# National PBM Drug Monograph
# Anidfulafungin (Eraxis™)
### VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

## EXECUTIVE SUMMARY

Anidulafungin is the third antifungal in the echinocandin class and was approved in 2006 for treatment of esophageal candidiasis and Candidemia and other forms of Candida infections (intra-abdominal abscess, and peritonitis). The other 2 agents in this class are caspofungin and micafungin.

Anidulafungin is active against most clinically relevant species of *Candida*. It also has activity against *Aspergillus spp*. In-vitro data show that anidulafungin is active against fluconazole-resistant *Candida*.

Two trials evaluated anidulafungin for treatment of candidemia and other candida infections. One was a dose-ranging study comparing anidulafungin 50mg, 75mg and 100mg once daily and the other compared anidulafungin 100mg once daily to fluconazole 400mg IV once daily. In the dose-ranging study, the primary outcome was global response in the evaluable patients, at the follow-up visit which took place 2-weeks after the end of therapy. The global response rate at follow-up was similar for the 75 and 100mg doses (90% and 89%) compared to a lower response rate with seen with the 50mg dose (72%).

In the pivotal trial, the primary outcome was global response at end of IV therapy in the modified intent-to-treat population. Successful global response was defined as clinical cure or improvement and documented or presumed microbiological eradication. The global success rate was 75.6% with anidulafungin and 60.2% with fluconazole (treatment difference 15.42% [95%CI 3.9, 27]). Global success at the 2-week and 6-week followup periods favored anidulafungin.

In a large pivotal trial for treatment of endoscopically confirmed esophageal candidiasis, anidulafungin 50mg once daily was compared to oral fluconazole 100mg once daily. The primary endpoint was endoscopic success in the evaluable groups at end of therapy. Endoscopic success was defined as cure (esophageal lesion grade =0) or improvement (decrease of $\geq$ 1 grade from baseline value) Anidulafungin IV was found to be non-inferior to oral fluconazole with 97.2% and 98.8% achieving cure or improvement. Clinical success was achieved in approximately 99% of patients in either group. Mycological success occurred in 86.7% of anidulafungin and 91% of fluconazole patients. Time to resolution of symptoms was 5 days and mean duration of treatment was 14 days in both groups. Endoscopic success at the 2-week followup was significantly higher with fluconazole (89.5% vs. 64.4%).

The majority of adverse events (AE) were considered to be mild-moderate in severity.

Anidulafungin is not a substrate, inducer, or inhibitor of CYP450 isoenzymes; therefore, significant drug interactions via this mechanism are not expected. No dosage adjustment of either drug is need when co-administered with voriconazole, tacrolimus, or cyclosporin. No adjustment of anidulafungin is needed when co-administered with amphotericin B or rifampin.

Anidulafungin is only available intravenously. For the treatment of candidemia or invasive candidiasis, the recommended dose is a 200mg loading dose on day 1 followed by 100mg daily thereafter. Duration of treatment is based on clinical response. In general, antifungal therapy should be continued for at least 14 days after the last positive culture. For the treatment of esophageal candidiasis, the recommended dose is a 100mg loading dose on day 1 then 50mg once daily thereafter. Patients should be treated for a minimum of 14 days and for at least 7 days after resolution of symptoms.

Anidulafungin is an alternative to azole antifungals or amphotericin B for treatment of candidemia or invasive candidiasis. For treatment of esophageal candidiasis, anidulafungin should be reserved for individuals who have contraindications, adverse events, significant drug interactions with azoles or amphotericin or who have infection with fluconazole-resistant *Candida*.

## INTRODUCTION

Anidulafungin is the 3rd antifungal in the echinocandin class, which includes caspofungin and micafungin.

## PHARMACOLOGY

The echinocandins inhibit the synthesis of (1, 3)-β-D-glucan, an essential component of fungal cell walls, resulting in interference with fungal cell wall synthesis.

## PHARMACOKINETICS

**Table 1**

| | |
|---|---|
| Cmax (steady-state) | 8.6mg/L (%CV 16.2) - healthy adults (200mg loading dose/ 100mg maintenance dose)<br>7.2 mg/L (%CV 23.3) - patients with fungal infections (200/100mg)*<br>4.2 mg/L (CV% 22.4)- patients with fungal infections (100/50mg)* |
| AUC (steady-state) | 111.8 mg·h/L (%CV 24.9) - healthy adults (200mg loading dose/ 100mg maintenance dose)<br>110.3 mg·h/L (%CV 32.5) - patients with fungal infections (200/100mg)*<br>55.2 mg·h/L (CV% 32.5)- patients with fungal infections (100/50mg)* |
| Clearance | 1L/h |
| Half-life | 26.5 hours |
| Volume of distribution | 30-50L |
| Protein binding | 84% |
| Metabolism | Undergoes slow non-enzymatic chemical degradation to a ring-opened peptide (no fungal activity) which is then converted to peptidic degradants and eliminated. |
| Elimination | 30% eliminated in feces (< 10% as intact drug)<br><1% eliminated in urine |

*Parameters estimated by population modeling
Data obtained from product package insert

- Gender: In multi-dose patient studies, drug clearance was approximately 22% faster in men. In healthy subjects, no difference in plasma concentration between men and women
- Age ≥ 65 vs. < 65 years clearance was 1.07L/h and 1.22 L/h respectively
- No increase in concentration in subjects with Child-Pugh class A, B, or C hepatic insufficiency. Slight decrease in AUC noted in subjects with Child-Pugh class C, but still within range of population estimates for healthy subjects
- Pharmacokinetics similar for subjects with normal renal function and those with mild, moderate, severe, or end-stage renal insufficiency.
- Pharmacokinetics similar among Whites, Blacks, Asians, and Hispanics

## MICROBIOLOGY

Anidulafungin is active against most clinically relevant species of Candida. In-vitro susceptibility of micafungin against the most common Candida spp. is shown in table 2.[1-4] Higher MIC values were seen for *C. parapsilosis.* Please note that methods for susceptibility testing and interpretive breakpoints for the echinocandins have not been established. Cross-resistance to amphotericin B and the azole antifungals is not expected due to differing mechanisms of action.

Emergence of resistance to anidulafungin has not been observed in clinical trials. Four-year surveillance data (2001-2004) with another echinocandin, caspofungin, showed no emergence of caspofungin-resistance.[5] However, a small number of case reports have described the emergence of resistance or reduced susceptibility to the echinocandins in patients treated with these agents.[6-8]

The development of echinocandin resistance may be through mutations in the FKS gene coding for the FKSp subunit of the glucan synthase complex. Other possible mechanisms may be via an overexpression of a cell wall transport protein (Sbe2p) and the presence of a drug efflux pump in the cell wall.[8, 16]

**Table 2: In-vitro activity of anidulafungin against the most common *Candida* spp.**

| Organism | Study | # isolates | $MIC_{90}$ (µg/mL) | MIC range |
|---|---|---|---|---|
| *C. albicans* | Ostrosky-Zeichner 2003* | 733 | 0.03 | - |
| | Espinel-Ingroff 2003 | 2394 | 0.01-0.5 | <0.01- > 8 |
| | Messer 2004 | 500 | 0.06 | ≤0.008-0.12 |
| | Pfaller 2005^ | 59 | 0.25 | 0.03-4 |

| | | | | |
|---|---|---|---|---|
| *C. glabrata* | Ostrosky-Zeichner 2003* | 458 | 0.13 | - |
| | Espinel-Ingroff 2003 | 993 | 0.03- 8 | <0.01- 8 |
| | Messer 2004 | 105 | 0.12 | ≤0.03-2 |
| | Pfaller 2005^ | 31 | 0.25 | 0.06-0.5 |
| *C. parapsilosis* | Ostrosky-Zeichner 2003* | 391 | 2 | - |
| | Espinel-Ingroff 2003 | 231 | 2- >8 | 0.01- >8 |
| | Messer 2004 | 106 | 4 | 0.12-8 |
| | Pfaller 2005^ | 11 | 8 | 4-8 |
| *C. tropicalis* | Ostrosky-Zeichner 2003* | 307 | 0.13 | - |
| | Espinel-Ingroff 2003 | 548 | 0.06-2 | 0.03 – 32 |
| | Messer 2004 | 106 | 0.06 | ≤0.008-2 |
| | Pfaller 2005^ | 7 | - | 0.12-2 |
| *C. krusei* | Ostrosky-Zeichner 2003* | 50 | 0.13 | - |
| | Espinel-Ingroff 2003 | 207 | 0.03-1.0 | <0.01-8 |
| | Messer 2004 | 23 | 0.06 | 0.03-0.12 |
| | Pfaller 2005^ | 4 | - | 0.12-0.25 |
| *C. lusitaniae* | Ostrosky-Zeichner 2003 | 20 | 0.25 | - |
| | Espinel-Ingroff 2003 | 81 | 0.12- > 8 | 0.03- ≥ 8 |
| | Messer 2004 | 13 | 1 | 0.016-4 |
| *C. dubliniensis* | Ostrosky-Zeichner 2003* | 18 | 0.06 | - |
| | Espinel-Ingroff 2003 | 92 | 0.06-4 | 0.12-8 |

MIC endpoints after 48 hours of incubation
*Data for Ostrosky-Zeichner is included in the review by Espinel-Ingroff. Because data were from isolates obtained in the U.S., results are also shown separately
^Data from phase 2 clinical trial in patients with candidemia/invasive candidiasis (Krause 2004)

Isolates resistant to fluconazole

In the study by Cuenca-Estrella, fluconazole resistance was defined as a MIC of ≥ 16mg/L and in Pfaller, it was defined as a MIC of ≥ 64mg/L.[9, 10] MIC values are shown in table 3. Anidulafungin was also found to be effective in clearing fluconazole-resistant C. albicans in a rabbit model of oropharyngeal and esophageal candidiasis.[11]

**Table 3: Susceptibility of fluconazole- resistant isolates of *Candida spp***

| Organism | Study | # isolates | $MIC_{90}$ (µg/mL) | MIC range |
|---|---|---|---|---|
| *C. albicans* | Cuenca-Estrella 2000 | 63 | 0.015 | ≤0.0002-0.015 |
| | Pfaller 2005 | 41 | 0.06 | 0.0007-0.5 |
| *C. glabrata* | Cuenca-Estrella 2000 | 42 | 0.12 | ≤0.0002-0.25 |
| | Pfaller 2005 | 110 | 0.06-0.12 | 0.0007-0.25 |
| *C. parapsilosis* | Cuenca-Estrella 2000 | 5 | - | 0.015-0.5 |
| *C. tropicalis* | Cuenca-Estrella 2000 | 15 | 0.06 | 0.0002-0.12 |
| *C. krusei* | Cuenca-Estrella 2000 | 28 | 0.03 | ≤0.0002-0.5 |
| | Pfaller 2005 | 146 | 1-2 | 0.007-2 |

Aspergillus

Anidulafungin is not approved to treat infections due to aspergillus; however, *in-vitro* activity has been shown against these organisms (table 4).[2] In another study, Messner et al. showed that the $MIC_{90}$ for *A. fumigatus* (30 isolates) was 0.03mcg/ml (range ≤0.008-8).[3]

**Table 4: In-vitro activity of micafungin against Aspergillus[2]**

| organism (# isolates) | *A. flavus* (53) | *A. fumigatus* (94) | *A. niger* (21) | *A. terreus* (10) |
|---|---|---|---|---|
| MIC (mcg/ml) | ≤0.03 – 0.12 | <0.01-0.12 | ≤0.03-0.06 | <0.03 |

**FDA INDICATIONS**

- Candidemia and other forms of Candida infections (intra-abdominal abscess, and peritonitis). Anidulafungin has not been studied in endocarditis, osteomyelitis, and meningitis due to Candida, or in sufficient numbers in neutropenic patients.
- Esophageal candidiasis

**VA ALTERNATIVES**

Fluconazole, itraconazole, amphotericin B

**DOSE**

Candidemia and other Candida infections (intra-abdominal abscess, and peritonitis): 200mg loading dose on day 1 followed by 100mg daily thereafter. Duration of treatment is based on clinical response. In general, antifungal therapy should be continued for at least 14 days after the last positive culture.
Esophageal candidiasis: 100mg loading dose on day 1 then 50mg once daily thereafter. Patients should be treated for a minimum of 14 days and for at least 7 days after resolution of symptoms.

Dosage adjustment not required based on gender age (geriatric), race, HIV status, hepatic or renal insufficiency. Anidulafungin is not dialyzable and may be administered without regard to timing of dialysis.

**PREPARATION/ADMINISTRATION**

- Anidulafungin is comes in a single use unit pack containing 50mg of anidulafungin and a 15ml diluent vial. Anidulafungin must be reconstituted with the companion diluent (20% w/w dehydrated alcohol in water for injection). Reconstituted solution must then be added to an IV bag or bottle containing 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP.
- The rate of infusion should not exceed 1.1mg/minute
- Unreconstituted vials and companion diluent should be stored at 77°F. Excursions between 59-86°F are permitted. Do not freeze.
- Reconstituted vials should be stored at 77°F. Excursions between 59-86°F are permitted. Reconstituted solution must be added to an IV bag or bottle containing 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP and administered within 24 hours. Do not freeze
- Diluted product should be stored at 77°F. Excursions between 59-86°F are permitted. Do not freeze

Note: The content of alcohol in a 100mg dose is estimated to be equal to ½ jigger of alcohol (or ½ glass of wine).

**EFFICACY**

Invasive Candidiasis

In a phase 2 dose-ranging trial (n=120) patients with invasive candidiasis and candidemia were randomized to anidulafungin 50mg, 75mg, or 100mg IV once daily.[12] A single loading dose of twice the maintenance dose was given on day 1. The primary outcome was global response in the evaluable (per protocol) patients, at the follow-up visit which took place 2-weeks after the end of therapy. The evaluable population was defined as having confirmed Candida infection and received ≥ 10 doses of study medication (or failed after ≥ 5 doses) and who were without protocol violations. Definitions for response are shown in table 5.

**Table 5: Phase 2 trial definitions**

| | |
|---|---|
| Successful global response | Successful clinical and microbiological responses |
| Successful clinical response (cure or improvement) | Cure = Resolution of signs and symptoms of infection and no need for additional antifungal therapy<br>Improvement = significant improvement of signs and symptoms at EOT ; continues therapy with oral agent |
| Successful microbiological response | Negative culture from a normally sterile site that was previously positive for *Candida* or inability to obtain cultures in a patient with a clinical response of success |

Of the 120 patients enrolled, only 83 completed the study to the end of therapy and 68 for the follow-up period. Of those not completing the study, 33 withdrawals were due to death. For the primary outcome, the global response rate at follow-up was similar for the 75 and 100mg doses (90% and 89%) compared to a lower response rate with seen with the 50mg dose (72%).

**Table 6: Results from phase 2 trial**

| | Anidulafungin 50mg | | Anidulafungin 75mg | | Anidulafungin 100mg | |
|---|---|---|---|---|---|---|
| | EOT | FU | EOT | FU | EOT | FU |
| Global response rate | 21/25 (84%) | 13/18 (72%) | 27/30 (90%) | 22/26 (85%) | 25/28 (89%) | 20/24 (83%) |
| Clinical response rate | 22/25 (88%) | 13/18 (72%) | 27/30 (90%) | 22/26 (85%) | 25/28 (89%) | 20/24 (83%) |
| Microbiological response rate | 21/25 (84%) | 14/18 (78%) | 28/30 (93%) | 22/26 (85%) | 25/28 (89%) | 21/24 (88%) |

In a separate publication, it was noted that there was a trend towards dose-related eradication of Candida; however, clinical success was not related to anidulafungin MICs.[4]

Data for a phase 3 pivotal trial were obtained from the product package insert.[16] Patients with invasive candidiasis or candidemia were randomized to receive anidulafungin 100mg IV daily or fluconazole 400mg IV daily (n=256). A single loading dose of twice the maintenance dose was given on day 1. Treatment was given for 14-42 days. A switch to oral fluconazole was allowed if the following conditions were met: ≥ 10 days IV therapy, able to tolerate oral medication, afebrile ≥ 24 hours, last culture negative for Candida. Patients were stratified by APACHE II score (≤ 20 and >20) and by the presence or absence of neutropenia. Among those enrolled, 97% were non-neutropenic and 81% had APACHE II scores < 20. Patients with *Candida* endocarditis, osteomyelitis, meningitis or infection due to *C. krusei* were excluded.

The primary outcome was global response at end of IV therapy in the modified intent-to-treat population (n=245). Successful global response was defined as clinical cure or improvement and documented or presumed microbiological eradication. Clinical improvement was defined as significant but incomplete resolution of signs and symptoms of the Candida infection and no additional antifungal treatment.

The median duration of IV therapy was 14 and 11 days for the anidulafungin and fluconazole groups respectively. Nearly 1/3 of patients in both groups continued with oral therapy for a median duration of 7 and 5 days respectively. 71.8% of the anidulafungin and 64% of fluconazole group completed the study and were followed up for 6 weeks. A statistically greater percentage of patients receiving anidulafungin had a globally successful outcome compared to fluconazole. However results from 1 study site contributed to the statistical difference in outcome. When this study was excluded from the analysis, anidulafungin was non-inferior to fluconazole.[17] The mortality rate was higher in the fluconazole group. Data separated for clinical cure versus clinical improvement and microbiological outcomes were not shown in the package insert.

**Table 7: Results from phase 3 trial in the modified intent-to-treat population**

| | Anidulafungin | Fluconazole | Tx diff [95%CI] |
|---|---|---|---|
| Global success* | 96/127 (75.6%) | 71/118 (60.2%) | 15.42 [3.9, 27] |
| Global success^ | 94/127 (74%) | 67/118 (56.8%) | 17.24 [2.9, 31.6] |
| Success at 2-wk FU | 82/127 (64.6%) | 58/118 (49.2%) | 15.41 [0.4, 30.4] |
| Success at 6-wk FU | 71/127 (55.9%) | 52/118 (44.1%) | 11.84 [-3.4, 27] |
| Overall study mortality | 29/127 (22.8%) | 37/118 (31.4%) | |
| Mortality during study therapy | 10/127 (7.9%) | 17/118 (14.4%) | |
| Mortality due to *Candida* | 2/127 (1.6%) | 5/118 (4.2%) | |

*at end of IV therapy
^at end of all therapy (IV + oral)

Esophageal candidiasis

There is 1 large pivotal trial (n=601) comparing anidulafungin to fluconazole using a non-inferiority design. Anidulafungin 50mg IV once daily was compared to oral fluconazole 100mg once daily.[13] A single loading dose of twice the maintenance dose was given on day 1. Therapy continued for 7 days after resolution of symptoms but not for <14 or > 21 days in total. Patients with evidence of systemic fungal infection or ulcerative esophageal lesions were excluded. Approximately 75% of the patients had AIDS and 80% had an endoscopy grade of 2 or 3. *C. albicans* was the sole pathogen in over 90% of cases.

The primary outcome was endoscopic response in the evaluable group at end of therapy (n=504). The evaluable population was defined as having completed > 10 days therapy, had an EOT assessment with a clinical outcome other than indeterminate, and had an endoscopic result recorded at EOT.

**Table 8: Definitions used in esophageal candidiasis trials**

| | | | | |
|---|---|---|---|---|
| **Mucosal grade** | **0**<br>normal esophageal mucosa | **1**<br>individual plaques each ≤ 2mm in diameter | **2**<br>individual plaques > 2mm in diameter | **3**<br>confluent plaques and/or increased friability of mucosa |
| **Endoscopic success** | Cure = complete resolution of esophageal lesions (grade 0)<br>Improvement = decrease of ≥ 1 grade from baseline value | | | |
| **Clinical success** | Absence or improvement of symptoms compared to baseline | | | |

| | |
|---|---|
| **Mycological success** | Proven or presumed eradication of *Candida* species present at baseline |

Anidulafungin IV was found to be non-inferior to oral fluconazole with 97.2% and 98.8% achieving endoscopic cure or improvement. Clinical success was achieved in approximately 99% of patients in either group. Mycological success occurred in 86.7% of anidulafungin and 91% of fluconazole patients. Time to resolution of symptoms was 5 days and mean duration of treatment was 14 days in both groups.

According to the product package insert, endoscopic relapse rate 2-weeks post-treatment was higher with anidulafungin (53.3%) than fluconazole (19.3%).

Aspergillosis

Anidulafungin in combination with liposomal amphotericin B (L-AmB) in the treatment of primary aspergillosis was evaluated in an open-label noncomparative pilot trial (n=30). Anidulafungin was dosed at 100mg daily (200mg LD) and L-AmB could be given in a dose up to 5mg/kg daily for a maximum duration of 90days (median duration was 22 days). The primary endpoint was clinical and radiologic response (global response) at end of therapy in the MITT group (n=25). Risk factors for aspergillosis were as follows: hematologic malignancy (n=17), AIDS (n=6), transplant (n=4), aplastic anemia (n=2). Among these patients, 14 were neutropenic. The lung was the most common site of infection, followed by CNS, liver, heart, bone, sinus, skin and prostate. (Data on file Pfizer)

**Table: Results in patients with aspergillosis**

| Global response | Clinical response | Radiologic response | Survival at end of study (6 weeks) |
|---|---|---|---|
| 28% | 44% | 28% | 43% |

Empiric use in febrile neutropenia

There are no trials at this time.

**SAFETY**

Safety has been evaluated in over 900 patients participating in phase 1 and clinical studies. Among these patients, 633 received the indicated daily dose of 50 or 100mg. Anidulafungin was administered for ≥ 14 days in 481 patients.[18]

In the combined phase 2-3 trials in candidemia, mortality in the anidulafungin group was 36/206 (17.6%) compared to 38/129 (30.4%) in the fluconazole group.[17] In the phase 3 esophageal candidiasis trial, there were 23 and 20 patients who died in anidulafungin and fluconazole groups respectively.

**Table 9: TEAE in ≥ 2% of patients in candidemia trial VER002-9**

| | Anidulafungin (n=131) | Fluconazole (n=125) |
|---|---|---|
| d/c treatment due to AE (n) | 12 | 21 |
| % patients with ≥ 1 TEAE | 24.4% | 26.4% |
| Increased ALT | 2.3% | 3.2% |
| Increased AST | 0.8% | 2.4% |
| Increased alk phos | 1.5% | 4.0% |
| Increased hepatic enzyme | 1.5% | 7.2% |
| Diarrhea | 3.1% | 1.6% |
| Hypokalemia | 3.1% | 2.4% |
| DVT | 0.8% | 2.4% |

Data from product package insert

**Table 10: TEAE in ≥ 1% of patients in esophageal candidiasis trial**

| | Anidulafungin (n=300) | Fluconazole (n=301) |
|---|---|---|
| % patients with ≥ 1 TEAE | 14.3% | 16.6% |
| Increased GGT | 1.3% | 1.3% |
| Increased ALT | - | 1.0% |
| Increased AST | 0.3% | 2.3% |
| Neutropenia | 1.0% | - |
| Leukopenia | 0.7% | 1.3% |
| Nausea | 1.0% | 1.0% |
| Vomiting | 0.7% | 1.0% |
| Dyspepsia aggravated | 0.3% | 1.0% |
| Headache | 1.3% | 1.0% |
| Rash | 1.0% | 0.7% |
| Phlebitis | 0.7% | 1.3% |
| Pyrexia | 0.7% | 1.0% |

There were no adverse events reported at a frequency of greater than 2%.
Data from product package insert

**LOOK-ALIKE/SOUND-ALIKE**

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for trade name Eraxis:
Eurax (crotamiton) – topical cream scabicidal, antipruritic

Exratuss (carbetapentane/chlorpheniramine/phenylephrine) - OTC oral suspension

LA/SA for generic name anidulafungin:
Use caution not to confuse with the other echinocandins caspofungin and micafungin

**DRUG INTERACTIONS**

Anidulafungin is not a substrate, inducer, or inhibitor of CYP450 isoenzymes; therefore, significant drug interactions via this mechanism are not expected. There are no drug interaction studies evaluating anidulafungin and sirolimus at this time.

**Table 11: Drug interactions[14-17]**

| n | subjects | Anidulafungin | | Results | Recommendation |
|---|---|---|---|---|---|
| 12 | healthy subjects | Anidulafungin 100mg (200mg loading dose) once daily on days 1-8 | Oral cyclosporine 1.25mg/kg BID on days 5-8 | No change in anidulafungin Cmax Anidulafungin AUC increased by 22% | no dosage adjustment needed for either drug |
| 17 | healthy subjects | Anidulafungin 100mg (200mg loading dose) daily | Oral voriconazole 200mg BID (400mg loading dose x 2) | Cmax and AUC of either drug not significantly altered | no dosage adjustment needed for either drug |
| 35 | healthy subjects | Anidulafungin 100mg (200mg loading dose) once daily on days 4-12 | Oral tacrolimus 5mg on day 1and day 13 | Cmax and AUC of either drug not significantly altered | no dosage adjustment needed for either drug |
| 27 | patients | anidulafungin | liposomal amphotericin B | No change in p-kinetics of anidulafungin + AMB compared to patients receiving anidulafungin alone | no dosage adjustment of anidulafungin needed |
| 27 | patients | anidulafungin | rifampin | No change in p-kinetics of anidulafungin + rifampin compared to patients receiving anidulafungin alone | no dosage adjustment of anidulafungin needed |

**COST**

The acquisition cost of anidulafungin and other antifungals used for the treatment of candidemia is shown below in table 12.

**Table 12: Acquisition cost of antifungals used for treatment of candidemia**

| Drug | Dose | Cost/ unit | Cost/day |
|---|---|---|---|
| Anidulafungin | 100mg daily (200mg loading dose)^ | $67.37/50mg vial | $134.74 |
| Micafungin | 100mg daily* | $66.51/ 50mg vial | $133.02 |
| Caspofungin | 50mg daily (70mg loading dose)^ | $228.19/ 50mg vial | $228.19 |
| Fluconazole | 400mg daily (800mg loading dose)^ | $16.08-19.68 (generic) | $16.08-19.68 |
| Voriconazole | 3-4mg/kg q 12h (6mg/kg q 12h x 2 doses loading dose)^ | $65.75/200mg vial | $131.50-197.25 (based on 70kg) |
| Amphotericin B (conventional) | 0.6-1.0mg/kg/day | $5.07/50mg vial | $5.07-7.10 (based on 70kg) |

| | | | |
|---|---|---|---|
| Liposomal amphotericin B | 3-5mg/kg | $52.76/50mg vial | $211.04-369.32 (based on 70kg) |

^Cost of loading dose not included
*Dose based on that used in clinical trial; not currently approved for candidemia
Does not include cost of IV bags, tubing, adjunctive drugs used to treat adverse reactions, laboratory monitoring, etc.

Table 13 compares the daily acquisition cost of the 3 echinocandins in the treatment of esophageal candidiasis. The majority of patients can be treated with oral fluconazole at a daily cost of $0.125 (tablets) or $1.05-2.00 (suspension) or itraconazole oral solution for $5.07.

**Table 13: Cost per day in esophageal candidiasis**

| Caspofungin | Micafungin | Anidulafungin |
|---|---|---|
| 50mg daily<br>$217.96<br>Mean duration of tx = 9.4 days (7-21d) | 150mg daily<br>$199.53<br>Mean duration of tx = 15days (10-30d) | 50mg daily (100mg LD)<br>$67.37 (does not include cost of LD)<br>Median duration of tx = 14 days |

## REFERENCES


1. Ostrosky-Zeichner L, Rex JH, Pappas PG, et al. Antifungal susceptibility survey of 2,000 bloodstream Candida isolates in the United States. Antimicrob Agents Chemother. 2003 Oct; 47(10):3149-54.

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**Prepared by: Deborah Khachikian, PharmD**
**Date: June 2006**

**Appendix 1: Candidemia trials (see page 11 for abbreviations used)**

| Study | Inclusion/ exclusion criteria | Dose | Demographics and baseline values | Results |
|---|---|---|---|---|
| Krause<br>Phase 2 trial<br>R, dose-ranging study<br><br>ANI 50mg (n=40)<br>ANI 75mg (n=40)<br>ANI 100mg (n=40) | ≥ 18 years old<br>expected survival > 72h<br>blood or tissue sample culture positive for Candida<br>≥1 sign or symptom of infection within 4 days prior to tx initiation<br><br>Exclusion<br>Therapeutic dose of antifungal therapy within 7 days of enrollment unless patient was designated as a treatment failure<br>pregnant/lactating | Loading dose of twice the maintenance dose<br><br>Maintenance dose:<br>50mg vs. 75mg vs. 100mg administered once daily<br><br>Tx continued for 2 weeks after resolution of infection and blood or tissue cultures were negative (or presumed negative if unobtainable) to a maximum of 42 days | **Values for 50mg/ 75mg/ 100mg**<br>**Age (years):** 52/ 54/ 59<br>**% male**: 33/ 53/ 45<br>**Weight (kg):** 68.9/ 76.1/ 70.6<br>**APACHE II score:** 13.4 ± 8.3/ 18.6 ± 9.7/ 15 ± 8.2<br>**% APACHE score ≥ 20:** 18/ 30/ 25<br>**% ANC < 500:** 18/ 13/ 10<br>**% diabetes:** 33/ 30/ 25<br>**% prior systemic antifungal tx:** 58/ 70/ 78<br>**% C. albicans**: 54/ 50/ 56<br>**% C. glabrata:** 30/ 25/ 38<br>**% C. parapsilosis:** 16/ 10/ 3<br>**% C. tropicalis:** 3/ 15/ 8<br>**% C. krusei:** 5/ 8/ 0<br>**Other:** 5/ 0/3 | **ANI 50mg** / **ANI 75mg** / **ANI 100mg**<br>completed study to EOT: 25/40 / 30/40 / 28/40<br>completed study to FU: 18/40 / 26/40 / 24/40<br>Global resp EOT: 21/25 (84%) / 27/30 (90%) / 25/28 (89%)<br>Global resp FU: 13/18 (72%) / 22/26 (85%) / 20/24 (83%)<br>Clinical resp EOT: 22/25 (88%) / 27/30 (90%) / 25/28 (89%)<br>Clinical resp FU: 13/18 (72%) / 22/26 (85%) / 20/24 (83%)<br>Micro resp EOT: 21/25 (84%) / 28/30 (93%) / 25/28 (89%)<br>Micro resp FU: 14/18 (78%) / 22/26 (85%) / 21/24 (88%)<br>median number of doses: 14 / 15 / 14 |
| VER002-9<br>Product package insert/FDA transcripts<br><br>MITT analysis (≥ 1 dose of medication and + culture for *Candida* from a normally sterile site)<br><br>randomized n=256<br>MITT pop n=245<br><br>Non-inferiority trial | ≥ 16 years old<br>≥ 1 positive blood culture or positive culture from a normally sterile site indicating candidemia or IC, respectively, within 96 hours of enrollment, and clinical evidence of active infection<br><br>Exclusions<br>≥ 48h of prior antifungal therapy, failed appropriate antifungal tx for the current infection , received prophylaxis with an azole for ≥ 1 week within 30 days of enrollment, suspected endocarditis, osteomyelitis, meningitis, or infected prosthesis<br>Infection due to *C. krusei*<br>ALT/AST > 10x ULN<br>T. bilirubin > 5 x ULN | Anidulafungin 100mg IV daily (LD 200mg on day 1)<br><br>Fluconazole 400mg IV daily (LD 800mg on day 1)<br><br>tx given for at least 14 and not more than 42 days<br><br>Able to switch to oral fluconazole after at least 10 days of IV tx if:<br>• able to tolerate oral medication<br>• afebrile for ≥ 24 hours<br>• Last blood culture negative for *Candida spp.*<br><br>patients stratified by APACHE II score (≤ 20 and >20) and by the presence or absence of neutropenia | **Values for anidulafungin/ fluconazole**<br>**Mean age (years):** 57/ 59<br>**% male:** 51.2%/ 50.8%<br>**CVP line:** 78%<br>**broad-spectrum antibiotics:** 69%<br>**recent surgery:** 42%<br>**recent hyperalimentation:** 25%<br>**malignancy:** 22%<br>***C. albicans*:** 64%/ 59%<br>***C. glabrata*:** 16%/ 25%<br>***C. parapsilosis*:** 10%/ 14%<br>***C. tropicalis*:** 12%/ 9%<br>Other non-albicans: 5%/ 3%<br>**ANC < 500:** 2.4%/ 3.4%<br>**APACHE II score ≤ 20:** 79.5%/ 83.1%<br>**Mean APACHE II score:** 15/ 14.4 | **Anidulafungin** / **Fluconazole** / **Tx diff [95%CI]**<br># drop-outs (all/ AE/ LOE): 34/12/11 / 48/21/16<br>completed study after 6 wks FU: 94/131 (71.8%) / 80/125 (64%)<br>Global success*: 96/127 (75.6%¶ / 71/118 (60.2%) / 15.42 [3.9, 27]<br>Global success^: 94/127 (74%) / 67/118 (56.8%) / 17.24 [2.9, 31.6]<br>Success at 2-wk FU: 82/127 (64.6%) / 58/118 (49.2%) / 15.41 [0.4, 30.4]<br>Success at 6-wk FU: 71/127 (55.9%) / 52/118 (44.1%) / 11.84 [-3.4, 27]<br>Persistent candidemia *: 6.3% / 14.4%<br>median duration of IV tx: 14 days / 11 days<br>% switching to oral: 26% / 28.8%<br>median duration of oral tx: 7 days / 5 days<br>Overall study: 29/127 (22.8%) / 37/118 (31.4%) |

| | | | | |
|---|---|---|---|---|
| | life expectancy ≤ 72h | | | mortality<br>mortality during study therapy 10/127 (7.9%) 17/118 (14.4%)<br>Mortality due to *Candida* 2/127 (1.6%) 5/118 (4.2%)<br>*at end of IV therapy in MITT population<br>^at end of all therapy (IV + oral) in MITT population<br>¶significant vs. fluconazole |

**Appendix 2: Esophageal candidiasis clinical trial (see below for abbreviations used)**

| | | | | |
|---|---|---|---|---|
| Krause 2004<br>R, DB, DD<br>S. Africa, Thailand, Argentina<br><br>N=601 (300 anidulafungin , 301 fluconazole)<br><br>Non-inferiority | 18-65 years old<br>Diagnosed esophageal candidiasis<br><br>Exclusions<br>Evidence of systemic fungal infection<br>Ulcerative esophageal lesions<br>Hypersensitivity to echinocandins<br>Systemic antifungals in the week before enrolment<br>Life expectancy < 2 months<br>Total bili > 3x ULN<br>Aminotransferases > 3 x ULN<br>ANC < 500<br>Platelets < 60, 000 | Anidulafungin 50mg **IV** daily (LD 100mg on day 1)<br>Fluconazole 100mg **oral** daily (LD 200mg on day 1)<br>Placebo<br><br>Therapy continued for 7 days after resolution of symptoms but not for <14 or > 21 days in total | **Values for anidulafungin/ fluconazole**<br>**Age (years):** 37.5 ± 10.4/ 37 ± 9.6<br>**% male:** 42.3/ 48.2<br>**% AIDS:** 74.3%/ 77.4%<br>**% endoscopy grade 1:** 20.3/ 17.6<br>**% endoscopy grade 2:** 37.3/ 33.6<br>**% endoscopy grade 3:** 42.3/ 48.8<br>**C. albicans as sole pathogen**: 401/442<br>**Antiretroviral use pre-study (n):** 3/ 7<br>**Antiretroviral started during study (n):** 26/ 58 | **Anidulafungin (IV) / Fluconazole (PO)**<br>evaluable population (n) 249 / 255<br>**Endoscopic response at end-of -therapy**<br>Evaluable pop. all/ cure/ improvement 97.2%/ 88%/ 9.2% / 98.8%/ 93.3% 5.5%<br>ITT population (all) 86.7% / 88%<br>Clinical success 246/249 (98.8%) / 254/255 (99.6)<br>Mycological success 156/180 (86.7%) / 169/ 186 (90.9%)<br>Time to resolution of sx 5 days / 5 days<br>Median duration of tx 14 days / 14 days<br>endoscopic success at 2-week followup 150/233 (64.4%) / 205/229 (89.5%)<br>Endoscopic relapse rate at 2-wk FU* 120/225 (53.3%) / 45/233 (19.3%)<br>results of intent-to-treat analysis similar to evaluable population<br>*data from the product package |

Abbreviations: ANI=anidulafungin; AE=adverse event; ANC=absolute neutrophil count; DB=double-blind; DD= double dummy; EOT=end of therapy; FU=follow up; IC=invasive candidiasis; ITT=intent-to-treat; LD=loading dose; LOE=lack of efficacy; MITT=modified intent-to-treat; R=randomized; sx=symptoms; tx=treatment; ULN=upper limit of normal