DRUG UTILIZATION R•E•V•I•E•W™

Pharmaceutical Care Across the Continuum

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IN THIS ISSUE

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Bush renews call for Medicare prescription drug card

Medication costs must be covered, pharmacy group says

The Bush administration may have failed in two attempts to offer a prescription drug discount plan, but that won't stop it from trying again.

In an address on March 4 to an American Medical Association conference, President Bush outlined his budgetary plan for Medicare reform. Included in his plan is the administration's newest proposal for Medicare prescription drug coverage.

Bush says his framework for Medicare reform gives seniors three choices:

• **Stay with the current Medicare system and receive help for prescription drugs.** Bush proposes that the government issue a discount card that would reduce the cost of prescription drugs for every senior by 10-25%. Medicare also would provide an annual $600 subsidy to low-income seniors to pay for prescription drugs, plus it would set annual limits on the amount seniors would have to spend out of pocket on drugs at no additional premium.

• **Choose an enhanced form of Medicare.** This option would include full coverage for preventive care, a comprehensive prescription drug benefit, protection against high out-of-pocket costs, and extra help for low-income seniors. Seniors would be able to choose their specialists, hospitals, and primary doctors.

The fee-for-service arrangement would offer seniors choices similar to those now enjoyed by members of Congress, who are given a broad choice among competing health care plans, Bush says.

• **Choose benefits available in managed care plans, including prescription drug coverage.** This option would place seniors in a network of doctors and would provide drug coverage.

As the program is being implemented, Bush suggests that all American seniors should receive a prescription drug discount card to use right away. In addition, low-income seniors would be eligible immediately for the annual $600 Medicare prescription benefit. Bush

has included $400 billion over 10 years in his budget to fund the proposal.

Pharmacists respond

One pharmacy advocacy group found it encouraging that the president seems committed to adding prescription drug coverage to Medicare. The American Pharmacists Association (APhA) in Washington, DC, however, is more cautious about the discount card portion of the proposal. "APhA opposes poorly designed discount card programs that fail to provide a true benefit for seniors," the association says.

A rational approach is to provide Americans access to the medications they need as well as pharmacy services to help them make the best use of their medications, says **John A. Gans**, PharmD, APhA executive vice president. "Something is wrong when we pay to diagnose a senior's condition, but then we don't cover the treatment he or she needs."

APhA has developed four principles for a high-quality Medicare pharmacy benefit:

- coverage of prescription medication costs — not just discounts;
- patient access to pharmacist-provided medication therapy management services;
- patient choice of providers;
- administrative efficiencies to ease patients' and providers' paperwork burden.

APhA, along with other pharmacy groups, plans to continue to work with the administration and Congress on a possible Medicare prescription drug benefit. ■

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Final HIPAA security standards released

HHS repeals National Drug Code as standard

The final security standards and transaction modifications for electronic health information are here at last. And non-retail pharmacies should be happy to hear that the U.S. Department of Health and Human Services (HHS) has repealed the National Drug Code (NDC) as the standard medical data code set for reporting drugs and biologics in all non-retail pharmacy transactions.

On Feb. 13, HHS announced the adoption of final security standards for protecting individually identifiable health information when it is maintained or transmitted electronically. At the same time, HHS announced the adoption of modifications to a number of the electronic transactions and code sets adopted as national standards. Both final regulations are required as part of the administrative simplification provisions contained in the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

The security standards were published in the Feb. 20 *Federal Register* and have an effective date of April 21, 2003. Most covered entities will have two years to comply with the standards; small health plans will have an additional year to comply, as HIPAA stipulates.

Many health care providers, however, fear that the delays in the publication of the final HIPAA privacy rule (effective for most covered entities on April 14) and the security standards will make

it more difficult for providers to become compliant by the deadline.

Under the security standards, health insurers, certain health care providers, and health care clearinghouses must establish procedures and mechanisms to protect the confidentiality, integrity, and availability of electronic protected health information. The rule requires covered entities to implement administrative, physical, and technical safeguards to protect electronic protected health information in their care.

The security standards are related closely to the final privacy standards. The two sets of standards use many of the same terms and definitions to make it easier for covered entities to comply.

In modifying the proposed transaction rule, HHS says it worked extensively with the Designated Standards Maintenance Organizations. By law, health plans, certain health care providers, and health care clearinghouses must use the final transaction standards for electronic health care transactions. Covered entities must comply with these modified transaction standards by Oct. 16, 2003.

Non-retail pharmacy settings will remain pretty much business as usual since HHS repealed the NDC standard in the final rule, says **Lynne Gilbertson**, director of standards development for National Council for Prescription Drug Programs in Scottsdale, AZ.

In the rule, HHS says it is aware that "retaining the NDC as the sole standard for institutional claims would pose significant operational issues for institutional pharmacies because of systems incompatibility among pharmacies, inpatient medical records, and inpatient accounting systems."

The NDC formats do not provide information related to actual dosages administered or provide a methodology for multiple billing increments, HHS says. "Attempts by the industry to develop a complete crosswalk from the current HCPCS [Healthcare Common Procedure Coding System] codes to the NDC have been unsuccessful."

HHS wanted to give covered entities the full range of choices in determining which code set to use with respect to claims. However, the rule does caution non-retail pharmacies about using "local codes," Gilbertson says. In the rules, HHS says covered entities that use HCPCS should use the established process for requesting new codes, rather than supplementing the code sets with locally developed ones. ■

Make an impact on the public's health

Pharmacists can treat patients collectively, too

Pharmacists are experts at dispensing the correct drug in the correct dosage to the correct patient. Two pharmacists, however, suggest that the profession can do a better job of considering the public, collectively, as a patient.

The profession can make a "gigantic impact on the public's health if pharmacists simply unite to focus their efforts on tackling problems," say **RADM John Babb**, RPh, MPA, and **Victoria J. Babb**, PharmD, in the article "Filling a prescription for the public's health," which was published in the January/February 2003 issue of the *Journal of the American Pharmaceutical Association* (available at www.aphanet.org/JAPhA/janfeb03pdfs/Babb(56-60).pdf).

RADM John Babb is director of the Commissioned Corps Readiness Force, Office of Emergency Response, Office of the Assistant Secretary for Public Health Emergency Preparedness, Rockville, MD. Victoria J. Babb is special assistant for counterterrorism, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, Rockville, MD.

In their article, the authors give several examples of ways pharmacists can treat the public's health. For example, many pharmacists didn't advise patients of the risks of troglitazone (Rezulin) after warnings were issued that the drug was hepatotoxic; patients continued to receive refills without additional information about the drug. Pharmacists also can play a primary role in reporting adverse drug events (ADEs) and combating drug resistance, the authors say.

A talk with RADM Babb

Drug Utilization Review recently spoke with RADM Babb about his motivation to write the article. Here is what he said:

Q: What prompted you to write the article?

A: A variety of things:

- my own observations that many pharmacists spend too little time talking to patients about their medication;
- too much of a tendency [of pharmacists] to

retreat behind the sign on the counter that reads, "If you have questions about your medication, please ask to speak to the pharmacist";

• too much focus on the mechanics of pharmacy vs. the art of pharmacy;

• a hesitancy to call physicians about prescriptions;

• too little information about the patient (such as labs, indication for the prescription, medical history, concomitant conditions, and other medications);

• a reliance on the physician to know what's best.

Q: Is this issue more urgent with community pharmacies than with health system pharmacies?

A: When you reflect on the huge amount of money spent on medication misadventures in this country . . . much of that money is related to what happens in hospitals and nursing homes.

Progressive hospitals put pharmacists on the floors with patients, talking to them, reviewing labs, and reading medical charts. Some recent studies have proven that pharmacists assigned to intensive care units actually decrease medication errors and costs. Other hospitals certainly have experienced their own share of ADEs — extended hospital stays due to drug problems, damaged patients, and deaths. So the problem is not confined to one group of organizations. In fact, since hospitalized patients usually are receiving more intensive medication regimens than other patients, the chance of drug problems occurring is significantly higher.

However, the most significant opportunities to talk to patients are in community pharmacies. [Per the article], that's where the majority of all those troglitazone prescriptions were being filled and refilled. That's where patients needed to speak to a pharmacist, and perhaps needed the intervention of a pharmacist. That's where millions of prescriptions are refilled every day; yet in many pharmacies, no one asks the patient, "What problems are you having with your medication?" Prescriptions continue to be refilled, and problems (which may seem unrelated to their medication as far as the patient can tell) are not addressed and can be exacerbated.

Q: What do you think takes away the opportunity for pharmacists to spend more time educating their patients?

A: Again, a long list:

• insufficient staffing;

• too little time to perform the necessary mechanics, let alone the art;

• hesitancy to question the prescriber;

• hesitancy to get into a potentially long, drawn-out discussion with a patient;

• patient unwillingness to spend any extra time in the pharmacy to thoroughly discuss their medication management;

• patient unwillingness to discuss what may be a "personal" situation outside the physician's office (i.e., exacerbation of benign prostatic hyperplasia while taking a decongestant, blood in the stool while taking nonsteroidal anti-inflammatory drugs, etc.);

• worst of all, some pharmacists do not feel comfortable with their knowledge about many drugs;

• and of course, some employers focus on quantity rather than quality, thus putting pressure on pharmacists to spend less time with patients.

Q: You mention the importance of paying attention to the Dear Healthcare Professional letters and Public Health Advisories. Why do pharmacists not always take these communications as seriously as they should?

A: I'm not sure why these letters and advisories are not taken more seriously. Perhaps there is the feeling that the physician will address the situation. Perhaps pharmacists are numbed by the numbers of warnings they see every day on their pharmacy computer system. At what point are warnings to be taken to heart and emphasized to the patient — or worse, to the physician? Pharmacists are inundated with warnings, so perhaps we miss the ones that are potentially life-changing or deadly. I'm not sure why we don't simply say to the patient, "Did your doctor have an opportunity to discuss this letter with you regarding drug XYZ?" Perhaps the prospect of a lengthy conversation or phone call with the physician is perceived as not productive.

Q: Do you recommend some kind of alert system in the pharmacy computer?

A: It certainly would be helpful to have a new or refilled prescription flagged automatically so that you can click on a recent letter or advisory, and then share the information with the patient if necessary. That way you would not have to rely on your memory for every warning letter, and you would have documentation at hand if questioned by the prescriber. One of the initiatives of

the Department of Health and Human Services is to find ways for innovations in information technology to improve patient care and patient outcomes. This sounds like an opportunity to make improvements.

Q: How do most pharmacists get information about ADEs?

A: While many patients are now sophisticated enough to read and understand the drug information sheets handed to them or access information on the Internet about their drug therapy, many more lack that level of understanding. How do joggers figure out by themselves that the ankle pain they are experiencing is a strong warning sign that they should see their doctor immediately if they are taking ciprofloxacin for an upper respiratory infection? What patients would expect that last night's fainting spell might be related to the clarithromycin medication they recently added to their ongoing Hismanal therapy — or that it could be symptomatic of a life-threatening side effect?

I submit that pharmacists have a role to play in 1) preventing ADEs from happening in the first place, 2) giving patients information about potential, significant ADEs, and 3) talking to patients about new problems they are experiencing. ■

Warfarin prevents recurrence of blood clots

Study shows no evidence of significant risks

A study of long-term, low-dose warfarin (Coumadin) in the prevention of blood-clotting disorders showed such promise that the National Institutes of Health, the trial's sponsor, stopped the study early.

The multi-center Prevention of Recurrent Venous Thromboembolism (PREVENT) trial found a 64% reduction in episodes of deep vein thrombosis (DVT) and pulmonary embolism in study participants taking low-dose warfarin compared to those taking a placebo. In addition, there was no evidence of significant risks such as major hemorrhage or other potential side effects of warfarin.

Until now, the current standard treatment for DVT and pulmonary embolism not associated with surgery or another specific cause is five to 10 days of intravenous or subcutaneous heparin followed by three to six months of full-dose warfarin, with a target international normalized ratio (INR) between 2.0 and 3.0. Therapy typically stops after the initial treatment period because long-term use of full-dose warfarin is associated with a substantial risk of major bleeding.

In the PREVENT trial, 508 patients with idiopathic venous thromboembolism who had received full-dose anticoagulation therapy for a median of 6.5 months were randomly assigned to placebo or low-intensity warfarin (target INR, 1.5-2.0). Participants were followed for an average of about two years for recurrent venous thromboembolism, major hemorrhage, and death.

Of 253 patients assigned to placebo, 37 had recurrent venous thromboembolism, as compared with 14 of 255 patients assigned to low-intensity warfarin, a risk reduction of 64%. Major hemorrhage occurred in two patients assigned to placebo and five assigned to low-intensity warfarin. Eight patients in the placebo group and four in the group assigned to low-intensity warfarin died. An analysis that combined the numbers of recurrent blood clots/cases of pulmonary embolism with the number of hemorrhages and deaths found a 48% reduction in risk for patients assigned to warfarin.

"The PREVENT results strongly suggest that long-term use of low-intensity warfarin should be considered a new standard of care for the management of venous thrombosis after stopping full-dose warfarin therapy," says **Paul Ridker**, MD, the principal investigator of PREVENT, professor of medicine at Harvard University in Cambridge, MA, and director of the Center for Cardiovascular Disease Prevention at Brigham and Women's Hospital in Boston.

The study gives a new use for a 50-year-old drug, Ridker says. In addition, warfarin is inexpensive and is available in generic form.

The study will appear in the April 10, 2003, issue of *The New England Journal of Medicine* (*NEJM*). *NEJM*, however, posted the results on its web site on Feb. 24 because of their importance.

In an accompanying editorial in *NEJM*, **Andrew I. Schafer**, MD, professor and chairman of the Department of Medicine of the University of Pennsylvania School of Medicine in Philadelphia, agrees that based on these data, it is reasonable for clinicians, "at least for now," to adopt this regimen. He notes that the recommendations may change with new research or as new drugs become available. ■

NEWS BRIEFS

HHS proposes smallpox vaccination compensation

The Department of Health and Human Services (HHS) has proposed a plan to create a smallpox vaccination compensation program to provide benefits to public health and medical response team members who are injured as a result of receiving the smallpox vaccine. This plan is in response to public health and medical response teams being vaccinated voluntarily against smallpox as part of an overall effort to better prepare the nation against terrorism.

The proposed compensation program includes elements similar to the benefits package currently available to police officers and firefighters. Under the Public Safety Officers Benefit program administered by the U.S. Department of Justice, the federal government currently pays a $262,100 death benefit and a $262,100 permanent and total disability benefit to police officers and firefighters. State and local governments provide short-term disability benefits and health care benefits.

The benefits package would be administered by HHS and would be retroactive to cover those who already have been vaccinated under the program. Besides the permanent and total disability benefit and the death benefit, the plan offers these two elements:

• **Temporary or partial disability benefit.** HHS would compensate individuals for two-thirds of lost wages after the fifth day away from work, up to a maximum of $50,000. This benefit would be secondary to any workers' compensation or disability insurance benefits that might be available to the individual.

• **Health care benefit.** HHS would compensate individuals for their reasonable out-of-pocket medical expenses for other than minor injuries. This benefit would be secondary to any health insurance benefit that might be available to the individual.

In addition, HHS would provide compensation to third parties who contract vaccinia from public health and medical response team workers who have been vaccinated.

In other smallpox news, the Centers for Disease Control and Prevention (CDC) in Atlanta reports that all states have submitted smallpox response plans, and smallpox vaccine was administered to 12,690 civilian health care and public health workers in 45 jurisdictions between Jan. 24 and Feb. 28. In February, the Department of Defense reported that two soldiers had experienced severe adverse reactions to the vaccine; both are now doing well. The CDC also emphasized the importance of proper vaccine site care after two women experienced probable cases of ocular vaccinia after they were exposed to the vaccination sites of military personnel. ▼

Counterfeit epoetin alfa presents hazard to patients

The U.S. Food and Drug Administration's (FDA's) Office of Criminal Investigation has uncovered the existence of contaminated counterfeit epoetin alfa (Procrit). Epoetin alfa is used to stimulate the production of red blood cells in humans to treat severe anemia.

As a result of investigative review and laboratory testing performed by the FDA, and in cooperation with Ortho Biotech Products, LP, Bridgewater, NJ, health care providers and consumers are being alerted to the existence of three lots of counterfeit product labeled as Procrit:

• P007645 — 40,000 units/mL, Expiration 10-2004
• P004677 — 40,000 units/mL, Expiration 02-2004
• P004839 — 40,000 units/mL, Expiration 02-2004

Ortho is issuing the warning to health care providers and others in a letter (also posted on its web site: www.orthobiotech.com/counterfeit/letter.html) because counterfeit epoetin alfa has been found to be contaminated with bacteria and therefore represents a significant potential hazard to consumers. In addition, FDA testing has demonstrated that some counterfeit product contains no active ingredient.

The FDA urges both health care providers and patients to check the packaging and vials very carefully before using this product. Anyone finding counterfeit product should not use it, should

quarantine it, and should immediately contact FDA's Center for Biologics Evaluation and Research at (800) 835-4709, prompt #1, then prompt #5; and Ortho Biotech at (800) 325-7504, prompt #2.

More details concerning the counterfeit product are available on Ortho's web site at www.procrit.com/counterfeit/letter.html.

The FDA's investigation into this matter is continuing. ▼

Adverse events associated with sirolimus (Rapamune)

Wyeth has received post-marketing reports of bronchial anastomotic dehiscence, including fatal cases, in patients treated with sirolimus in combination with tacrolimus and corticosteroids.

Two centers have reported this serious adverse event in lung transplant recipients in whom this immunosuppressive regimen was initiated at the time of transplantation. At one center, four of 15 patients enrolled in an investigator-sponsored study developed bronchial anastomotic dehiscence; a fatal outcome was identified in three of these four patients. Further information regarding these patients will be published in *Transplantation* in 2003. The second center reported two cases of bronchial anastomotic dehiscence, one of which was fatal.

In its "Dear Health Care Provider" letter, Wyeth states that "the safety and efficacy of Rapamune as immunosuppressive therapy has not been established in lung transplant patients, and, therefore, such use is not recommended." The prescribing information for sirolimus has been updated to include new information in the boxed warnings section.

To read the MedWatch 2003 safety summary, including a link to the "Dear Healthcare Professional" letter, go to: www.fda.gov/medwatch/SAFETY/2003/safety03.htm#rapamu. ▼

FDA proposes standards for dietary supplements

The U.S. Food and Drug Administration (FDA) has proposed a new regulation to require current good manufacturing practices (CGMPs) in dietary supplements' manufacturing, packing, and holding. The proposed rule would establish standards to ensure that dietary supplements and dietary ingredients are not adulterated with contaminants or impurities and are labeled to reflect the active ingredients and other ingredients in the product.

This proposed rule includes requirements for designing and constructing physical plants, establishing quality control procedures, and testing manufactured dietary ingredients and dietary supplements. It also includes proposed requirements for maintaining records and for handling consumer complaints related to CGMPs.

This proposal is intended to cover all types of dietary supplements. However, to limit any disruption for dietary supplements produced by small businesses, the FDA is proposing a three-year phase-in of a final rule for small businesses. The proposal includes flexible standards that can evolve with improvements in the state of science, such as validating tests for identity, purity, quality, strength, and composition of dietary ingredients. ▼

APhA releases patient, pharmacist publications

The American Pharmacists Association (APhA) in Washington, DC, recently released several publications that are of benefit to patients and pharmacists. They include:

• **2003 series of Patient Education Brochures.** These newly designed brochures provide consumer-friendly information on important health

COMING IN FUTURE MONTHS

- FDA requires bar coding on medications
- Guidelines for lung cancer treatment
- A look at new technology
- Efforts to combat antibiotic resistance
- The impact of pharmacy on larger clinical trial sizes

topics and help patients understand their medications. For more information, call APhA at (202) 429-7537.

• ***Allen's Compounded Formulations: The Complete U.S. Pharmacist Collection.*** This publication is a collection of the monthly column, "Contemporary Compounding," from the national pharmacy journal *U.S. Pharmacist*. The 168 preparations presented in the collection span the 15-year existence (1988-2002) of the column. Written by Lloyd V. Allen, Jr., PhD, RPh, the collection includes basic formulas that provide for some uniformity of preparation as well as a starting point for further modification for specific patients. For more information, call (800) 878-0729.

• ***Pharmacist Disease Management Credentialing: Diabetes, 2nd ed.*** This review book is designed to help pharmacists who are preparing for the National Institute for Standards in Pharmacist Credentialing Disease State Management Examination. Consisting of three self-study modules, the book will help pharmacists integrate diabetes education and management into their practice and become comfortable with their role in the care of patients with diabetes. For more information, call (800) 878-0729. ■

New FDA Approvals

The U.S. Food and Drug Administration (FDA) recently approved the following drug:

• *Pyridostigmine bromide by the U.S. Army Medical Research and Materiel Command.*

The FDA has approved pyridostigmine bromide to increase survival after **Soman "nerve gas" poisoning**, which causes loss of muscle control and death from respiratory failure. The product is approved for combat use by United States military personnel.

Pyridostigmine bromide is the first drug approved under an FDA rule that allows use of animal data for evidence of the drug's effectiveness for certain conditions when the drug cannot be ethically or feasibly tested in humans. Evidence of the effectiveness of pyridostigmine bromide as a pretreatment for exposure to Soman was obtained primarily from studies in monkeys and guinea pigs.

A leaflet that explains the drug's uses, benefits, and side effects will be provided to military personnel when the drug is distributed. The leaflet advises that pyridostigmine bromide should not be used by persons who have a history of bowel or bladder obstruction or sensitivity to certain medicines used during surgery (like physostigmine). Side effects that may occur include stomach cramps, diarrhea, nausea, frequent urination, headaches, dizziness, shortness of breath, worsening of peptic ulcer, blurred vision, and watery eyes.

The approved dose of pyridostigmine bromide for Soman pretreatment is one 30 mg tablet every 8 hours. The leaflet states that pyridostigmine should be started at least several hours before exposure to Soman and emphasizes that it must be discontinued upon exposure to nerve gas, at which point the antidotes atropine and pralidoxime are given. ■

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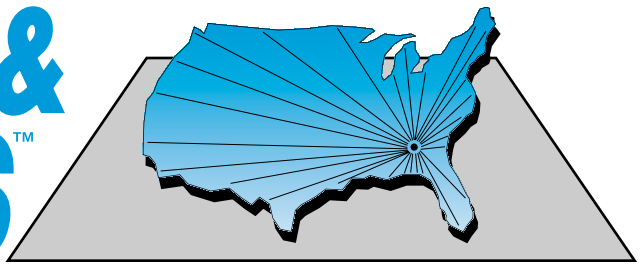

Voriconazole formulary evaluation

By **Stacey Breeding**, PharmD candidate
Samford University
Birmingham, AL

Voriconazole is a new broad-spectrum triazole antifungal. Other drugs in the triazole class are fluconazole and itraconazole.

Mechanism of action

Voriconazole acts primarily by inhibiting the fungal cytochrome P-450-dependent enzyme 14-alpha-sterol demethylase. This is an essential step in the ergosterol biosynthesis pathway that is necessary for the production of a functional cell wall and sustained growth of the fungi.

Pharmacokinetics

General. Voriconazole displays non-linear pharmacokinetics due to the saturation of its metabolism. Increasing the dose correlates with disproportionate rises in plasma concentrations.

Recommended loading-dose schedules reach steady-state concentrations at 24 hours. Without a loading dose, voriconazole concentrations do not reach steady state until day six of the twice-daily dosing regimen.

Absorption. The intravenous-to-oral dosing bioavailability is approximately 96%. Maximum plasma concentrations can be achieved one to two hours after administration.

Distribution. The volume of distribution for voriconazole at steady-state concentration is 4.6 L/kg. Protein binding is independent of plasma concentrations and estimated to be 58%.

Metabolism. Voriconazole is significantly metabolized by the human hepatic cytochrome P-450 enzyme CYP2C19, which exhibits genetic polymorphism. The enzymes CYP2C9 and CYP3A4 also are involved in the drug's metabolism. The major metabolite, an N-oxide derivative, has minimal antifungal activity.

Elimination. Due to extensive hepatic metabolism, less than 2% of the dose is excreted unchanged in the urine.

The half-life of voriconazole is dose-dependent and cannot be used to predict the accumulation or elimination of the drug.

Indications. Voriconazole is indicated for use in the treatment of invasive aspergillosis. It also is indicated for the treatment of serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* spp., including *F. solani*, in patients intolerant of or refractory to other therapy.

Dosage

Intravenous (IV) voriconazole should be administered with a loading dose of 6 mg/kg every 12 hours for two doses, followed by a maintenance dose of 4 mg/kg every 12 hours. If patients are intolerant of treatment, the maintenance dose may be reduced to 3 mg/kg. The intravenous dose should be given over one to two hours and should not exceed 3 mg/kg per hour.

Due to the drug's 96% bioavailability, switching from IV to PO therapy is appropriate when clinically indicated.

If initiated as oral therapy, a loading dose of 400 mg every 12 hours should be given on day one. The oral maintenance dose of voriconazole is 200 mg every 12 hours for patients who weigh more than 40 kg. For patients who weigh less than 40 kg, a maintenance dose of 100 mg every 12 hours should be given. If a patient experiences an inadequate response, increase the 200 mg every 12 hours dosage to 300 mg every 12 hours, and increase the 100 mg every 12 hours dosage to 150 mg every 12 hours. If patients are unable to tolerate therapy, reduce the dose in 50 mg increments to 200 mg every 12 hours or 100 mg every 12 hours for patients who weigh less than 40 kg.

Table 1: Clinical endpoints of voriconazole vs. fluconazole

	Esophagoscopy EOT **Primary endpoint**		Symptoms EOT **Secondary endpoint**	
	Voriconazole	Fluconazole	Voriconazole	Fluconazole
Category	n = 115	n = 141	n = 200	n = 191
Cure	109 (94.8)	127 (90.1)	164 (82.0)	159 (83.2)
Improvement	4 (3.5)	7 (5.0)	12 (6.0)	15 (7.9)
Failure	2 (1.7)	7 (5.0)	12 (6.0)	12 (6.3)
Can't evaluate	NA	NA	12 (6.0)	5 (2.6)

Note: Data are number (%) of patients; EOT = end of treatment; and NA = not applicable

The dosing of voriconazole is equivalent for all indications.

Voriconazole tablets should be taken at least one hour before or one hour after meals. When multiple doses of voriconazole are administered with high-fat meals, the mean C_{max} and area under the curve are reduced by 34% and 24%, respectively.

Clinical studies

Treatment of candidiasis. Esophageal candidiasis is a common problem in immunocompromised patients. Up to 50% of AIDS patients acquire the infection during their illness. Due to severe morbidity and possible dissemination of this infection, prompt treatment with a systemic antifungal is required. Fluconazole is first-line therapy in the treatment of esophageal candidiasis because of its tolerability and rapid resolution of symptoms. However, approximately 5% of oral and esophageal candidiasis in patients with advanced AIDS is now becoming refractory to fluconazole.

Study: Ally R, Schurmann D, Kreisel W, et al. A randomized, double-blind, double-dummy, multicenter trial of voriconazole and fluconazole in the treatment of esophageal candidiasis in immunocompromised patients. *Clin Infect Dis* 2001; 33:1447-1454.

Purpose: To compare the efficacy, safety, and tolerability of voriconazole and fluconazole in immunocompromised patients with proven esophageal candidiasis.

Study design: Randomized, double-blind, double-dummy, multicenter, comparative, non-inferiority study.

Methods:

— 487 patients screened for inclusion.

— 391 patients randomized: 200 voriconazole patients, 191 fluconazole patients.

— Patients had to be diagnosed with esophagitis confirmed by esophagoscopy, plus positive microscopy and mycological culture from a brush or tissue biopsy of esophageal lesions before receiving antifungal therapy.

— Patients received either voriconazole 200 mg bid or fluconazole 400 mg (day 1), then 200 mg every day.

— Treatment was continued for seven days following resolution of all clinical signs and symptoms, but did not exceed 42 days of therapy.

— Primary endpoint was to prove non-inferiority based on treatment response assessed by esophagoscopy on day 43 or at the end of treatment.

— Voriconazole was considered not to be inferior if the lower limit of the approximate two-sided 95% confidence interval (CI) for the difference in success rates (cured + improved) between the two groups at the end of treatment did not fall below -0.15 (-15%).

— Secondary efficacy endpoints included the resolution of symptoms and the time to clinical cure determined by symptomatic assessments.

Results: The success rate (cured + improved) for esophageal candidiasis as assessed by esophagoscopy was 98.3% for voriconazole and 95.1% for fluconazole with a difference of -3.2% (95% CI for a difference of -1.0 to 7.5). Because the lower limit is above the predefined non-inferiority margin, voriconazole was shown as not inferior to fluconazole in this study. **(See Table 1, above.)**

Safety: Treatment-related adverse events occurred in 60 patients (30%) taking voriconazole as compared to 27 patients (14%) in the fluconazole group. In the voriconazole group, five patients (2.5%) discontinued the drug due to treatment-related adverse events, as opposed to one patient (0.5%) in the fluconazole group. Eighty percent of

voriconazole discontinuations were due to mild-to-moderate visual disturbances. Seven patients (3.5%) in the voriconazole group vs. two patients (1%) taking fluconazole discontinued therapy due to lab abnormalities.

Conclusion: Voriconazole is at least as effective as fluconazole in the treatment of proven esophageal candidiasis in immunocompromised patients. However, more treatment-related adverse events occurred in the voriconazole group (30% vs. 14%), which may limit use for this indication.

Strengths:

— Randomized, double-blind, double-dummy, multicenter trial.

— Well-defined inclusion criteria.

— Specific guidelines for esophagoscopy assessments of primary endpoint.

Limitations:

— Small sample size.

— Patients did not receive a loading dose of voriconazole.

— The exact method of deriving statistical significance was not stated for the primary endpoint.

— The intention-to-treat population was not included in primary endpoint analysis.

Treatment of aspergillosis. Invasive aspergillosis is a devastating infection that develops mostly in immunocompromised patients. The incidence of infection occurs in 5% to more than 20% of patients in high-risk groups. Amphotericin B deoxycholate (amp B) is considered first-line therapy, but the response rate is less than 40%, and treatment can be limited by poor tolerability and nephrotoxicity. The lipid formulations of Amp B are equally effective and less nephrotoxic, but more costly.

Study: Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002; 347:408-415.

Purpose: To compare efficacy, safety, and tolerability of voriconazole with those of amp B for the primary therapy of acute aspergillosis in immunocompromised patients.

Study design: Randomized, unblended, comparative trial.

Methods:

— 277 patients randomized: 144 in the voriconazole group, 133 in the amphotericin B group.

— No significant differences in baseline characteristics of patients.

— Patients must be immunocompromised and diagnosed with probable or definite invasive aspergillosis.

— Definite invasive aspergillosis was defined as a clinically compatible illness plus one or more of the following: isolation of aspergillus species from a normally sterile site; hyphae consistent with the presence of aspergillus in a biopsy specimen or aspirate, plus culture of aspergillus from the same organ; radiologic evidence of pulmonary lesions that were not attributable to other factors and a culture of bronchoalveolar-lavage fluid that was positive for aspergillus; or tracheobronchial lesions confirmed by bronchoscopy, with a positive culture for aspergillus.

— Probable invasive aspergillosis was defined as a clinically compatible illness plus one or more of the following: hyphae consistent with the presence of aspergillus in a biopsy specimen or aspirate but without culture; the presence of a halo or an air-crescent sign on a CT scan of the lung; radiologic evidence of new pulmonary lesions not attributable to other factors with either hyphae consistent with the presence of aspergillus in bronchoalveolar-lavage fluid or sputum or a sputum culture that was positive for aspergillus; clinical evidence of sinusitis, opacification of a sinus on CT or MRI, and positive histopathological examination or culture of aspergillus from a lesion in the nose or paranasal sinus; or tracheobronchial lesions confirmed by bronchoscopy and a positive finding on histopathological or microscopic examination of a biopsy specimen or bronchoalveolar-lavage fluid.

— Patients received either intravenous voriconazole (two doses of 6 mg/kg on day 1, then 4 mg/kg twice daily for at least seven days, after which patients could be switched to 200 mg orally twice daily) or intravenous amp B (1-1.5 mg/kg/d).

— Duration of therapy was 12 weeks.

— Primary endpoint was to prove non-inferiority of voriconazole to amp B in relation to successful outcomes (complete + partial response) at 12 weeks.

— Voriconazole was considered not to be inferior to amp B if the lower limit of the voriconazole response rate minus the difference in amp B response rate was above -20 percentage points.

— A blinded data review committee assessed the adverse events, lab abnormalities, and global response at week 12.

Results: The successful outcome (complete + partial response) at week 12 in the voriconazole group was significantly better than the amp B group. The absolute difference was 21.2%, with a 95% CI for the difference of 10.4-32.9 percentage points. The lower limit of the CI was above zero, indicating voriconazole to be associated with a

more successful outcome. The medium duration of voriconazole therapy was 77 days, vs. 10 days in the amp B group. **(See Table 2, at right.)**

Other licensed antifungal therapy was given to 52 patients in the voriconazole group. The first other licensed antifungal therapy was amp B deoxycholate in 20 patients, a lipid formulation of amp B in 14 patients, itraconazole in 17 patients, and a combination in one patient. Other licensed antifungal therapy was given to 107 patients in the amp B group. The first other licensed antifungal therapy was a lipid formulation of amp B in 47 patients, itraconazole in 38 patients, and another antifungal drug or a combination of drugs in 22 patients.

Safety: Treatment-related adverse events occurred less frequently in the voriconazole group (343 events) than in the amp B group (421 events), P = 0.02. Visual disturbances were most common in the voriconazole group (44.8%). These disturbances were described as blurred vision, altered visual perception, altered color perception, and photophobia. All were transient and resolved without intervention. Severe adverse events developed in 26 patients (13.4%) in the voriconazole group in contrast to 45 (24.3%) in the amp B group. The most common severe adverse events were renal impairment (19 patients, 10%) in the amp B group and liver function abnormalities (7 patients, 4%) in the voriconazole group.

Conclusion: Voriconazole demonstrated noninferiority to amp B as initial treatment for invasive aspergillosis.

Strengths:

— Clearly defined guidelines for inclusion in study.

— Blinded review committee performed inclusion data and successful outcome interpretation.

Limitations:

— Small sample size.

— Study was unblended.

— Researchers employed by or have consulted for Pfizer.

— Patients who displayed intolerance or lack of response to either initial therapy could be switched to other antifungal therapy and be included in the results.

Study: Denning DW, Ribaud P, Milpied N, et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. *Clin Infect Dis* 2002; 34:563-571.

Purpose: To evaluate the efficacy and safety of voriconazole in immunocompromised patients with proven invasive aspergillosis (IA).

Table 2: Results of trial comparing voriconazole vs. amphotericin B

	Response rates at week 12	
	Voriconazole	Amphotericin B
Response	n = 144	n = 133
Successful outcome	76 (52.8)	42 (31.6)
Complete response	30 (20.8)	22 (16.5)
Partial response	46 (31.9)	20 (15.0)
Unsuccessful outcome	68 (47.2)	91 (68.4)
Stable disease	8 (5.6)	8 (6.0)
Failure of therapy	55 (38.2)	78 (58.6)
Indeterminate	5 (3.5)	5 (3.8)

Note: Data are number (%) of patients.

Study Design: Open, noncomparative, multicenter study.

Methods:

— 137 patients received at least one dose of drug.

— 137 patients were included in the safety analysis, and 116 patients were included in the efficacy analysis.

— Patients were diagnosed with either probable or definite IA.

— Definite IA required histopathologic evidence of tissue invasion with hyphae morphologically consistent with aspergillus species or positive culture of aspergillus from a sterile site obtained by an invasive procedure.

— Probable IA required radiologic evidence suggestive of acute IA.

— Intravenous therapy started initially with a loading dose of 6 mg/kg every 12 hours on day 1, followed by 3 mg/kg every 12 hours lasting six to 27 days. IV therapy then could be switched to oral voriconazole 200 mg every 12 hours for four to 24 weeks. Doses could be increased to 250 mg after one week and then to 300 mg twice daily if the response was inadequate.

— Primary endpoint was to compare response rates according to underlying disease, site of infection, and whether patient received primary or salvage therapy.

— Each patient was assessed on the basis of a case report form, copies of imaging investigations (x-ray, CT scan, and MRI scans, if available), and bronchoscopy results.

Results: Voriconazole was given as primary therapy to 60 (52%) of 116 patients. Thirty-one patients (25%) had received prior prophylactic antifungal therapy for less than one week. Salvage therapy was given to 56 patients (48%). Out of 116 patients, 16 (14%) had a complete response to voriconazole therapy, 40 (34%) had

a partial response, and 24 (21%) had a stable response. **(See Table 3, below.)** Treatment failures occurred in 36 patients (31%). Death occurred during or 90 days following treatment in 67 (58%) of patients. Of these patients, 31 (59%) died as a result of IA, 21 (40%) died as the result of another cause with IA, and one died without IA.

Safety: During the study, investigators noted 95 (15%) adverse events. The most common were rash (12 patients), visual disturbances (15 patients), and elevated liver function tests (20 patients). All 20 patients with elevated liver function tests and four patients with rashes discontinued therapy.

Conclusion: Overall, the infections of 48% of patients had a complete or partial response, and 31% failed to respond to therapy. The greatest benefit was seen in hematology patients (58% response rate vs. 27% failure rate). In other studies, amp B had a response rate of 35% in the same patient population. In the highest-risk group (allogenic hematopoietic stem cell transplant), the failure rate was 35% in comparison to 85% failure rates with amp B therapy according to other studies. Voriconazole was shown to be more efficacious as primary rather than salvage therapy.

Limitations:

— Small sample size.

— Noncomparative, open-label study.

— Financially supported by Pfizer.

— Patients on previous antifungal therapy were included in the study, and reasons or circumstances for switching therapy were not stated in the report.

— IV maintenance dose given was 3 mg/kg twice daily (normal maintenance dose is 4 mg/kg

Table 3: Results at end of therapy and by site or type of disease

Response at the end of therapy, by patient group

	Global response, number (%)				
Patient group	Complete	Partial	Stable	Failure	Total
Hematological disorders	16 (24)	23 (34)	10 (15)	18 (27)	67
Allogenic HSCT	0	6 (26)	8 (35)	9 (39)	23
Solid-organ transplantation	0	3 (50)	2 (33)	1 (17)	6
AIDS	0	1 (20)	0	4 (80)	5
Other	0	7 (47)	4 (27)	4 (27)	15
Total	16 (14)	40 (34)	24 (21)	36 (31)	116 (100)

Note: HSCT = hematopoietic stem cell transplant

Response at end of therapy, by site or type of disease or by prior treatment

	Response to treatment, number (%)				
Site or type	Complete	Partial	Stable	Failure	Total
Pulmonary	15 (18)	35 (42)	16 (19)	18 (21)	84
Cerebral	0	3 (16)	5 (26)	11 (58)	19
Disseminated	1 (17)	2 (33)	0	3 (50)	6
Sinus	0	0	2 (40)	3 (60)	5
Other	0	0	1 (50)	1 (50)	2
Previous therapy					
Primary	10 (17)	25 (42)	11 (18)	14 (23)	60 (52)
Salvage	6 (11)	15 (27)	13 (23)	22 (39)	56 (48)
Total	16 (14)	40 (34)	24 (21)	36 (31)	116 (100)

Table 4: Comparison of voriconazole and liposomal amphotericin B

Response to empirical therapy

Response indicator Difference	Voriconazole n = 415	Liposomal amphotericin B n = 422	Point estimate for the percentage (95% CI)
Overall response -- number (%)	108 (26.0)	129 (30.6)	-4.5 (-10.6 to 1.6)
No breakthrough fungal infections within seven days of EOT	407 (98.1)	401 (95.0)	+3.1 (0.6 to 5.5)
Survival seven days after EOT	382 (92.0)	397 (94.1)	-2.0 (-5.5 to 1.4)
No discontinuation before recovery from neutropenia	374 (90.1)	394 (93.4)	-3.2 (7.0 to 0.5)
Resolution of fever during neutropenia	135 (32.5)	154 (36.5)	-4.0 (-10.4 to 2.5)
Complete/partial response in baseline fungal infections	6/13 (46.2)	4/6 (66.7)	-20.5 (-67.0 to 25.9)

twice daily).

Empiric therapy in neutropenic patients. Prolonged neutropenia often develops in patients during cancer chemotherapy and organ transplantation. In patients with persistent or relapsing fevers, clinicians commonly suspect a fungal infection and thus treat it empirically. Amphotericin B is the drug of choice in this patient population.

Study: Walsh TJ, Pappas P, Winston DJ, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med* 2001; 346:225-234.

Purpose: To determine non-inferiority of voriconazole to liposomal amp B in overall success rates of empiric antifungal therapy.

Study Design: Open-label, prospective, multicenter, international comparative trial.

Methods:

— 837 patients in the modified intention-to-treat population.

— 415 voriconazole patients and 422 liposomal amp B patients.

— Patients must be neutropenic and febrile for more than 96 hours while on antibiotic therapy.

— Patients must have undergone cancer chemotherapy or organ transplantation.

— On day 1, patients received a loading dose of 6 mg/kg every 12 hours X two doses, then a maintenance dose of 3 mg/kg every 12 hours (or 200 mg every 12 hours at least three days after IV therapy). Liposomal amp B was given at 3 mg/kg IV every day. Voriconazole could be increased to 4 mg/kg every 12 hours IV or 300 mg every 12 hours orally if warranted. Liposomal amp B could be increased to 6 mg/ kg/day or decreased to 1.5 mg/kg/day.

— Patients continued therapy for up to three days after neutrophil recovery or a maximum of 12 weeks of therapy

— The primary endpoint was to determine non-inferiority of response rates. Non-inferiority was defined as the difference in success rates between treatment groups of no more than 10 percentage points. Secondary endpoints were the five components of the composite outcome score. The composite outcome score included lack of breakthrough fungal infection, survival of seven days post-therapy, therapy not discontinued prematurely, resolution of fever during neutropenia, and successful treatment of any baseline fungal infection.

Results: The overall success rates for voriconazole did not meet the requirements for non-inferiority. **(See Table 4, above.)** The 95% CI falls just outside the predefined lower limit of -10 percentage points. Of the secondary endpoints, the only significant difference was in the documented breakthrough fungal infections. Documented breakthrough fungal infection developed in eight patients receiving voriconazole and 21 patients receiving liposomal amphotericin B (P = 0.02). The reduction in invasive fungal infections was particularly apparent in the stratified cohort of patients at high risk (those with allogeneic transplants or relapsed leukemia). Among these patients, those receiving voriconazole had fewer documented breakthrough fungal infections than

those receiving liposomal amp B (2 of 143 [1.4%] vs. 13 of 141 [9.2%], P = 0.03).

Safety: There were no significant differences between treatment groups in hepatotoxicity or rise in serum creatinine levels (more than 2X baseline). Twenty-two percent of patients in the voriconazole group developed visual disturbances. Nineteen patients (0.05%) in the voriconazole and 23 (0.05%) in the amp B group discontinued therapy due to toxic effects.

Conclusion: Voriconazole did not meet the predefined requirements of non-inferiority of response for use as empiric antifungal therapy in neutropenic patients. The safety profiles of voriconazole and liposomal amp B were comparable, except for the visual disturbances in the voriconazole group.

Limitations:

— Open label.

— Results of a subgroup analysis (number of breakthrough fungal infections) were reported as significant in favor of voriconazole, when there

Table 5: Adverse reactions

Reaction	Voriconazole n = 1493	Itraconazole n = 366	Fluconazole n = 4000	Amphotericin n = 556	Caspofungin n = 69
Visual disturbances	30%	——	——	——	——
Hallucinations	2.5%	——	——	——	——
Dizziness	1.3%	1%	——	——	——
Headache	3.2%	2%	1.9%	6%	6%
Fever	6.2%	——	——	14%	2.9%
Chills	4.1%	——	——	18%	——
Flushing	——	——	—— ——	2.9	
Rash	6%	3%	1.8%	4%	——
Phlebitis	3%	3%	——	——	2.9%
Nausea	5.9%	8%	3.7%	9%	2.9%
Vomiting	4.8%	4%	1.7%	8%	2.9%
Diarrhea	1.1%	6%	1.5%	6%	——
Gastrointestinal hemorrhage	——	——	——	4%	——
Tachycardia	2.5%	——	——	——	——
Hypotension	1.7%	——	——	——	——
Heart arrest	——	——	——	6%	——
Hypertension	1.9%	——	——	5%	——
Multiple organ failure	——	——	——	11%	——
Respiratory failure	——	——	——	8%	——
Dyspnea	——	——	——	7%	——
Kidney failure	0.5%	——	——	5%	——
Creatinine increased	0.3%	2%	——	11%	——
Alkaline phosphatase increased	3.6%	2%	——	< 3%	2.9%
Hyperbilirubinemia	0.8%	4%	——	4%	——
Hepatic enzymes increased	1.9%	2%	——	< 3%	——
Hypokalemia	1.6%	5%	——	5%	2.9%
Leukopenia	0.3%	——	——	4%	——
Thrombocytopenia	0.5%	——	——	5%	——

was no statistically significant evidence of efficacy in the primary endpoint of the trial. Some experts believe primary endpoints must show significance before a subgroup analysis can be evaluated and the results interpreted.

Drug interactions

Of all the antifungals, voriconazole and itraconazole have the most clinically significant drug interactions. Voriconazole is contraindicated in patients taking sirolimus, rifampin, ergot alkaloids, carbamazepine, long-acting barbiturates, pimozide, and quinidine. Many of these drugs are taken by the patient population most likely to acquire a serious fungal infection. The most notable are rifampin for HIV and transplant patients, immunosuppressants for solid organ and bone marrow transplantations, chemotherapeutic agents, and antiretroviral agents.

Adverse reactions

The most common adverse event for voriconazole is visual disturbances. **(See Table 5, p. 7.)** In all studies involving voriconazole, this event occurred in approximately 30% of patients. The events were reported to be transient and mild-to-moderate in severity.

Warnings/precautions for voriconazole

— Visual disturbances have been noted in approximately 30% of patients. If treatment continues past 28 days of therapy, visual acuity, visual field, and color perception tests should be performed.

— Hepatic toxicity has occurred during clinical trials. The effects normally are reversible upon discontinuation of voriconazole.

— Pregnancy category D.

— Voriconazole tablets contain lactose and should not be given in patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.

— Anaphylactoid-like reactions can develop during intravenous therapy.

— Use caution when administering IV therapy to patients with CrCl < 50 mL/min due to the accumulation of the intravenous vehicle, SBECD. If warranted, these patients could be switched to oral maintenance therapy.

— Patients should not drive at night while taking voriconazole.

— In patients with mild-to-moderate hepatic cirrhosis (Child-Pugh Class A and B), the standard loading dose should be used, but the maintenance dose should be halved.

Monitoring of voriconazole

Liver function tests (baseline and during therapy), renal function tests, serum electrolytes (especially potassium), and visual testing (after 28 days of therapy).

Summary and recommendations

In the only clinical trial published comparing fluconazole to voriconazole in the treatment of oral candidiasis, voriconazole did not prove to be significantly more efficacious. Voriconazole has more drug interactions, adverse effects, and monitoring requirements and is more costly. Some in vitro studies show voriconazole to be efficacious in treating fluconazole-resistant non-albicans *Candida* infections. A small trial involving 12 advanced HIV patients with fluconazole-refractory oroesophageal candidiasis showed favorable clinical responses in 10 of the patients. More studies will need to be performed to use voriconazole for fluconazole-resistant *Candida* species. Clinical trials are now under way for the treatment of voriconazole in invasive candidiasis.

Conventional amp B is first-line therapy in the treatment of invasive aspergillosis, but is limited by its nephrotoxicity. Patients on conventional amp B who experience nephrotoxicity then are switched to an expensive lipid formulation. In the only published study comparing conventional amp B to voriconazole in the treatment of aspergillosis, the response rates were significantly greater in the voriconazole group (52.8% vs. 31.6%). A noncomparative study showed a 48% response rate to voriconazole therapy. Although further studies need to be conducted or published before changes are made to standard therapy guidelines, voriconazole shows the most benefit in the treatment of aspergillosis.

Voriconazole can be used as first-line therapy in the treatment of invasive pulmonary and extrapulmonary aspergillosis. The drug also may be used as salvage therapy in patients refractory to or intolerant of amp B or lipid forms of amp B in the treatment of invasive aspergillosis. It should be used as a second-line agent in the treatment of esophageal candidiasis in patients refractory to or intolerant of azoles. Lastly, it can be used in the treatment of serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* spp., including *F. solani*, and in patients intolerant of or refractory to amp B.