Drug Class Review Monograph – GPI Class 11 – Antifungals

Review Time Frame: 02/2016 – 04/2017
Previous Class Review: 05/2016

Background:
Antifungals include:

- Azoles are the largest antifungal class and work by altering the fungal cell membrane. They inhibit the cytochrome P450-dependent enzyme lanosterol 14-alpha-demethylase, which is necessary for the conversion of lanosterol to ergosterol. Ergosterol is a vital component of the cellular membrane of fungi, and disruptions in its biosynthesis cause significant damage to the cell membrane by increasing its permeability, resulting in cell lysis and death.
- Terbinafine, an allylamine, interferes with fungal sterol biosynthesis by inhibiting the enzyme squalene monooxygenase, a key enzyme in sterol biosynthesis in fungi. This results in a deficiency in ergosterol within the fungal cell wall and leads to fungal cell death.
- Flucytosine, a nucleoside analog, penetrates fungal cells and is converted to fluorouracil which competes with uracil, interfering with fungal RNA and protein synthesis.
- Nystatin binds to sterols in fungal cell membrane, changing the cell wall permeability and allowing for leakage of cellular contents.
- Griseofulvin inhibits fungal cell mitosis at metaphase and binds to human keratin, making it resistant to fungal invasion.
- Echinocandins inhibit synthesis of 1,3-beta-D-glucan, a major fungal cell wall component. Depletion of 1,3-beta-D-glucan results in osmotic instability and fungal cell death.

New treatment guideline recommendations:

- In the 2016 clinical practice guideline for the management of candidiasis, the Infectious Diseases Society of America (IDSA) offers updated recommendations for proven or suspected invasive candidiasis based on new data available since the 2009 guideline:
    - There are 4 classes of systemic antifungal agents effective for the treatment of invasive candidiasis: polyenes (amphotericin B [AmB]), triazoles (fluconazole, itraconazole, voriconazole, posaconazole), echinocandins (caspofungin, anidulafungin, micafungin), and flucytosine. The echinocandins are the preferred agents for most episodes of candidemia and invasive candidiasis with the exception of central nervous system (CNS), eye, and urinary tract infections.
    - In critically ill patients with suspected invasive candidiasis, empiric antifungal therapy with an echinocandin (alternatives: fluconazole, lipid formulation AmB) is recommended.
    - In patients in adult intensive care units at high risk of invasive candidiasis, prophylaxis with fluconazole (alternative: an echinocandin) is recommended.
    - In neonatal invasive candidiasis, treatment with AmB deoxycholate (alternatives: fluconazole, lipid formulation AmB) is recommended. Echinocandins should be used with caution and are generally limited to salvage therapy.

Newly approved drugs:

- None identified

Newly approved formulations:
- None identified

Newly approved generics:
- None identified

Discontinued drugs:
- None identified

FDA Safety Alerts/black box warnings:
- 04/26/2016: FDA Drug Safety Communication: FDA to review study examining use of oral fluconazole (Diflucan) in pregnancy (refer to page 3 for full detail).
- 05/19/2016: FDA Drug Safety Communication: FDA warns that prescribing of Nizoral (ketoconazole) oral tablets for unapproved uses including skin and nail infections continues; linked to patient death (refer to page 3 for full detail).

Pipeline alerts:
Agents pending FDA approval include:
- None identified

References:

1. Ashley ED, Perfect JR. Pharmacology of azoles. Kauffman CA, Thorner AR. (Ed), UpToDate. Waltham MA. Accessed April 2016.
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2017. URL: http://www.clinicalpharmacology-ip.com/. Accessed May 2017.
3. US Script Oracle PBM: Medi-Span® Master Drug Data Base. May 2016.
4. Food and Drug Administration. WWW.FDA.GOV. Accessed May 2017.
5. Pappas PG, Kaufmann CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016; 62(4): e1-e50.
6. Envolve Pharmacy Solutions internal pipeline database. Accessed May 2017.

(FDA Drug Safety Communications, continued from page 2)

FDA Drug Safety Communication: FDA to review study examining use of oral fluconazole (Diflucan) in pregnancy
[04-26-2016]
The U.S. Food and Drug Administration (FDA) is evaluating the results of a Danish study that conclude there is a possible increased risk of miscarriage with the use of oral fluconazole (Diflucan) for yeast infections. We are also reviewing additional data and will communicate our final conclusions and recommendations when our review is complete.

Health care professionals should be aware that the Centers for Disease Control and Prevention guidelines recommend only using topical antifungal products to treat pregnant women with vulvovaginal yeast infections, including for longer periods than usual if these infections persist or recur.

Patients who are pregnant or actively trying to get pregnant should talk to their health care professionals about alternative treatment options for yeast infections.

Oral fluconazole is used to treat yeast infections of the vaginal area, mouth, and esophagus, which is the tube that connects the mouth to the stomach. It is also used to treat a fungal infection of the brain and spinal cord called cryptococcal meningitis that most often affects people with weakened immune systems, and used to prevent yeast infections that can spread to the rest of the body in cancer patients who have a weakened immune system. It is available under the brand name Diflucan and also as generics.

The current FDA drug label states that data available from studies in people do not suggest an increased risk of problems during pregnancy or abnormalities in developing babies when women are exposed to a single 150 mg dose of oral fluconazole to treat vaginal yeast infections. However, high doses of oral fluconazole (400-800 mg/day) taken by pregnant women for much longer than a single dose have resulted in reports of abnormalities at birth. In the Danish study, most of the oral fluconazole use appeared to be one or two doses of 150 mg.

Until FDA's review is complete and more is understood about this study and other available data, we advise cautious prescribing of oral fluconazole in pregnancy.

We urge both healthcare professionals and patients to report adverse events involving fluconazole to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

FDA Drug Safety Communication: FDA warns that prescribing of Nizoral (ketoconazole) oral tablets for unapproved uses including skin and nail infections continues; linked to patient death
[05-19-2016]
The U.S. Food and Drug Administration (FDA) is warning health care professionals to avoid prescribing the antifungal medicine ketoconazole oral tablets to treat skin and nail fungal infections. Use of this medication carries the risk of serious liver damage, adrenal gland

problems, and harmful interactions with other medicines that outweigh its benefit in treating these conditions, which are not approved uses of the drug.

We approved label changes for oral ketoconazole tablets in 2013 to reflect these serious risks and to remove the indication for treatment of skin and nail fungal infections. However, an FDA safety review found that oral ketoconazole continues to be prescribed for these types of conditions. In the 18 months ending in June 2015, skin and nail fungal infections were the only diagnoses cited for the use of oral ketoconazole in an office-based physician surveys database. Since the 2013 labeling change, one patient death has been reported to the FDA due to liver failure associated with oral ketoconazole prescribed to treat a fungal infection of the nails.

Health care professionals should use ketoconazole tablets only to treat serious fungal infections when no other antifungal therapies are available. Skin and nail fungal infections in otherwise healthy persons are not life-threatening, and so the risks associated with oral ketoconazole outweigh the benefits. Other treatment options are available over-the-counter and by prescription, but are also associated with risks that should be weighed against their benefits.

Patients should discuss with their health care professionals the risks and benefits of available therapies before using any medicine to treat skin and nail fungal infections. Patients taking ketoconazole tablets should seek medical attention right away if they experience any of these signs and symptoms of liver problems, which include loss of appetite, nausea, vomiting, or abdominal discomfort; yellowing of the skin or the whites of the eyes (jaundice); unusual darkening of the urine or lightening of the stools; or pain and discomfort in the right upper abdomen where the liver is located.

Ketoconazole in tablet form is indicated to treat serious infections caused by fungi and should be used only when other effective therapy is not available or tolerated. It works by killing the fungus or preventing it from growing. During the 12-month period ending in June 2015, approximately 217,000 patients received dispensed prescriptions for oral ketoconazole from U.S. outpatient retail pharmacies. Ketoconazole is only available as a generic. The topical forms of ketoconazole that are applied to the skin or nails have not been associated with liver damage, adrenal problems, or drug interactions.

In a July 2013 Drug Safety Communication, we warned that ketoconazole tablets should not be used as a first-line treatment for any fungal infection because it can cause severe liver injury and adrenal gland problems, and advised it can lead to harmful interactions with other medicines. We determined that the risks outweigh the benefits for treating skin and nail fungal infections and approved label changes removing this indication from the drug label and limited its labeled indication to treating only serious fungal infections.

We urge health care professionals and patients to report side effects involving ketoconazole to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.