

## Echinocandin STEPS

November 14, 2007

<b>Recommendation</b>	Place in therapy of echinocandins has not been fully established. All have similar adverse drug reaction profiles. Caspofungin has the most clinical experience and the most indications. It is also the only agent of the echinocandins approved for treatment of aspergillosis and for empiric therapy in neutropenic patients. However, it is more poorly tolerated compared to the other agents, and requires adjustment in hepatic impairment. At this time, it is recommended that echinocandins be reserved for patients who are at high-risk of infection with fluconazole-resistant <i>Candida</i> species, or who are intolerant of fluconazole therapy. Decision among the agents may be based on cost since there are more similarities than differences in this class of drugs. Unless there are other contracts available, Cancidas appears to be the most cost-effective at this time.		
<b>Brand Name</b> <b>Generic Name</b>	<b><u>Eraxis</u></b> <b>Anidulafungin</b>	<b><u>Cancidas</u></b> <b>Caspofungin</b>	<b><u>Mycamine</u></b> <b>Micafungin</b>
<b>Safety</b>	+	=	=
<b>Drug Interactions</b>	Not a substrate, inhibitor or inducer of cytochrome P450enzymes. Metabolism by slow chemical degradation at physiologic pH and temp. Would not expect drug interactions, however, one PK study showed increased cyclosporine levels	May decrease tacrolimus levels. Cyclosporine may increase levels. Inducers (i.e rifampin, carbamazepine, phenytoin, nevirapine) may decrease levels.	May increase sirolimus and nifedipine levels. Do not mix or co-infuse with other medications.
<b>Pregnancy/Lactation</b>	Category C (Bone abnormalities in rabbits) Excretion in breast milk unknown	Category C (bone abnormalities) Excretion in breast milk unknown	Category C (abortions and visceral abnormalities) Excretion in breast milk unknown
<b>Pediatric</b>	Safety and Efficacy not established. Has been used in a limited number of children 2-17 years of age without unusual ADR's	Safety and efficacy not established	Safety and efficacy not established in children < 16years
<b>Elderly</b>	No adjustments necessary.	No adjustments necessary. Pharmacokinetics, efficacy and ADR's similar to younger adults	No dosage adjustment necessary. Increased sensitivity cannot be ruled out
<b>Renal/Hepatic Impairment</b>	No dosage adjustment necessary. Purported to be safe in patients with hepatic insufficiency due to unique metabolism. In PK studies, levels were not increased in patients with hepatic insufficiency. However, clinical studies excluded patients with elevated LFT's. Not dialyzable – can be administered without regard to dialysis	Reduce dose to 35mg daily for moderate hepatic impairment (Child Pugh score 7-9). Clinical experience lacking in patients with severe hepatic impairment – use caution. Not dialyzable	No dosage adjustment necessary in mild to moderate hepatic impairment. Not studied in patients with severe hepatic impairment – use caution. Not dialyzable
<b>Contraindications</b>	Known hypersensitivity to product, formulation, or other echinocandins		
<b>Precautions</b>	Elevated LFT's and worsening hepatic failure reported. Monitor for worsening LFT's. Histamine-mediated reactions related to the infusion rate may occur. Do not exceed 1.1mg/min rate of infusion. Safety and efficacy has not been established for neutropenic patients or those with endocarditis, osteomyelitis, or meningitis <i>Candida</i> infections.	May cause elevated LFT's. Avoid co-administration with cyclosporine due to high frequency of LFT elevation. Limited data for treatment duration longer than 4 weeks.	Anaphylactic reaction including shock. New-onset or worsening hepatic failure. Use caution in pre-existing mild-moderate hepatic impairment. Hemolytic anemia and hemoglobinuria reported. May cause elevations in LFT's

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<b>Tolerability</b>	=	-	=
	<p>Histamine-mediated reactions</p> <p>Most common: hypokalemia (3%)</p> <p>&lt;2%: fever, chills, N/V, ↑ SCr, LFT's increased, HA, Neutropenia, leukopenia, phlebitis, ↑bilirubin</p> <p>Nephrotoxicity/renal failure and anemia not reported</p>	<p>Histamine-mediated reactions</p> <p>Most common: fever (3–26%), chills (up to 14%), N/V (2-6%), HA (11%), nephrotoxicity (2-8%, defined as SCr &gt; 2x baseline), hypokalemia (4-11%), ↑LFT's (3-13%), phlebitis (up to 16%), ↑bilirubin (3%), anemia 4%, neutropenia (2-3%), leukopenia (5-6%)</p>	<p>Histamine-related reactions have occurred</p> <p>Most common: N/V (3%), ↑LFT's (2-3%)</p> <p>&lt;2%: fever, chills, serum creatinine ↑, renal failure, hypokalemia, phlebitis, neutropenia, leukopenia, anemia, and ↑bilirubin levels</p>
<b>Efficacy</b>	=	+	-
<b><i>FDA-approved indications</i></b>	<p>Treatment of the following fungal infections:</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Candidemia and other Candida infections including intra-abdominal abscesses and peritonitis</li> <li><input type="checkbox"/> Esophageal candidiasis</li> </ul>	<ul style="list-style-type: none"> <li><input type="checkbox"/> Empiric antifungal treatment in febrile neutropenic patients</li> <li><input type="checkbox"/> Treatment of the following fungal infections: <ul style="list-style-type: none"> <li>○ Candidemia and other Candida infections including intra-abdominal abscesses, peritonitis, and pleural space infections</li> <li>○ Esophageal candidiasis</li> <li>○ Invasive aspergillosis in patients who are refractory to or intolerant of other therapies</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li><input type="checkbox"/> Treatment of esophageal candidiasis</li> <li><input type="checkbox"/> Prophylaxis of Candida infections in patients undergoing HSCT</li> </ul>
<b><i>Unlabeled Uses</i></b>		<ul style="list-style-type: none"> <li><input type="checkbox"/> Prophylaxis of invasive fungal infection</li> </ul>	<ul style="list-style-type: none"> <li><input type="checkbox"/> Aspergillosis</li> <li><input type="checkbox"/> Candidemia</li> </ul>
<b><i>Pharmacology</i></b>	Inhibits synthesis of beta-(1,3)-D-glucan, an essential component of the fungal cell wall		
<b><i>Microbiology</i></b>	<p>Highly active against: <i>C. albicans</i>, <i>C. glabrata</i>, <i>C. tropicalis</i>, <i>C. krusei</i></p> <p>Active against: <i>C. parapsilosis</i>, <i>C. guilliermondii</i>, and <i>C. lusitaniae</i></p> <p>Active against Candida spp. resistant to other anti-fungals including amphotericin B and the triazoles</p> <p>Generally cross-resistance across the echinocandin class, although Eraxis is active against some strains of <i>C. glabrata</i> resistant to Cancidas</p> <p>Fungistatic against <i>Aspergillosis spp.</i> Fungicidal against <i>Candida</i></p>		

**Clinical Studies**

**Anidulafungin**

1. Anidulafungin vs Fluconazole for esophageal candidiasis. Clin Infect Dis. 2004;39:850-2. Randomized, double-blind study (n=601). Patients received anidulafungin 100mg on day 1 followed by 50mg daily or oral fluconazole 200mg on day 1 followed by 100mg per day. Endoscopic success occurred in 97.2% and 98.8% respectively (95% CI, -4.1-0.8). Relapse rates at 2 weeks were 53% and 19% respectively (p<0.001). Authors attributed this difference to higher anti-retroviral therapy in the fluconazole group.
2. Anidulafungin vs. Fluconazole for invasive candidiasis. NEJM. 2007;356:2474-2482. Randomized, non-inferiority trial. Patients received either IV anidulafungin (200mg on Day 1 and then 100mg daily) or IV fluconazole (800mg on Day 1, then 400mg daily). At the end of therapy, treatment was successful in 75.6% vs. 60.2% respectively (95% CI 3.9 – 27). Although the difference was significant, this study was designed to detect only inferiority. Also, there was a potential “center effect”. When the largest study site was removed there was no significant difference. Dose of fluconazole may not be high enough. Fluconazole 800mg q24h is suggested for patients who do not improve or who are unstable (per Sanford guide)

**Caspofungin**

1. Caspofungin vs. Amphotericin in neutropenic fever. NEJM. 2004;351:1391-402. Randomized, double-blind, multi-national study (n = 1095). Patients received either caspofungin 70mg loading dose followed by 50mg per day or liposomal amphotericin B 3mg/kg daily. Overall favorable response was achieved 33.9% of the caspofungin group and 33.7% of liposomal amphotericin B group (95% CI, -5.6-6%). Significantly more patients in the amphotericin B group discontinued therapy due to ADR's (8 vs 5%, p = 0.04).
2. Caspofungin vs. Fluconazole in esophageal candidiasis. Am J Med. 2002;113:294-9. Randomized, double-blind study (n = 177). Patients received caspofungin 50mg or fluconazole 200mg IV daily for 7 to 21 days. Favorable response rates were achieved in 81% of the caspofungin group and 85% of the fluconazole group; symptoms recurred after 4 weeks in 28% and 17% of patients, respectively (p=0.19). This was a mostly HIV population.
3. Caspofungin vs. Amphotericin in invasive candidiasis. NEJM. 2002;347:2020-2029. Patients received either caspofungin 70mg loading dose followed by 50mg per day or amphotericin B 0.6 – 0.7mg/kg if non-neutropenic, 0.7 – 1mg/kg per day if neutropenic (n = 239). Favorable response at end of IV therapy was achieved in 73.4% of the caspofungin group and 61.7% of the conventional amphotericin B group (p=0.09). More ADR's in the amphotericin group (58% vs 29%, p=0.02)

**Micafungin**

1. Micafungin vs. fluconazole for prophylaxis during neutropenia in HSCT. Clin Infect Dis. 2004;39:1047-16. Phase 3, randomized, double-blind, multicenter study (n=882). Pediatric and adult patients received either micafungin 50mg (1mg/kg for patients weighing < 50kg) or fluconazole 400mg (8mg/kg for patients weighing < 50kg). More patients receiving micafungin had clinical success, defined as absence of invasive fungal infections through the end of the 4-week period, compared to those receiving fluconazole (80% vs. 73.5%, respectively; p=0.03). At the end of treatment there were more patients in the fluconazole group who had probable or proven breakthrough aspergillosis (p=0.71).
2. Micafungin vs. Caspofungin for treatment of candidemia. Clin Infect Dis. 2007;45:883-893. International, randomized, double-blind trial (n=595). Patients received micafungin 100mg, micafungin 150mg or caspofungin (70mg on day 1 and 50mg thereafter). Treatment was successful for 76.4% in the micafungin 100mg group, 71.4% in the micafungin 150mg group and 72.3% in the caspofungin group. No significant differences in mortality, relapsing and emergent infections, or ADR's.

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<b>Price</b>	=/+	+	-
Usual Dose for esophageal candidiasis	100mg IV loading dose followed by 50mg IV daily x14days	50mg IV daily x14days	150mg IV daily x 14 days
Relative acquisition cost for Treatment	\$	\$	\$\$\$
Usual dose for invasive candidemia	200mg IV loading dose followed by 100mg daily x14days	70mg IV loading dose followed by 50mg daily x14days	100mg IV daily x14days (unlabeled use)
Relative acquisition cost for treatment	\$\$	\$	\$\$
<b>Simplicity</b>	+	=	-
	<ul style="list-style-type: none"> <li><input type="checkbox"/> Given daily</li> <li><input type="checkbox"/> Does not require dosage adjustment for liver failure</li> <li><input type="checkbox"/> Loading dose required for all indications</li> <li><input type="checkbox"/> Reconstituted with companion diluent</li> <li><input type="checkbox"/> Vial stored at room temp</li> <li><input type="checkbox"/> Do not shake</li> <li><input type="checkbox"/> Stable for 24hrs at room temp</li> <li><input type="checkbox"/> No warning regarding co-infusing with other drugs – Compatibility info exists</li> <li><input type="checkbox"/> Suggested monitoring: LFT's</li> </ul>	<ul style="list-style-type: none"> <li><input type="checkbox"/> Given daily</li> <li><input type="checkbox"/> Requires dosage adjustment for liver impairment</li> <li><input type="checkbox"/> Loading dose required for some indications</li> <li><input type="checkbox"/> Do not use dextrose to dilute</li> <li><input type="checkbox"/> Vial is refrigerated</li> <li><input type="checkbox"/> Reconstituted vial must be used immediately</li> <li><input type="checkbox"/> After dilution, stable for 24hrs at room temp and 48hrs under refrigeration</li> <li><input type="checkbox"/> Do not mix or co-infuse with other drugs per PI – however compatibility info exists</li> <li><input type="checkbox"/> Suggested monitoring: CBC, LFT's, serum electrolytes (esp. Ca, Mg, K)</li> </ul>	<ul style="list-style-type: none"> <li><input type="checkbox"/> Given daily</li> <li><input type="checkbox"/> Does not require adjustment for mild hepatic impairment – unknown in severe hepatic impairment</li> <li><input type="checkbox"/> No loading dose required</li> <li><input type="checkbox"/> Must be diluted with NS</li> <li><input type="checkbox"/> Vials stored at room temp</li> <li><input type="checkbox"/> Do not vigorously shake vial</li> <li><input type="checkbox"/> Give over 1 hour</li> <li><input type="checkbox"/> 150mg is a common dose but it only comes in 50 and 100mg vials</li> <li><input type="checkbox"/> Protect from light</li> <li><input type="checkbox"/> Stable for 24hrs at room temp</li> <li><input type="checkbox"/> Do not mix or co-infuse with other drugs – however, compatibility info exists</li> <li><input type="checkbox"/> Suggested monitoring: CBC, LFT's, renal function tests</li> </ul>