the outpatient retail setting decreased by nearly 40 percent from approximately 358,000 patients in the year ending in June 2013 to approximately 217,000 patients in the year ending in June 2015.[54]

FDA also obtained information on the indications for which ketoconazole has been prescribed from an office-based physician survey database,[55] which identifies and provides national estimates on the number of "drug use mentions" for drug products by diagnoses from monthly surveys of a sample of 3,200 U.S. office-based physicians.[56] From January 2012 through June 2013, the most common diagnoses associated with use of oral ketoconazole were mainly skin infections, with dermatomycosis accounting for the top diagnosis with 57.5 percent of all drug use mentions (254,000) and dermatophytosis accounting for 25 percent of drug use mentions (111,000), followed by candidiasis with 6 percent drug use mentions (26,000).

FDA re-assessed the indications for which ketoconazole was used after the labeling changes of July 26, 2013 using the same office-based physician survey database. For the 18-month time period from January 2014 through June 2015, skin infections accounted for all of the diagnoses reported in association with the use of oral ketoconazole with 164,000 total drug use mentions. This was less than half the mentions for skin infections when compared to the 18-month time period from January 2012 through June 2013. However, it should be noted that while these data

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national estimates of drug use. (The estimates are national estimates, but no statistical tests were performed to determine statistically significant changes over time or between products.)

[54] FDA also obtained information from this database on approximate drug utilization in the year ending June 2013 for other azoles to provide context for evaluating ketoconazole use: fluconazole had 8,137,000 patients who received dispensed prescriptions, terbinafine had 1,165,000 patients, griseofulvin had 325,000 patients and itraconazole had 64,000 patients. In the year ending June 2015, fluconazole had 8,327,000 patients who received a dispensed prescription, terbinafine had 1,224,000 patients, griseofulvin had 280,000 patients and itraconazole had 64,000 patients. The two recent studies, which are small subsets of antifungal use, show comparatively different use trends. In the Kao Taiwanese study (2002 to 2008) there were 90,847 patients using oral antifungals 2002-2008, griseofulvin (N= 18,677), terbinafine (N=12,376), ketoconazole (N= 57,321), fluconazole (N=3,793) and itraconazole (N=8,368). In the Lo Re study, there were 178,879 fluconazole users, 14, 296 ketoconazole users and 1653 itraconazole users.

[55] This information was retrieved through inVentiv Health Research & Insights, LLC from January 2012 through June 2013 and January 2014 through June 2015. Extracted Aug 2015. Treatment Answers and Treatment Answers with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday each month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

[56] The term "drug use mentions" refers to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnoses for which the drug is mentioned. It is important to note that a "drug use mention" does not necessarily result in a prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

provide useful information on prescribing patterns, the office-based survey database is best utilized to describe the common indications for use of a drug in the outpatient setting. Because of the small sample size captured for ketoconazole, the data may not reliably capture uncommon indications for use. In addition, this data source may not capture diagnoses such as those made in the inpatient setting.[57]

To address some of these limitations, FDA initiated a Sentinel System analysis to complement the drug use analyses from the proprietary databases. The Sentinel System is FDA's automated database for conducting active safety surveillance of medical products in a large network of electronic health care databases.[58] In this instance, the advantages of the Sentinel System are that the database (1) includes inpatient hospitalization information, (2) covers a large population (~116 million patients from 2009 to 2015), and (3) is compiled by 16 different data partners. Therefore, the Sentinel System may be able to capture use of ketoconazole for uncommon diseases, such as systemic fungal infections.

Using the data from the Sentinel System, FDA confirmed that ketoconazole use decreased after the 2013 safety labeling change. The trend of decreasing utilization identified in the nationally projected IMS data was also seen in data from the Sentinel System.[59] Importantly, the data indicated that there are patients who are prescribed ketoconazole for the labeled indications, although these represent a small percentage of total prescriptions. The data confirmed that after 2013, ketoconazole continues to be prescribed mainly for the indications that were removed from the label (fungal dermatophyte infections and various candida infections).[60]

The significance of the drug utilization data to the safety analysis of ketoconazole is that these data demonstrate a strong trend since 2013 that ketoconazole use is declining. However, these

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[57] However, a diagnosis such as a systemic fungal infection could potentially be captured in this database because these patients may require long courses of outpatient treatment following inpatient stay.

[58] The FDA's Sentinel Initiative webpage can be found at www.fda.gov/safety/fdasSentinelInitiative/default.htm. Sentinel enhances FDA's ability to proactively monitor the safety of medical products. Through the Sentinel System, FDA can rapidly and securely access information from large amounts of electronic healthcare data, such as electronic health records, insurance claims data, and registries, from a diverse group of data partners. https://www.sentinelsystem.org/.

[59] The numbers for ketoconazole use taken from the Sentinel database, unlike the information from the IMS Health database, do not represent a national estimate of ketoconazole use. The Sentinel data represent patient use from approximately 116 million patients identified through 16 data partners (with identifying information removed). Based on the structure of the database, FDA does not have an estimate of national use from Sentinel, although the specific patient-level information is particularly instructive for ketoconazole use because it provides information on use in these uncommon disease indications. Comparing the calendar year in Sentinel before and after the 2013 labeling change, ketoconazole use decreased 43% (N=52,160 in 2012, N=29,945 in 2014).

[60] The Sentinel System analysis concluded that no more than 21 ketoconazole users had a diagnosis code for the approved labeled systemic fungal infections in 2014 out of the total 29,945 ketoconazole users identified. However, in the Sentinel System analysis, the majority of users did not have an associated diagnosis code to identify the indication for use. Unfortunately, this is a known limitation of using administrative claims data to study indications for drug use. While we did not validate diagnosis codes, those codes appeared within a reasonable time frame of antifungal use, so the likelihood that the coded medical condition is accurate is probably high.

data also indicate that ketoconazole continues to be prescribed for superficial fungal infections that are no longer approved indications for use.

C. Additional Considerations

The Petition attempts to quantify the "serious hepatotoxicity" caused by ketoconazole.[61] Specifically, the Petition argues that ketoconazole may have caused 616 cases of acute liver injury. However that estimate is based on the incidence of liver injury from the Garcia Rodriguez study, which is then used to calculate an estimate of current liver injury based on recent drug utilization data. The resulting number cannot be supported for several reasons.

First, the calculation assumes that the currently dispensed number of ketoconazole prescriptions is equal to the number of unique ketoconazole users. This is an over estimation of the population at risk, because one patient can receive more than one prescription over the 1-year period. Second, the Garcia Rodriguez study has insufficient power to provide a precise risk estimate.[62] Third, as discussed above, there are two more recent studies that reported on the absolute risk of acute liver toxicity associated with ketoconazole that question the conclusions of the Garcia Rodriguez study. Specifically, the observed risk in Garcia Rodriguez was four to five times higher than in one of the newer studies.

The Petition argues that FDA should adhere to the positions on ketoconazole taken by EMA and the Infectious Disease Society of America (IDSA). FDA did consider (and consult with) EMA during the 2013 safety review. However, EMA's conclusions are only one piece of information the Agency considered; the decision to keep ketoconazole on the market is based on its use in the United States. One important consideration in the decision was that certain fungal infections are endemic in the United States but are not endemic in Europe. The fact that histoplasmosis, coccidioidomycosis, and blastomycosis do not occur in Europe creates a different balance of the benefits and risks associated with the use of ketoconazole. The balance tips toward risks and appears to support the subsequent removal of ketoconazole from the marketplace in Europe. In the United States, although uncommon, these three endemic mycoses must be treated and there are benefits in having effective options available for treating these fungal infections. FDA has also noted the increasing incidence of endemic mycoses in the elderly, a growing population group within the U.S. Thus, the risks associated with ketoconazole are offset by its benefit as a potential alternative treatment when other effective antifungal therapies are not available or tolerated in the U.S.

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[61] Petition at 2-3, 6-8, and 16.

[62] The Garcia Rodriguez study observed a total of five cases of acute liver injury from patients exposed to any antifungal studied, including two cases in the ketoconazole-exposed group. The observed incidence rate of acute liver injury among ketoconazole users had a wide confidence interval, (95% confidence interval 36.8 to 488 per 100,000 person-months). A study with such a wide confidence interval provides an unreliable estimate of the incidence of acute liver injury. Furthermore, three-fourths of the 73 candidate cases of acute liver injury identified in the study were excluded after adjudication by three investigators, meaning that the findings of this study were heavily dependent on how cases were adjudicated. A few cases more or less in the ketoconazole exposed groups would have given a much different incidence rate, limiting the robustness of the findings.

The position of IDSA is another piece of information FDA considered. As discussed in the Petition, the IDSA treatment guidelines state that ketoconazole should not be considered first-line treatment for endemic fungal infections and this statement is consistent with ketoconazole's currently labeled indications for use in patients who do not have other treatment options.[63] Although there are other treatment options available for certain endemic mycoses, itraconazole is contraindicated in congestive heart failure, so maintaining ketoconazole as a treatment option is important. Ketoconazole is the only oral antifungal agent approved for coccidioidomycosis and it shares labeled indications with itraconazole for blastomycosis and histoplasmosis. No other oral antifungal agent is approved by FDA for all of these indications.

Finally, FDA disagrees with the Petition's assertion that FDA's efforts to restrict the use of ketoconazole are futile.[64] The current data clearly demonstrate that the use of ketoconazole has decreased substantially after the July 2013 labeling changes. We believe that the issued DSCs and required SLCs are adequate to guide the safe use of ketoconazole for its approved indications.

To summarize, there are limited treatment options for patients who have endemic mycoses, the effects of which can be serious and life-threatening. FDA's updated analyses support the Agency's conclusion that the risks and benefits of ketoconazole remain favorable for treatment of patients with these systemic fungal infections who do not have other treatment options.

V. CONCLUSION

For the foregoing reasons, the Petition is denied. FDA will continue to monitor available safety information as it relates to ketoconazole and take any further action as is appropriate.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[63] Petition at 11-13.

[64] Petition at 16.