

# Continuing Education for Pharmacists

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## New Anti-infective Drugs for 2006: Eraxis and Prezista

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**Goals.** The goals of this lesson are to provide background information on candidal and human immunodeficiency virus (HIV) infections, and review two new drugs approved during 2006 to treat them.

**Objectives.** At the conclusion of this lesson, successful participants should be able to:

1. explain the etiology, incidence, and pathophysiology of candidal and HIV infections;
2. describe the pharmacologic profiles and list therapeutic considerations for anidulafungin and darunavir; and
3. select from a list, the indications, mechanisms of action, adverse effects, warnings and toxicities, drug interactions, and benefits and limitations of anidulafungin and darunavir.

### Fungal Infections

Pathogenic fungi that infect humans are saprophytes (live on dead or decaying organic matter), and cause infection when airborne



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spores invade the tissue of the lungs or paranasal sinus, or when hyphae (fungal filaments) or spores are inadvertently inoculated into the skin or cornea. Infection (other than ringworm) from another person is extremely rare. Hospitalized patients with fungal infections, therefore, do not usually require isolation. Ingestion of fungi rarely causes infection. *Candida albicans*, a normal inhabitant of the mouth and intestine, rarely reaches deeper tissues, but infection can occur when mucosal or cutaneous barriers are damaged by disease, surgery, trauma, or catheterization. Exposure to fungi may impart partial protection against reinfection. People living in areas where fungal organisms are endemic are less subject to infection than newcomers into the area.

**Epidemiology.** *C. albicans* is the most common cause of mucosal candidiasis, being responsible for about half of all cases of *Candida* infections in hospitalized patients. *Candidiasis* is a general term that describes a number of clinical syndromes caused by *Candida*. *Candida* species, taken together, constitute the leading cause of *nosocomial* (hospital or institutionally acquired) blood infections in the U.S. Candidiasis is often preceded by increased *Candida* colonization (i.e., superinfection) due to broad-spectrum antibiotic therapy. Oropharyngeal thrush is especially prone to occur in neonates and individuals with diabetes mellitus or HIV infection, and is common in persons with poorly fitting dentures. Vulvovaginal candidiasis is especially common during the third trimester of pregnancy. *Candida* can enter the urinary tract through an indwelling bladder catheter. Cutaneous candidiasis usually involves macerated skin, such as that in the diapered area of infants. The fungus can pass from the colonized surface into blood (*candidemia*) or deep tissue when the integrity of the mucosa or skin

### New Anti-infective Drugs of 2006

| Trade/Generic Name<br>(Sponsor/Manufacturer)  | Dosage<br>Form              | Indication   | Date<br>Approved |
|---|-----------------------------|--|------------------|
| Eraxis/anidulafungin<br>(Roerig/Pfizer)       | solution for<br>IV infusion | treatment of <i>Candidemia</i> & other forms of <i>Candida</i> infections;<br>esophageal candidiasis | 2/06             |
| Prezista/darunavir<br>(Tibotec/Ortho Biotech) | tablets                     | treatment of human immunodeficiency virus (HIV) infection  | 6/06             |

is violated, as for example, by perforation of the gastrointestinal tract through trauma, surgery, peptic ulceration, or by mucosal damage due to cytotoxic drug therapy used for treating cancer. Although *Candida* is not a normal resident of the skin, secretions from the mouth, rectum, or vagina, as well as drainage from surgical wounds or tracheostomy sites, can contaminate the hub or skin site of a catheter in an umbilical or central vein. Intravenous drug abuse or third-degree burns are other conditions that can lead to deep candidiasis.

Esophageal candidiasis is one of the most common deep-seated candidal infections and is often asymptomatic. Other times, it can cause substernal pain or a sense of obstruction on swallowing, and may be mistaken for cardiac pain. Most lesions occur in the distal third of the esophagus. Esophageal candidiasis can cause bleeding and impaired gastrointestinal function. It is often associated with significant morbidity, but is seldom fatal.

Invasive fungal infections constitute one of the most important causes of morbidity and mortality in immunocompromised patients and hematopoietic stem cell transplantation recipients. Over the past 25 years, the incidence of invasive fungal infections has increased markedly, as much as 25 percent in hematopoietic stem cell transplantation recipients, and up to 50 percent in HIV-infected persons. *C. albicans* and *Aspergillus* species account for the majority of cases.

### **Eraxis** (anidulafungin)

Historically, the mainstay for management of invasive fungal infections has been amphotericin B. A broad-spectrum antifungal with potent fungicidal activity, amphotericin B is characterized by a notorious toxicity profile. A search, therefore, has been underway for effective but less toxic antifungals. The azole derivatives, itraconazole and fluconazole, were introduced in

the 1980s; however, their use, despite widespread acceptance, has been limited by their narrow spectra of activity and increasing concern regarding the emergence of azole-resistant *Candida* species. More recently, drug development has focused on a new class of antifungals, the echinocandins ("candins"), which currently includes caspofungin (Cancidas) and micafungin (Mycamine), and now, anidulafungin, a semisynthetic cyclic lipopeptide. The echinocandin antifungals have shown clinical efficacy and a more favorable adverse-event profile compared to older antifungal agents.

**Mechanism of Action/Microbiology.** Anidulafungin is a non-competitive inhibitor of 1,3- $\beta$ -D-glucan synthase, a fungus-specific enzyme complex that is required for synthesis of 1,3- $\beta$ -D-glucan, an essential component of fungal, but not mammalian, cell walls. The fungal cell wall provides shape and stability and serves as a protective barrier against injury and osmotic instability, conditions that can lead to cell lysis and fungal cell death. It also possesses adhesive molecules that permit the fungus to attach to and invade the host. Glucan is critical to fungal cell walls, and comprises 30 to 60 percent of *Candida* cell walls. When 1,3- $\beta$ -D-glucan synthase is inhibited, the fungal cell forms a wall deficient in 1,3- $\beta$ -D-glucan. As a result, the integrity of the cell wall is compromised and cells can become irregularly shaped and swollen. Mature cells also often fail to separate from the parent cells, and instead form aberrant buds. Anidulafungin exhibits *in vitro* activity against *C. albicans*, *C. glabrata*, *C. parapsilosis*, and *C. tropicalis*, including strains resistant to fluconazole; *Aspergillus*; and *Pneumocystis*. Emergence of resistance to anidulafungin has not been studied; it remains active against *C. albicans* that is resistant to fluconazole. Cross-resistance with other echinocandins has not been substantiated to date.

**Adverse Effects and Warnings.** Histamine-mediated symptoms have been reported with Eraxis, including rash, urticaria, flushing, pruritus, dyspnea, and hypotension. These events are rare when the rate of infusion does not exceed 1.1 mg/min.

Drug safety was assessed in 929 individuals. A total of 633 patients received Eraxis at daily doses of either 50 or 100 mg. Four hundred eighty-one patients received Eraxis for  $\geq 14$  days. Adverse events reported in  $\geq 2$  percent of subjects included diarrhea; increased ALT, AST, alkaline phosphatases and hepatic enzyme levels; hypokalemia; and deep vein thrombosis.

### **Drug Interactions.**

Anidulafungin has a unique mechanism of elimination. It is eliminated by slow chemical degradation (90 percent of a dose) with less than 10 percent eliminated as intact drug in the feces. Thus, it is not significantly metabolized by human cytochrome P450 or by isolated human hepatocytes, and does not significantly inhibit the activities of clinically important human CYP isoforms (1A2, 2C9, 2D6, 3A4). It is only moderately bound to plasma proteins. No clinically relevant interactions have been reported with drugs likely to be co-administered with anidulafungin.

**Indications and Uses.** Eraxis is indicated for use in the treatment of the following fungal infections: esophageal candidiasis, and candidemia and other forms of *Candida* infections (intra-abdominal abscess, and peritonitis). The drug has not been studied in endocarditis, osteomyelitis, and meningitis due to *Candida*, and has not been studied in sufficient numbers of neutropenic patients to assess its efficacy in this group. Specimens for fungal culture and other laboratory studies should be obtained prior to therapy. Therapy may be initiated before the results of the cultures and other laboratory studies are known. Once these results become available, antifungal therapy should be adjusted accordingly.

**Dosage, Administration, and Availability.** Like other echinocandins, anidulafungin is administered by intravenous infusion. The recommended dose for candidemia and other *Candida* infections (intra-abdominal abscess, and peritonitis) is 200 mg on Day 1, followed by 100 mg daily thereafter. Duration of treatment should be based on the patient's clinical response; usually, antifungal therapy should continue for at least 14 days after the last positive culture. The recommended dose for esophageal candidiasis is a single 100 mg loading dose on Day 1, followed by 50 mg daily thereafter. The rate of infusion should not exceed 1.1 mg/min. Eraxis should be continued for a minimum of 14 days, and for at least seven days following resolution of symptoms. Because of the risk of relapse of esophageal candidiasis in patients with HIV infections, suppressive antifungal therapy may be considered after a course of active treatment. No dosing adjustments are required for patients with renal or hepatic insufficiency or persons with HIV infection, patients using concomitant medications, or those in other special populations.

Eraxis is supplied in single-use vials containing 50 mg of anidulafungin.

## HIV

The human immunodeficiency virus (HIV) has been the focus of in-depth scientific inquiry since its identification two decades ago as the causative agent for acquired immune deficiency syndrome (AIDS). HIV, in fact, is the most widely studied virus in history. The incidence of AIDS in the U.S. increased rapidly from its onset, peaked in the early 1990s, and then declined somewhat beginning in the mid-1990s. Today, the number of persons in the U.S. living with HIV is increasing, partly due to longer lifespan resulting from effective drug therapy and improved lifestyles. Nonetheless, AIDS results in more than 15,000 deaths each

year in the U.S. with more than 2.8 million deaths each year worldwide.

**Epidemiology.** HIV is transmitted primarily by behaviors that encourage exchange of blood or body fluids containing the virus and/or HIV infected cells. The virus has been identified in blood and blood products, semen, vaginal secretions, breast milk, tears, urine, cerebrospinal fluid, and saliva; however, only HIV in blood, semen, breast milk, and vaginal fluids is a serious source of infection.

Transmission via sexual contact depends on the type and frequency of encounters, and presence of risk factors such as unprotected sex. The greatest risk for HIV transmission is associated with blood transfusion, needle sharing by illicit drug addicts, anal intercourse, and percutaneous needlestick injuries.

**Immune Defects.** The hallmark of AIDS is a deficiency within the immune system that leads to increased susceptibility to fatal opportunistic infections. This occurs because the virus invades and destroys CD4<sup>+</sup> lymphocytes (i.e., T-helper cells), its primary target. CD4<sup>+</sup> T-lymphocytes normally assist B cells in producing antibodies, stimulate T-cytotoxic cells (CD8<sup>+</sup>) to lyse virus-infected cells and tumor cells, and activate the body's macrophages to eliminate intracellular pathogens. Inactivation and/or destruction of CD4<sup>+</sup> T-lymphocytes compromise cell-mediated and humoral-immunity mechanisms, which in turn increase susceptibility to opportunistic pathogens.

**Antiretroviral Therapy.** Treatment of HIV infection improved with the advent of combination antiretroviral drug therapy in 1996. More than 20 newer drugs that are indicated specifically for the treatment of HIV infection have been developed since the original drug, zidovudine, was first introduced into clinical medicine. Many of the newer antiretroviral therapies offer added dosing convenience and improved safety profiles.

Antiretroviral therapy has resulted in improved quality of life,

with substantial decreases in premature mortality. The drugs still do not cure HIV infection or eliminate the syndrome of events associated with the disease, primarily because the pool of latently infected CD4<sup>+</sup> T cells is established in the earliest stages of acute HIV infection, and these events persist even with prolonged suppression of plasma concentrations of virus.

**Protease Inhibitors.** Since the introduction of saquinavir in 1995, protease inhibitors, used in combination with other anti-retrovirals, have resulted in significant reductions in morbidity and mortality in patients with advanced HIV infection. The protease inhibitor drugs share many characteristics that favor them as components of highly active antiretroviral therapy (HAART), such as the ability to reduce the viral load within a few days after beginning treatment. Their advantages, however, must be balanced against several disadvantages such as a large number of drug interactions, requirement for multiple daily dosing with high pill burdens, and dietary restrictions that often lead to drug nonadherence. Cross-resistance with other protease inhibitors has been observed. Protease inhibitors are also associated with numerous adverse reactions that often limit treatment. These include gastrointestinal disturbances (common to all members of the class), lipid abnormalities, glucose intolerance, insulin resistance and type 2 diabetes, body fat abnormalities, hepatotoxicity, and bone demineralization.

## Prezista (darunavir)

With these advantages and disadvantages for protease inhibitors noted, the newest antiretroviral drug, darunavir, was approved, to be taken concurrently with ritonavir (Norvir). Ritonavir inhibits hepatic cytochrome P450 (CYP3A) enzymes, the intestinal P-glycoprotein efflux pump, and possibly intestinal CYP3A, such

that there is a significant increase in blood levels of darunavir when co-administered with ritonavir, compared with darunavir administered without ritonavir.

**Mechanism of Action/Microbiology.** The HIV enzyme *protease* is required for viral infectivity. It cleaves the viral (Gag-Pol) polyproteins into active viral enzymes (reverse transcriptase, protease, and integrase) and structural proteins. All protease inhibitors, including darunavir, bind reversibly to the active site of HIV-1 and HIV-2 protease to prevent it from cleaving the viral precursor polyproteins, and thereby block subsequent viral maturation. Infected cells that are subjected to a protease inhibitor produce viral particles that are immature and noninfectious; therefore, HIV infectivity is checked.

**Adverse Effects and Warnings.** The most common adverse events reported in >10% of subjects in premarketing clinical trials, were diarrhea, nausea, headache, and nasopharyngitis. Due to the need for co-administration of Prezista with 100 mg of ritonavir, the ritonavir prescribing information should be consulted for ritonavir-associated adverse reactions. Because it contains a sulfur moiety, Prezista should not be taken by patients allergic to sulfonamide-derivative drugs.

**Drug Interactions.** Prezista and ritonavir both inhibit CYP3A. Co-administration of Prezista and ritonavir with drugs that are primarily metabolized by CYP3A may, therefore, result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events. The product information leaflet (package insert) should be consulted for the extensive list of interactive drugs.

Co-administration of Prezista is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-

threatening events (i.e., drugs with a narrow therapeutic index). These drugs include dihydroergotamine, ergonovine, ergotamine, methylergonovine, pimozide, midazolam, and triazo-lam. The manufacturer also warns against taking St. John's Wort. The statement to patients and health care professionals: "*Find out about medicines that should not be taken with Prezista*" is included on the product's label.

**Indications and Uses.** Prezista, co-administered with 100 mg ritonavir, and with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus infection in antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor.

**Dosage, Administration, and Availability.** The recommended dose of Prezista is 600 mg (two 300 mg tablets) twice daily along with ritonavir 100 mg twice daily and with food. The tablets should be swallowed whole with liquid such as water or milk and not be crushed or chewed.

There are no data regarding the use of Prezista in patients with varying degrees of hepatic impairment; therefore, specific dosage recommendations cannot be made. No dose adjustment is required in patients with moderate renal impairment. There are no pharmacokinetic data available in HIV-1 infected patients with severe renal impairment or end stage renal disease. When administered with food, the  $C_{max}$  and AUC of darunavir, co-administered with ritonavir, are approximately 30 percent higher relative to the fasting state. Therefore, Prezista tablets should always be taken with food. The type of food does not affect exposure to the "drug."

Prezista tablets are available as oval-shaped, film-coated tablets containing darunavir ethanolate equivalent to 300 mg of darunavir per tablet. Prior to opening the bottle, Prezista should be stored in a

refrigerator. After opening, the tablets may be stored at room temperature but must be used within 60 days.

**Note.** FDA has initiated the "compassionate" new drug approval process that allows adding a new drug to the existing therapy of HIV patients to see if there is any improvement. After safety of the newer drug has been established, it can be marketed with stipulations. Prezista is approved for the treatment of HIV in treatment-experienced adults who do not respond to other antiretroviral drugs. Another stipulation is that its manufacturer is required to conduct several post-marketing trials to verify and describe the clinical benefits of Prezista. The same is true for other manufacturers of new antiretroviral drugs.

Another important reason for accelerated approval of new antiretroviral drugs such as Prezista is that it is now known that treatment with only one drug will quickly result in viral resistance and treatment failure. Currently, the treatment of choice is to use two, three, or more antiretroviral drugs that have different pharmacologic actions, for reasons mentioned earlier. In fact, four two-drug combinations and one three-drug combination product have already been approved and more are on the way.