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Class Update with New Drug Evaluation: Oral Antifungals

Month/Year of Review: July 2015
New Drug: isavuconazole (a.k.a. isavunconazonium sulfate)
Current Status of PDL Class: See Appendix 1.

Date of Last Review: March 2013
Brand Name (Manufacturer): Cresemba™ (Astellas Pharma US, Inc.)
Dossier Received: Yes[1]

Research Questions:

- Is there any new evidence of effectiveness or safety for oral antifungals since the last review that would change current PDL or prior authorization recommendations?
- Is there evidence of superior clinical cure rates or morbidity rates for invasive aspergillosis and invasive mucormycosis for isavuconazole over currently available oral antifungals?
- Is there evidence of superior safety or tolerability of isavuconazole over currently available oral antifungals?
- Is there evidence of superior effectiveness or safety of isavuconazole for invasive aspergillosis and invasive mucormycosis in specific subpopulations?

Conclusions:

- There is low level evidence that griseofulvin has lower mycological cure rates and higher relapse rates than terbinafine and itraconazole for adult onychomycosis.[2] There is high level evidence that terbinafine has more complete cure rates than itraconazole (55% vs. 26%) for adult onychomycosis caused by dermatophyte with similar discontinuation rates for both drugs.[2] There is low level evidence itraconazole has higher complete cure rates than terbinafine (92% vs. 40%) for *Candida* onchomycosis.[2]
- Ketoconazole is associated with increased risk of liver injury, adrenal insufficiency and drug interactions.[3]
- There is high level evidence that voriconazole and posaconazole prevent more fungal infections in high risk hematology patients than fluconazole and itraconazole (OR= 0.47, 95% CI 0.32 – 0.69, I^2=0%, p=0.0001) with no difference in overall mortality or withdrawal due to adverse events.[4]
- There is moderate level evidence that isavuconazole is non-inferior to voriconazole to reduce all-cause mortality at 42 days from invasive aspergillosis in adult patients with hematologic malignancy (18.6% vs. 20.2%; adjusted absolute risk difference (AARD) = -1.0%; 95% CI -8.0%, 5.9%, Δ 10%).[5]
- There is low level evidence from a very small (n=37), open-label, non-comparative phase 3 trial that isavuconazole is effective for mucormycosis.[5]
- There is insufficient comparative safety data for isavuconazole to draw conclusions.[5]
- There are no data regarding use of isavuconazole in specific populations (e.g. elderly, pediatrics).[5]

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Date: July 2015

Recommendations:

- Update the prior authorization criteria to reflect changes to the OHP prioritized list **(Appendix 5).**
- Maintain open access to fluconazole due to high level of evidence for multiple indications (including pediatric candidiasis).
- Maintain clinical prior authorization requirement for griseofulvin, itraconazole and terbinafine due to limited role outside of non-funded onychomycosis.
- Make ketoconazole non-preferred due to increased risk of hepatotoxicity, adrenal insufficiency and drug interactions.
- Allow open access to voriconazole for hematology, oncology and infectious disease specialty prescribers to cover invasive aspergillosis when MMIS functionality allows. All other prescribers would continue to require a clinical prior authorization.
- No other PMPDP changes recommended.

Purpose for Class Update:

Isavuconazole (Cresemba™) was approved by the United States Food and Drug Administration (FDA) in March 2015 for invasive aspergillosis and invasive mucormycosis in adults.[6] This review evaluates its place in therapy and reconsiders current coverage policies in light of any new evidence and changes to the Oregon Health Plan (OHP) prioritized list.[7]

Previous Conclusions and Recommendations (2010):

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harm/adverse events
- Recommend inclusion of at least one medication from this group
- Recommend including nystatin for pediatric use

Background:

The oral antifungal class was ranked 82nd by net OHP fee-for-service drug costs in Q1-2015 ($21,000). Generic fluconazole was associated with 78% of claims and generic nystatin 18% of claims. **Appendix 1** provides a summary of FDA approved and off-label indications for oral and buccal antifungals as reported in Micromedex™.[8] The OHP prioritized list ranks candidiasis of the mouth, skin and nail at line 590, dermatophytosis of the scalp, hand, body at line 547, and dermatophytosis of the nail, groin and foot at line 495.[7] The funding line is currently line 476.[7] Many of these indications are funded on line 141 if they occur in an immunocompromised host.[7] But, notably, onychomycosis is not on line 141 and is not funded except under the co-morbidity rules.[7]

Superficial dermatophyte infections (i.e. ringworm) of the skin and scalp are very common occurring at a 10-20% lifetime incidence in the general population.[9] These specific infections are characterized by itchy, red skin lesions.[10] The majority of cases are caused by *Epidermophyton, Trichophyton* and *Microsporum* which survive on keratin.[11] They can be spread via close person-to-person contact or contact with infected pets. The infections are named by location (e.g. tinea capitis and tinea pedis).[11] Topical antifungals (except nystatin) are recommended and effective for treatment[11] but oral antifungals are indicated for immunocompromised patients.[10] Secondary bacterial infections are a potential complication.[10] Tinea unguium (i.e. onychomycosis) is a dermatophyte infection of the nails though *Candida* accounts for 5–10% of all cases.[2] It is a cosmetic concern but can also cause mild to moderate pain resulting in difficulty in wearing footwear and walking.[2,12] It can serve as a reservoir for fungi that spreads to feet, hands and groin and may increase the risk of secondary bacterial infection for immunocompromised patients.[12] Topical antifungals are not generally effective for onychomycosis and even oral therapy has a high rate of initial treatment failure.[12] Recurrence rates are 40%-70%.[2]

Oral candidiasis (i.e. thrush) is the most common fungal infection in humans with reported asymptomatic carrier rates of up to 75%.[13] The highest rates of symptomatic disease are in patients with impaired immune systems (e.g. patients infected with human immunodeficiency virus [HIV], patients on the extremes of age, and oncology chemotherapy or organ transplant patients).[13] Other risk factors include use of inhaled corticosteroids or use of broad spectrum antibiotics.[13] Complications of oral candidiasis are uncommon but mouth pain may lead to nutritional deficit.[13] Topical therapies (troches, buccal tablets or suspensions) can be effective for mild disease but systemic fluconazole is recommended for all patients (including children).[13] Relapse rates in clinical trials range from 28-75% of patients.[13]

The incidence of invasive fungal infections has increased in the last decade, likely because of the increasing number of patients at risk due to advances in oncology chemotherapy, hematopoietic stem cell transplant and organ transplant.[14] Candidiasis and aspergillosis are the most common pathogens.[14] Mucormycosis is still rare but increasing in prevalence.[14] Other systemic fungal infections include by histoplasmosis, coccidioidomycosis, cryptococcosis, blastomycosis, paracoccidioidomycosis, and sporotrichosis.[14] Generally, in the immunocompetent host, these cause mild or asymptomatic disease but can become invasive in immunocompromised hosts.[14] *Fusarium* and *Cryptococcus* species are additional opportunistic fungi.[14]

Candida infections "range from non–life-threatening mucocutaneous disorders to invasive disease that can involve any organ."[15] Most severe cases affect immunocompromised or critically ill patients where mortality rates are highest.[15] The Infectious Diseases Society of America (IDSA) published evidence-graded treatment guidelines for localized (e.g. vulvovanginal, urinary tract, or esophageal) and systemic infections, including complications such as endocarditis and meningitis, in 2009.[15] Fluconazole is recommended as initial treatment for most localized and systemic infections in immunocompetent adults and children due to its good bioavailability, penetration into the central nervous system and intraocular pentration.[15] The other azole antifungals (itraconazole and voriconazole) demonstrate similar activity against *Candida.*[15] Central nervous system infections or infections in immunocompromised patients require initial treatment with intravenous antifungals (e.g. caspofungin, micafungin or amphotericin B) but recommendations include a step down to oral fluconazole upon improvement.[15] All azoles and flucytosine should be avoided in pregnant women due to documented birth defect risks.[15] Fluconazole is an initial recommendation for antifungal prophylaxis for adult and pediatric patients at high risk of candidiasis (e.g. organ transplant patients, intensive care patients in units with high rates of candidiasis, patients with chemotherapy-induced neutropenia and stem cell transplant patients with neutropenia).[15]

Aspergillus species are associated with allergic bronchopulmonary aspergillosis, which occurs almost exclusively in patients with cystic fibrosis or asthma and is generally treated with steroids.[16] Oral azole antifungals may be used to reduce steroid doses.[16] Other clinical forms of aspergillosis include chronic infection, which affects patients with underlying lung disease, and invasive pulmonary aspergillosis affecting patients with prolonged neutropenia, advanced HIV infection, inherited immunodeficiency and patients who have undergone allogeneic hematopoietic stem cell transplantation or lung transplantation.[16,17] It is the most common fungal pathogen in febrile neutropenic patients.[17] Invasive disease focuses in the lungs and sinuses but may disseminate.[17] Voriconazole is recommended as primary treatment for most patients though; few randomized trials have been performed.[17] Posaconazole or itraconazole are recommended for prophylaxis in high-risk patients.[17]

Mucormycosis, caused by fungi commonly found in soils and decaying vegetation (e.g. *Rhizopus, Mucor, Lichtheimia*), is responsible for serious rhino-orbital-cerebral and pulmonary infections in immunocompromised hosts and diabetics with ketoacidosis.[18,19] *Rhizopus* thrives in high glucose, acidic conditions.[18] It also prefers a high iron environment which is accentuated in the presence of deferoxime and the iron-chelates it produces.[18] While rare (0.4 – 1.7 cases per million/year), it is highly fatal (24-49%).[19] Mucormycosis appears more prevalent after natural disasters (e.g. tornados), in combat zones and is associated with penetrating trauma.[18,19] Current treatment recommendations include surgical debridement and amphotericin B.[18]

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls was conducted. The Medline search strategies used for this review are available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines.

Systematic Reviews:

Onychomycosis

A fair quality systematic review of oral onychomycosis therapy published in December 2013 included 46 placebo or active RCTs of terbinafine, fluconazole, itraconazole, posaconazole, griseofulvin, and ketoconazole and compared clinical or mycological cure rates.[20] Study rigor was not reported. There was no formal pooling of results but the authors concluded fluconazole, itraconazole and terbinafine were effective. Terbinafine produced the "best result" when dermatophyte was the pathogen and the azoles were recommended for *Candida* infections.[20]

Gupta and Paquet published a fair quality qualitative systematic review of oral onychomycosis therapy in children that included 26 publications.[21] Case reports (18) and retrospective studies (3) were also included because of the lack of information in this population.[21] Interventions included terbinafine, itraconazole, griseofulvin and fluconazole.[21] Sample sizes were very small (1 – 19).[21] Outcomes were converted to "complete cure", defined as 100% visual clearing of the nail or negative fungal culture, in order to pool the data.[21] Overall, oral therapy resulted in a complete cure rate in 70.8% of patients (n=151).[21] The authors concluded systemic antifungals for pediatric onychomycosis was safe and effective.[21]

Aspergillosis

Cochrane published a systematic review of the effectiveness and safety of antifungal therapies for allergic bronchopulmonary aspergillosis in people with cystic fibrosis.[22] Four trials were identified but no studies met the inclusion criteria.

Antifungal prophylaxis in hematology patients

Ping et al. published a good quality meta-analysis comparing oral first generation azoles (fluconazole and itraconazole) to oral second generation azoles (voriconazole and posaconazole) for prophylaxis of fungal infections in hematology patients.[4] Four RCTs (n=2267) were included that reported proved or probable invasive fungal infections as the outcome.[4] Second generation azoles reduced the odds of fungal infection (OR= 0.47, 95% CI 0.32 – 0.69, I^2=0%, p=0.0001).[4] There was no difference between the regimens on overall mortality or withdrawal due to adverse events.[4]

New Guidelines:

Onychomycosis

British Association of Dermatologists (BAD) produced a good quality guideline for management of onychomycosis that was intended for implementation by the British National Health Service.[2] Twelve weeks of itraconazole and 12-16 weeks of terbinafine are recommended first line treatment for adult toenail onychomycosis based upon at least one high-quality meta-analysis, systematic review or RCT.[2] Terbinafine has reported better complete cure rates (100% absence of clinical signs and negative mycology results) than itraconazole (55% vs. 26%) and lower relapse rates (23%-21% vs. 53%-48%) for dermatophyte onychomycosis.[2] Itraconazole is considered more effective for *Candida* onychomycosis.[2] Terbinafine is well tolerated but there have been rare reports of Stevens–Johnson syndrome, and serious hepatic toxicity in patients with existing liver disease.[2] Reported adverse effects of itraconazole included hepatitis and prolonged QT interval. Discontinuation was similar for both drugs and lower if either was given as a pulse regimen rather than continuously.[2] Fluconazole is recommended for patients unable to tolerate itraconazole or terbinafine based upon at least one high-quality systematic review of case–control or cohort studies.[2] Griseofulvin has poor oral bioavailability unless taken with fatty foods, lower mycological cure (negative mycology results but clinical signs remain) rates (30–40%) and higher relapse rates so, is not recommended unless other drugs are unavailable or contraindicated based upon well-conducted case–control or cohort studies with a low risk of confounding, bias or chance.[2] Reported adverse effects included nausea and rashes in 8–15% of patients.[2] The BAD also provide recommendations in special populations.[2] Onychomycosis is present in up to 33% diabetics and considered a predictor for the development of diabetic foot ulcers.[2] There is reportedly a prevalence of 30% in HIV patients.[2] Terbinafine is recommended for both cases due to lower risk of drug interactions and high efficacy.[2] Recommendations for children are similar to adults but with lower levels of evidence.

Invasive fungal infections in cancer patients

The Infectious Diseases Working Party of the German Society of Hematology and Oncology updated treatment recommendations for fungal infections in cancer patients.[23] The guideline focused on patients with solid tumors or hematologic malignancies and includes treatment of acute invasive infections caused by *Aspergillus, Candida, Cryptococcus, Scedosporium, Fusarium, Zygomycetes,* and *Trichosporon.* The literature search end date was June 2012.[23] IDSA evidence levels were used: I- at least 1 properly conducted RCT, II- at least 1 well-designed, non-randomized controlled clinical trial or dramatic results of uncontrolled experiments, III – expert opinion.[23] Intravenous therapies are frequently required for initial therapy with step-down to oral therapies when clinically indicated. Oral therapies include: voriconazole (level I) is recommended for invasive aspergillosis and posaconazole is second-line treatment (level II).[23] Voriconazole or fluconazole is recommended (level I) for candidemia in non-neutropenic patients.[23] Posaconazole is recommended first-line for mucormycosis (level III).[23] Voriconazole is recommended for the very rare *Scedospoirum* and *Trichosporon* infections and fusariosis (level III).[23] Posaconazole is recommended for *Scedospoirum* (level III).[23]

Mucormycosis

The European Conference on Infections in Leukemia published diagnosis and treatment guidelines for mucormycosis.[24] Evidence is very limited because of the rarity of the disease. The guidelines apply to all patients (hematologic and non-hematologic) because existing studies are in mixed populations.[24] A consensus based approach was used using IDSA evidence levels where possible: I- at least 1 properly conducted RCT, II- at least 1 well-designed, non-randomized controlled clinical trial or dramatic results of uncontrolled experiments, III – expert opinion.[24] The conference attendees acknowledge relationships with multiple manufacturers and the conference was funded by an unrestricted grant from Astellas Pharma, Gilead Sciences, Mercke Sharp Dohme, Pfizer and Schering Plough.[24] Amphotericin B deoxycholate is recommended (level II) and is FDA-approved for mucormycosis. Posaconazole is recommended second-line (level II) and for maintenance treatment (level III) using data from 2 separate but overlapping compassionate use protocols (n=104).[24] Overall, 73% of patients survived 1

month post-therapy for the infection. Isavuconazole *in vitro* activity is mentioned in the guidelines but clinical data were not available at the time of publication.[24]

European Society for Clinical Microbiology and Infectious Diseases and European Confederation of Medical Mycology published joint clinical guidelines for the diagnosis and management of mucormycosis.[19] The methods for evidence gathering, grading (IDSA) and consensus approach were published for transparency.[19] Multiple industry funding declarations encompass more than one complete page of the publication.[19] Posaconazole is recommended for prophylaxis in neutropenic or graft versus host disease patients in an "outbreak situation" (level III) but the authors acknowledge this is a contrived situation.[19] Posaconazole is recommended second-line for treatment (level II) based upon the compassionate use data mentioned above and only if liposomal amphotericin B in not effective or not tolerated.[19] Isavuconazole is not mentioned in the guidelines.

Hyalohyphomycosis

European Society for Clinical Microbiology and Infectious Diseases and European Confederation of Medical Mycology published joint clinical guidelines for a heterogeneous group of mycoses defined by the presence of hyaline hyphae.[19] This includes the genera of *Fusarium, Scedosporium, Acremonium, Scopulariopsis, Purpureocillium* and *Paecilomyces* which are increasingly affecting severely immunocompromised patients.[19] The guideline covers epidemiology, clinical spectrum, diagnosis and therapy, mainly for species associated with the genera *Fusarium* and *Scedosporium*. The methods for evidence gathering, grading (IDSA) and consensus approach were published for transparency.[19] Voriconazole is recommended first-line treatment for both species (level II) with posaconazole recommended for *Fusarium* salvage treatment (level II).[19]

New Safety Alerts:

Ketoconazole – 7/26/2013[3]

The FDA updated the label to limit the use of oral ketoconazole due to potentially fatal liver injury, risk of drug interactions and adrenal gland problems. It should only be used for treatment of fungal infections when alternative antifungal therapies are not available or not tolerated. The black box warning was revised to include a contraindication in patients with liver disease. Serious liver damage has occurred in patients on high doses for short duration and low doses for long duration with no other obvious signs of liver injury. Ketoconazole may cause adrenal insufficiency by decreasing the production of corticosteroids.

New Formulations or Indications:

No new indications or formulations identified.

Randomized Controlled Trials:

50 potentially relevant clinical trials were identified from the literature search. After further review, 0 trials were relevant head-to-head comparisons of oral antifungals and were therefore excluded.

NEW DRUG EVALUATION:

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

ClinicalTrials.gov lists 29 studies but, the majority is pharmacokinetic and drug interaction studies.[25] There is 1 Phase 2/3 study listed (NCT00413439 – prophylaxis in chemotherapy patients, n=18) and 3 phase 3 (NCT00413218 - invasive *Candida* treatment, n=450; NCT00634049 aka VITAL – renally impaired aspergillosis treatment, n=150; NCT00412893 aka SECURE – invasive aspergillosis treatment, n=527).[25] NCT00412893 has results posted.[25] No published placebo-controlled trials of isavuconazole were identified (see **Appendix 4)**. The manufacturer's dossier identifies a New England Journal of Medicine publication of the SECURE trial is pending.[1] The FDA Summary Review identified 2 Phase 3 studies, one in patients with invasive aspergillosis (presumably SECURE) and another in patients with invasive fungal disease including invasive mucormycosis (presumably VITAL).[5] The FDA narrative[5] is summarized below.

Clinical Efficacy[5]:
Isavuconazole 200 mg intravenous (IV) loading dose 3 times per day for 2 days followed by 200 mg IV or orally once a day was compared to voriconazole 6 mg/kg IV every 12 hours for 24 hours followed by 4 mg/kg IV or orally every 12 hours in a randomized, double-blind, non-inferiority study of invasive aspergillosis treatment. Patients were treated for 7 days after resolution of all clinical signs of infection, or a maximum of 84 days. The non-inferiority delta was 10% for the primary endpoint for all-cause mortality through day 42 and was judged to be reasonable by the FDA reviewer. Patients were adults, primarily with hematologic malignancy. Patients with a creatinine clearance of less than 50mL/min were excluded. The trial enrolled 527 patients but excluded 11 because they did not take the study drug, leaving 258 in each group. After randomization, patients were screened against criteria for proven, probable, possible or no invasive fungal disease. An additional 244 patients were excluded from the modified intention-to-treat (mITT) population because they did not meet the criteria for proven or probable invasive fungal disease. The mITT population consisted of 123 isavuconazole and 108 voriconazole patients. Using the ITT, the rate of all-cause mortality at day 42 was 18.6% in the isavuconazole group compared to 20.2% in the voriconazole group, with an adjusted absolute risk difference (AARD) of -1.0% (95% CI -8.0%, 5.9%), thus meeting the non-inferiority delta. This was confirmed with the mITT (AARD = -2.7% 95% CI -13.65, 8.2%).

The second trial was an open-label, non-comparative trial for treatment of invasive fungal disease caused by *Aspergillus* in patients with renal impairment or caused by rare filamentous fungi. Only the rare filamentous fungi results were used by the FDA for the invasive mucormycosis indication. Survival status was recorded at Days 42, 84 and 4 weeks after the last dose of isavuconazole, with Day 42 designated by the FDA as the most relevant endpoint. The mITT-*Mucorales* population included patients classified as having infection due *Mucorales* only (n=37). The all-cause mortality at day 42 was 14/37 (37.8%). These results were compared to 2 epidemiologic reports (n=22, n=241) where untreated mucormycosis mortality ranged from 95% to 97%. Patients were also matched to 3 controls who received amphotericin B from the Fungiscope Registry Database. The results of the matched control mortality comparison were: isavuconazole 7/21 (33.3%; 95% CI 14.6%, 57.0%) and amphotericin B 13/33 (39.4%; 95% CI 22.9%, 57.9%).

Clinical Safety[5]:
The safety database consists of 1692 subjects, including 1145 healthy volunteers from Phase 1 and 2 studies. The mean duration of exposure was 60 days. The SECURE trial treatment-emergent adverse events were more common in the voriconazole group (59.8%) than the isavuconazole group (42.4%, $p < 0.001$) and fewer isavuconazole patients withdrew due to adverse events (14.4% versus 22.8%, p=0.017).[1] Exclusion criteria from the SECURE study included hepatic dysfunction, patients with creatinine clearance of < 50ml/min, chronic aspergillosis, aspergilloma or allergic aspergillosis, previous antifungal therapy of more

than 4 days, CD4 counts < 200 cells/mm or AIDS, mechanical ventilation or a case that is unlikely to survive 30 days.[1] Data are still insufficient to draw definite conclusions about the relative safety of isavuconazole in a clinical setting.

Pharmacology and Pharmacokinetic Properties[26]:

Parameter	
Mechanism of Action	"Isavuconazole inhibits the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14-alpha-demethylase. This enzyme is responsible for the conversion of lanosterol to ergosterol. An accumulation of methylated sterol precursors and a depletion of ergosterol within the fungal cell membrane weakens the membrane structure and function. Mammalian cell demethylation is less sensitive to isavuconazole inhibition."[26]
Oral Bioavailability	98% (with or without food)
Distribution and Protein Binding	Volume of distribution ~450 liters; 99% protein bound, predominantly to albumin
Elimination	46.1% feces; 45.5% urine
Half-Life	130 hours
Metabolism	prodrug isavuconazonium sulfate is rapidly hydrolyzed in blood to isavuconazole; isavuconazole is CYP 3A4 and 3A5 substrate

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21. Gupta AK, Paquet M. Systemic antifungals to treat onychomycosis in children: a systematic review. *Pediatr Dermatol*. 2013;30(3):294-302. doi:10.1111/pde.12048.

22. Elphick HE, Southern KW. Antifungal therapies for allergic bronchopulmonary aspergillosis in people with cystic fibrosis. [Review][Update of Cochrane Database Syst Rev. 2012;6:CD002204; PMID: 22696329]. *Cochrane Database Syst Rev*. 2014. doi:10.1002/14651858.CD002204.pub3.

23. Mousset S, Buchheidt D, Heinz W, et al. Treatment of invasive fungal infections in cancer patients—updated recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Ann Hematol*. 2014;93(1):13-32. doi:10.1007/s00277-013-1867-1.

24. Skiada A, Lanternier F, Groll AH, et al. Diagnosis and treatment of mucormycosis in patients with hematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia (ECIL 3). *Haematologica*. 2013;98(4):492-504. doi:10.3324/haematol.2012.065110.

25. Isavuconazole - List Results. *ClinicalTrials.gov*. https://clinicaltrials.gov/ct2/results?term=isavuconazole&Search=Search. Accessed May 13, 2015.

26. Astellas Pharma US, Inc. Cresemba label. March 2015. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207500Orig1s000lbl.pdf. Accessed May 12, 2015.

Appendix 1: Oral Antifungal Agents and Indications[8]

PDL	Generic	Dermatomycosis*	Onychomycosis^	Oropharyngeal candidiasis*	Candidiasis	Aspergillosis	Other fungal infections	Prophylaxis in high-risk patients (adult)
Y	CLOTRIMAZOLE (TROCHE)			FDA				FDA: candidiasis (oropharyngeal)
Y	FLUCONAZOLE (ORAL)	off-label	off-label	FDA	FDA: esophagus, urogenital, sepsis off-label: other sites		FDA: cryptococcal meningitis off-label: blastomycosis coccidioidomycosis cryptococcosis (pulmonary) histoplasmosis sporotrichosis (lymphocutaneous)	FDA: candidiasis off-label: candidiasis (pediatric) histoplasmosis coccidioidomycosis
Y	KETOCONAZOLE (ORAL)						FDA if intolerant or failed other therapies: blastomycosis, coccidioidomycosis, chromoblastomycosis, histoplasmosis, paracoccidioidomycosis	
Y	NYSTATIN (SUSP)			FDA				off-label: candidiasis (oropharyngeal)
Y	NYSTATIN (ORAL)				FDA: gastrointestinal			
N	FLUCYTOSINE (ORAL)			FDA	FDA		FDA: cryptococcosis, cryptococcal meningitis off-label: cryptococcosis (pulmonary)	
N	GRISEOFULVIN	FDA	FDA					
N	ITRACONAZOLE (ORAL)	off-label	FDA	FDA	FDA: esophagus	FDA	FDA: blastomycosis, histoplasmosis off-label: chromoblastomycosis, coccidioidomycosis, cryptococcosis, cryptococcal meningitis paracoccidioidomycosis, sporotrichosis	off-label: candidiasis(oropharyngeal) coccidioidomycosis, histoplasmosis
N	MICONAZOLE (BUCCAL)			FDA				
N	POSACONAZOLE (ORAL)			FDA	FDA: disseminated off-label: esophagus	FDA	off-label: fusarium	off-label: candidiasis (esophagus)
N	TERBINAFINE (ORAL)	FDA	FDA					
N	VORICONAZOLE (ORAL)			off-label	FDA: esophagus, sepsis, disseminated	FDA	FDA: scedosporium, apiospermum & fusarium species off-label: blastomycosis	off-label: aspergillosis

*Not funded by OHP unless present in immunocompromised host; ^Not funded by OHP

Appendix 2: Abstracts of Clinical Trials - No head to head RCTs of oral antifungals identified.

Appendix 3: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CRESEMBA safely and effectively. See full prescribing information for CRESEMBA.

CRESEMBA® (isavuconazonium sulfate)
Capsules for oral administration
For Injection for intravenous administration
Initial U.S. Approval: 2015

----------INDICATIONS AND USAGE----------

CRESEMBA is an azole antifungal indicated for use in the treatment of:

- Invasive aspergillosis (1.1).
- Invasive mucormycosis (1.2).

----------DOSAGE AND ADMINISTRATION----------

- CRESEMBA for injection must be administered through an in-line filter over a minimum of 1 hour (2.1).
- Loading Dose: 372 mg isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) every 8 hours for 6 doses (48 hours) via oral (2 capsules) or intravenous administration (1 reconstituted vial) (2.2).
- Maintenance Dose: 372 mg isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) once daily via oral (2 capsules) or intravenous administration (1 reconstituted vial) starting 12 to 24 hours after the last loading dose (2.2).
- Capsules can be taken with or without food (2.2).

----------DOSAGE FORMS AND STRENGTHS----------

- CRESEMBA capsules contain 186 mg of isavuconazonium sulfate (equivalent to 100 mg of isavuconazole) (3).
- CRESEMBA for injection is supplied in a single-dose vial as a sterile lyophilized powder containing 372 mg of isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) (3).

----------CONTRAINDICATIONS----------

- Hypersensitivity to CRESEMBA (4).
- Coadministration with strong CYP3A4 inhibitors, such as ketoconazole or high-dose ritonavir (4, 7).
- Coadministration with strong CYP3A4 inducers, such as rifampin, carbamazepine, St. John's wort, or long acting barbiturates (4, 7).
- Use in patients with familial short QT syndrome (4).

----------WARNINGS AND PRECAUTIONS----------

- Hepatic Adverse Drug Reactions: Serious hepatic reactions have been reported. Evaluate liver-related laboratory tests at the start and during the course of CRESEMBA therapy (5.1).
- Infusion-related reactions were reported during intravenous administration of CRESEMBA. Discontinue the infusion if these reactions occur (5.2).
- Hypersensitivity Reactions: Serious hypersensitivity and severe skin reactions, such as anaphylaxis or Stevens Johnson syndrome, have been reported during treatment with other azole antifungal agents. Discontinue CRESEMBA for exfoliative cutaneous reactions (5.3).
- Embryo-Fetal Toxicity: Do not administer to pregnant women unless the benefit to the mother outweighs the risk to the fetus. Inform pregnant patients of the hazard (5.4).
- Drug Interactions: Review patient's concomitant medications. Several drugs may significantly alter isavuconazole concentrations. Isavuconazole may alter concentrations of several drugs (5.5, 7, 12.3).
- Drug Particulates: Intravenous formulation may form insoluble particulates following reconstitution. Administer CRESEMBA through an in-line filter (2.4, 5.6).

----------ADVERSE REACTIONS----------

Most frequent adverse reactions: nausea, vomiting, diarrhea, headache, elevated liver chemistry tests, hypokalemia, constipation, dyspnea, cough, peripheral edema, and back pain (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Astellas Pharma US, Inc. at 1-800-727-7003 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- CYP3A4 inhibitors or inducers may alter the plasma concentrations of isavuconazole (7).
- Appropriate therapeutic drug monitoring and dose adjustment of immunosuppressants (i.e., tacrolimus, sirolimus, and cyclosporine) may be necessary when co-administered with CRESEMBA (7).
- Drugs with a narrow therapeutic window that are P-gp substrates, such as digoxin, may require dose adjustment when administered concomitantly with CRESEMBA (7).

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: CRESEMBA should only be used if the benefits to the mother outweigh the risk to the fetus. Inform pregnant woman of risk (8.1).
- Mothers should not breast feed children while taking CRESEMBA (8.3).
- Use in patients with severe hepatic impairment only when the benefits outweigh the risks; clinical monitoring for CRESEMBA-related adverse reactions is recommended (8.7).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2015

Appendix 4: Medline Search Strategy

Database(s): Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to May Week 1 2015
Search Strategy:

#	Searches	Results
1	exp fluconazole/ or exp itraconazole/ or exp voriconazole/	11748
2	exp clotrimazole/ or exp miconazole/	3117
3	exp Ketoconazole/	5093
4	exp Nystatin/	2962
5	exp Flucytosine/	2442
6	Griseofulvin/	2931
7	antifungal agents/ or exp fluconazole/ or exp flucytosine/ or exp griseofulvin/ or exp itraconazole/ or exp ketoconazole/ or exp miconazole/ or exp nystatin/ or exp voriconazole/	56350
8	POSACONAZOLE.mp.	1372
9	TERBINAFINE.mp.	1996
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	57439
11	exp blastomycosis/ or exp candidiasis/ or exp candidiasis, chronic mucocutaneous/ or exp candidiasis, cutaneous/ or exp candidiasis, invasive/ or exp candidiasis, oral/ or exp coccidioidomycosis/ or exp cryptococcosis/ or exp meningitis, cryptococcal/ or blastomycosis/ or candidiasis, chronic mucocutaneous/ or candidiasis, cutaneous/ or chromoblastomycosis/ or exp hyalohyphomycosis/ or exp aspergillosis/ or exp fusariosis/ or exp paracoccidioidomycosis/ or exp sporotrichosis/ or tinea/ or onychomycosis/ or exp tinea capitis/ or exp tinea favosa/ or exp tinea pedis/ or exp tinea versicolor/ or exp fungemia/ or exp candidemia/ or exp histoplasmosis/ or exp aspergillosis, allergic bronchopulmonary/ or exp neuroaspergillosis/ or exp trichosporonosis/ or exp zygomycosis/ or exp mucormycosis/	71615
12	10 and 11	19985
13	limit 12 to (english language and humans and yr="2013 -Current")	1295
14	limit 13 to (meta analysis or systematic reviews)	50

1. Javed F, Samaranayake LP, Romanos GE. Treatment of oral fungal infections using antimicrobial photodynamic therapy: a systematic review of currently available evidence. *Photochem Photobiol Sci.* 2014;13(5):726-34. doi:10.1039/c3pp50426c EXCLUDED - INTERVENTION

2. Dolton MJ, McLachlan AJ. Voriconazole pharmacokinetics and exposure-response relationships: assessing the links between exposure, efficacy and toxicity. *Int J Antimicrob Agents.* 2014;44(3):183-93. doi:10.1016/j.ijantimicag.2014.05.019 EXCLUDED-OUTCOME

3. Badiee P, Hashemizadeh Z. Opportunistic invasive fungal infections: diagnosis & clinical management. *Indian J Med Res.* 2014;139(2):195-204. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com.liboff.ohsu.edu/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=24718393. Accessed May 08, 2015. EXCLUDED – DESIGN

4. Gupta AK, Elewski BE, Sugarman JL, et al. The efficacy and safety of efinaconazole 10% solution for treatment of mild to moderate onychomycosis: a pooled analysis of two phase 3 randomized trials. *J Drugs Dermatol.* 2014;13(7):815-20. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com.liboff.ohsu.edu/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=25007364. Accessed May 08, 2015. EXCLUDED – INTERVENTION

5. Yao ZW, Lu X, Shen C, Lin DF. Comparison of flucytosine and fluconazole combined with amphotericin B for the treatment of HIV-associated cryptococcal meningitis: a systematic review and meta-analysis. *Eur J Clin Microbiol Infect Dis.* 2014;33(8):1339-44. doi:10.1007/s10096-014-2074-2 EXCLUDED - INTERVENTION

6. Austin CL, Finley PJ, Mikkelson DR, Tibbs B. Mucormycosis: a rare fungal infection in tornado victims. *J Burn Care Res.* 2014;35(3):e164-71. doi:10.1097/BCR.0b013e318299d4bb EXCLUDED – DESIGN

7. Elphick HE, Southern KW. Antifungal therapies for allergic bronchopulmonary aspergillosis in people with cystic fibrosis. *Cochrane Database Syst Rev.* 2014;11:CD002204. doi:10.1002/14651858.CD002204.pub3 INCLUDED

8. Scudeller L, Viscoli C, Menichetti F, et al. An Italian consensus for invasive candidiasis management (ITALIC). *Infection.* 2014;42(2):263-79. doi:10.1007/s15010-013-0558-0 EXCLUDED – DESIGN

9. Hentrich M, Schalk E, Schmidt-Hieber M, et al. Central venous catheter-related infections in hematology and oncology: 2012 updated guidelines on diagnosis, management and prevention by the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology. *Ann Oncol.* 2014;25(5):936-47. doi:10.1093/annonc/mdt545 EXCLUDED - INTERVENTION

10. El-Gohary M, van Zuuren EJ, Fedorowicz Z, et al. Topical antifungal treatments for tinea cruris and tinea corporis. *Cochrane Database Syst Rev.* 2014;8:CD009992. doi:10.1002/14651858.CD009992.pub2 EXCLUDED-INTERVENTION

11. Gupta AK, Lyons DC. Pityriasis versicolor: an update on pharmacological treatment options. *Expert Opin Pharmacother.* 2014;15(12):1707-13. doi:10.1517/14656566.2014.931373 EXCLUDED - DESIGN

12. Margarido Lda C. Oral treatments for fungal infections of the skin of the foot. *Sao Paulo Med J.* 2014;132(2):127. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com.liboff.ohsu.edu/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=24714996. Accessed May 08, 2015. EXCLUDED – UNAVAILABLE AT OHSU.

13. Gisi U. Assessment of selection and resistance risk for demethylation inhibitor fungicides in Aspergillus fumigatus in agriculture and medicine: a critical review. *Pest manag sci.* 2014;70(3):352-64. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com.liboff.ohsu.edu/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=24123539. Accessed May 08, 2015. EXCLUDED - OUTCOME

14. Gupta AK, Lane D, Paquet M. Systematic review of systemic treatments for tinea versicolor and evidence-based dosing regimen recommendations. *J Cutan Med Surg.* 2014;18(2):79-90. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com.liboff.ohsu.edu/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=24636433. Accessed May 08, 2015. EXCLUDED - OUTCOME

15. Tortorano AM, Richardson M, Roilides E, et al. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: Fusarium spp., Scedosporium spp. and others. *Clin Microbiol Infect.* 2014;20 Suppl 3:27-46. doi:10.1111/1469-0691.12465 INCLUDED

16. Cornely OA, Arikan-Akdagli S, Dannaoui E, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. *Clin Microbiol Infect.* 2014;20 Suppl 3:5-26. doi:10.1111/1469-0691.12371 INCLUDED

17. Jorgensen KJ, Gotzsche PC, Dalboge CS, Johansen HK. Voriconazole versus amphotericin B or fluconazole in cancer patients with neutropenia. *Cochrane Database Syst Rev.* 2014;2:CD004707. doi:10.1002/14651858.CD004707.pub3 EXCLUDED NO RECENT STUDIES IN UPDATE

18. de Sa DC, Lamas AP, Tosti A. Oral therapy for onychomycosis: an evidence-based review. *Am J Clin Dermatol.* 2014;15(1):17-36. doi:10.1007/s40257-013-0056-2 INCLUDED

19. Drgona L, Khachatryan A, Stephens J, et al. Clinical and economic burden of invasive fungal diseases in Europe: focus on pre-emptive and empirical treatment of Aspergillus and Candida species. *Eur J Clin Microbiol Infect Dis.* 2014;33(1):7-21. doi:10.1007/s10096-013-1944-3 EXCLUDED - OUTCOME

20. Mousset S, Buchheidt D, Heinz W, et al. Treatment of invasive fungal infections in cancer patients-updated recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Ann Hematol.* 2014;93(1):13-32. doi:10.1007/s00277-013-1867-1 INCLUDED

21. Gupta AK, Paquet M, Simpson F, Tavakkol A. Terbinafine in the treatment of dermatophyte toenail onychomycosis: a meta-analysis of efficacy for continuous and intermittent regimens. *J Eur Acad Dermatol Venereol.* 2013;27(3):267-72. doi:10.1111/j.1468-3083.2012.04584.x EXCLUDED - INTERVENTION

22. Leroux S, Ullmann AJ. Management and diagnostic guidelines for fungal diseases in infectious diseases and clinical microbiology: critical appraisal. *Clin Microbiol Infect.* 2013;19(12):1115-21. doi:10.1111/1469-0691.12426 EXCLUDED - INTERVENTION

23. Kisand K, Peterson P. Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy and other primary immunodeficiency diseases help to resolve the nature of protective immunity against chronic mucocutaneous candidiasis. *Curr Opin Pediatr.* 2013;25(6):715-21. doi:10.1097/MOP.0000000000000028 EXCLUDED - INTERVENTION

24. Skupien JA, Valentini F, Boscato N, Pereira-Cenci T. Prevention and treatment of Candida colonization on denture liners: a systematic review. *J Prosthet Dent.* 2013;110(5):356-62. doi:10.1016/j.prosdent.2013.07.003 EXCLUDED - INTERVENTION

25. Montravers P, Dupont H, Eggimann P. Intra-abdominal candidiasis: the guidelines-forgotten non-candidemic invasive candidiasis. *Intensive Care Med.* 2013;39(12):2226-30. doi:10.1007/s00134-013-3134-2 EXCLUDED - DESIGN

26. Bassetti M, Marchetti M, Chakrabarti A, et al. A research agenda on the management of intra-abdominal candidiasis: results from a consensus of multinational experts. *Intensive Care Med.* 2013;39(12):2092-106. doi:10.1007/s00134-013-3109-3 EXCLUDED - DESIGN

27. Veeravagu A, Ludwig C, Camara-Quintana JQ, Jiang B, Lad N, Shuer L. Fungal infection of a ventriculoperitoneal shunt: histoplasmosis diagnosis and treatment. *World Neurosurg.* 2013;80(1-2):222.e5-13. doi:10.1016/j.wneu.2012.12.016 EXCLUDED – DESIGN

28. Stein Gold LF, Parish LC, Vlahovic T, et al. Efficacy and safety of naftifine HCl Gel 2% in the treatment of interdigital and moccasin type tinea pedis: pooled results from two multicenter, randomized, double-blind, vehicle-controlled trials. *J Drugs Dermatol.* 2013;12(8):911-8. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com.liboff.ohsu.edu/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=23986165. Accessed May 08, 2015. EXCLUDED - INTERVENTION

29. Rebolledo M, Sarria JC. Intra-abdominal fungal infections. *Curr Opin Infect Dis.* 2013;26(5):441-6. doi:10.1097/01.qco.0000433309.21148.f7 EXCLUDED - DESIGN

30. Pammi M, Holland L, Butler G, Gacser A, Bliss JM. Candida parapsilosis is a significant neonatal pathogen: a systematic review and meta-analysis. *Pediatr Infect Dis J.* 2013;32(5):e206-16. doi:10.1097/INF.0b013e3182863a1c EXCLUDED - INTERVENTION

31. Kanji JN, Laverdiere M, Rotstein C, Walsh TJ, Shah PS, Haider S. Treatment of invasive candidiasis in neutropenic patients: systematic review of randomized controlled treatment trials. *Leuk Lymphoma.* 2013;54(7):1479-87. doi:10.3109/10428194.2012.745073 EXCLUDED – INTERVENTION

32. Aung AK, Teh BM, McGrath C, Thompson PJ. Pulmonary sporotrichosis: case series and systematic analysis of literature on clinico-radiological patterns and management outcomes. *Med Mycol.* 2013;51(5):534-44. doi:10.3109/13693786.2012.751643 EXCLUDED – DESIGN

33. Lu S, Lu C, Zhang J, Hu Y, Li X, Xi L. Chromoblastomycosis in Mainland China: a systematic review on clinical characteristics. *Mycopathologia.* 2013;175(5-6):489-95. doi:10.1007/s11046-012-9586-z EXCLUDED - INTERVENTION

34. Ramsamy Y, Muckart DJ, Han KS. Microbiological surveillance and antimicrobial stewardship minimise the need for ultrabroad-spectrum combination therapy for treatment of nosocomial infections in a trauma intensive care unit: an audit of an evidence-based empiric antimicrobial policy. *SAMJ, S. Afr. med. j..* 2013;103(6):371-6. doi:10.7196/samj.6459 EXCLUDED - INTERVENTION

35. Colombo AL, Guimaraes T, Camargo LF, et al. Brazilian guidelines for the management of candidiasis - a joint meeting report of three medical societies: Sociedade Brasileira de Infectologia, Sociedade Paulista de Infectologia and Sociedade Brasileira de Medicina Tropical. *Braz J Infect Dis.* 2013;17(3):283-312. doi:10.1016/j.bjid.2013.02.001 EXLCUDED - UNAVAILABLE

36. Barrett ME, Heller MM, Stone HF, Murase JE. Raynaud phenomenon of the nipple in breastfeeding mothers: an underdiagnosed cause of nipple pain. *JAMA Dermatol..* 2013;149(3):300-6. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com.liboff.ohsu.edu/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=23682366. Accessed May 08, 2015. EXCLUDED - INTERVENTION

37. Ping B, Zhu Y, Gao Y, Yue C, Wu B. Second- versus first-generation azoles for antifungal prophylaxis in hematology patients: a systematic review and meta-analysis. *Ann Hematol.* 2013;92(6):831-9. doi:10.1007/s00277-013-1693-5 INCLUDED

38. Gupta AK, Paquet M. Systemic antifungals to treat onychomycosis in children: a systematic review. *Pediatr Dermatol.* 2013;30(3):294-302. doi:10.1111/pde.12048 INCLUDED

39. Skiada A, Lanternier F, Groll AH, et al. Diagnosis and treatment of mucormycosis in patients with hematological malignancies: guidelines from the 3rd European Conference

on Infections in Leukemia (ECIL 3). *Haematologica.* 2013;98(4):492-504. doi:10.3324/haematol.2012.065110 INCLUDED

40. Rosa MI, Silva BR, Pires PS, et al. Weekly fluconazole therapy for recurrent vulvovaginal candidiasis: a systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol.* 2013;167(2):132-6. doi:10.1016/j.ejogrb.2012.12.001 EXCLUDED - INTERVENTION

41. Hamada Y, Okuma R, Katori Y, et al. Bibliographical investigation (domestic and overseas) on the treatment of endogenous Candida endophthalmitis over an 11-year period. *Med Mycol J.* 2013;54(1):53-67. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com.liboff.ohsu.edu/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=23470956. Accessed May 08, 2015. EXCLUDED - DESIGN

42. Njei B, Kongnyuy EJ, Kumar S, Okwen MP, Sankar MJ, Mbuagbaw L. Optimal timing for antiretroviral therapy initiation in patients with HIV infection and concurrent cryptococcal meningitis. *Cochrane Database Syst Rev.* 2013;2:CD009012. doi:10.1002/14651858.CD009012.pub2 EXCLUDED - INTERVENTION

43. Mori M, Fukushima K, Miharu M, Goto H, Yoshida M, Shoji S. A retrospective analysis of voriconazole pharmacokinetics in Japanese pediatric and adolescent patients. *J Infect Chemother.* 2013;19(1):174-9. doi:10.1007/s10156-012-0438-z EXCLUDED - OUTCOME

44. Volk B, Tiu A, St Anna L. Clinical Inquiry: which oral antifungal works best for toenail onychomycosis?. *J. FAM. PRACT.*. 2013;62(2):100-1. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com.liboff.ohsu.edu/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=23405380. Accessed May 08, 2015. EXCLUDED - DESIGN

45. Harrison D, Muskett H, Harvey S, et al. Development and validation of a risk model for identification of non-neutropenic, critically ill adult patients at high risk of invasive Candida infection: the Fungal Infection Risk Evaluation (FIRE) Study. *Health Technol Assess.* 2013;17(3):1-156. doi:10.3310/hta17030 EXCLUDED - INTERVENTION

46. Randhawa HS, Chowdhary A, Kathuria S, et al. Blastomycosis in India: report of an imported case and current status. *Med Mycol.* 2013;51(2):185-92. doi:10.3109/13693786.2012.685960 EXCLUDED – DESIGN

47. Gupta AK, Drummond-Main C, Paquet M. Evidence-based optimal fluconazole dosing regimen for onychomycosis treatment. *J Dermatolog Treat.* 2013;24(1):75-80. doi:10.3109/09546634.2012.703308 EXCLUDED - INTERVENTION

48. Gupta AK, Drummond-Main C. Meta-analysis of randomized, controlled trials comparing particular doses of griseofulvin and terbinafine for the treatment of tinea capitis. *Pediatr Dermatol.* 2013;30(1):1-6. doi:10.1111/j.1525-1470.2012.01866.x EXCLUDED - INTERVENTION

49. Gupta AK, Elewski BE, Sugarman JL, et al. The efficacy and safety of efinaconazole 10% solution for treatment of mild to moderate onychomycosis: a pooled analysis of two phase 3 randomized trials. *J Drugs Dermatol.* 2014;13(7):815-20. Cited in: Ovid MEDLINE(R) Corrections at http://ovidsp.ovid.com.liboff.ohsu.edu/ovidweb.cgi?T=JS&PAGE=reference&D=medc&NEWS=N&AN=25007364. Accessed May 08, 2015. EXCLUDED - INTERVENTION

50. Scudeller L, Viscoli C, Menichetti F, et al. An Italian consensus for invasive candidiasis management (ITALIC). *Infection.* 2014;42(2):263-79. doi:10.1007/s15010-013-0558-0 EXCLUDED – DUPLICATE (SEE ABOVE)

Database(s): Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to May Week 1 2015
Search Strategy:

#	Searches	Results
1	exp fluconazole/ or exp itraconazole/ or exp voriconazole/	11748
2	exp clotrimazole/ or exp miconazole/	3117
3	exp Ketoconazole/	5093
4	exp Nystatin/	2962
5	exp Flucytosine/	2442
6	Griseofulvin/	2931
7	antifungal agents/ or exp fluconazole/ or exp flucytosine/ or exp griseofulvin/ or exp itraconazole/ or exp ketoconazole/ or exp miconazole/ or exp nystatin/ or exp voriconazole/	56350
8	POSACONAZOLE.mp.	1372
9	TERBINAFINE.mp.	1996
10	exp blastomycosis/ or exp candidiasis/ or exp candidiasis, chronic mucocutaneous/ or exp candidiasis, cutaneous/ or exp candidiasis, invasive/ or exp candidiasis, oral/ or exp coccidioidomycosis/ or exp cryptococcosis/ or exp meningitis, cryptococcal/ or blastomycosis/ or candidiasis, chronic mucocutaneous/ or candidiasis, cutaneous/ or chromoblastomycosis/ or exp hyalohyphomycosis/ or exp aspergillosis/ or exp fusariosis/ or exp paracoccidioidomycosis/ or exp sporotrichosis/ or tinea/ or onychomycosis/ or exp tinea capitis/ or exp tinea favosa/ or exp tinea pedis/ or exp tinea versicolor/ or exp fungemia/ or exp candidemia/ or exp histoplasmosis/ or exp aspergillosis, allergic bronchopulmonary/ or exp neuroaspergillosis/ or exp trichosporonosis/ or exp zygomycosis/ or exp mucormycosis/	71615
11	isavuconazole.mp.	78
12	1 or 2 or 4 or 5 or 6 or 7 or 8 or 9 or 11	57440
13	10 and 12	19985
14	limit 13 to (english language and humans and yr="2013 -Current" and (clinical trial, phase iii or randomized controlled trial))	55

1. Shi TW, Zhang JA, Zhang XW, Yu HX, Tang YB, Yu JB. Combination treatment of oral terbinafine with topical terbinafine and 10% urea ointment in hyperkeratotic type tinea pedis. *Mycoses.* 2014;57(9):560-4. doi:10.1111/myc.12198 EXCLUDED - INTERVENTION

2. Marr KA, Schlamm HT, Herbrecht R, et al. Combination antifungal therapy for invasive aspergillosis: a randomized trial. *Ann Intern Med.* 2015;162(2):81-9. doi:10.7326/M13-2508 EXCLUDED - COMPARISON

3. Jarratt M, Jones T, Adelglass J, et al. Efficacy and safety of once-daily luliconazole 1% cream in patients >12 years of age with interdigital tinea pedis: a phase 3, randomized, double-blind,vehicle-controlled study. *J Drugs Dermatol.* 2014;13(7):838-46. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com.liboff.ohsu.edu/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=25007368. Accessed May 08, 2015. EXCLUDED - INTERVENTION

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12. Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N Engl J Med.* 2014;370(26):2487-98. doi:10.1056/NEJMoa1312884 EXCLUDED - INTERVENTION

13. Benjamin DK Jr, Hudak ML, Duara S, et al. Effect of fluconazole prophylaxis on candidiasis and mortality in premature infants: a randomized clinical trial. *JAMA.* 2014;311(17):1742-9. doi:10.1001/jama.2014.2624 EXCLUDED - COMPARISON

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17. Jones TM, Jarratt MT, Mendez-Moguel I, et al. A randomized, multicenter, double-blind, vehicle-controlled study evaluating the efficacy and safety of luliconazole cream 1% once daily for 7 days in patients aged > 12 years with tinea cruris. *J Drugs Dermatol.* 2014;13(1):32-8. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com.liboff.ohsu.edu/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=24385117. Accessed May 08, 2015. EXCLUDED - INTERVENTION

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ointment compared to bifonazole-urea ointment for removal of the clinically infected nail in toenail onychomycosis: a randomized evaluator-blinded controlled study. *Dermatology.* 2013;226(1):5-12. doi:10.1159/000345105 EXCLUDED - INTERVENTION

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41. Friedlander SF, Chan YC, Chan YH, Eichenfield LF. Onychomycosis does not always require systemic treatment for cure: a trial using topical therapy. *Pediatr Dermatol.* 2013;30(3):316-22. doi:10.1111/pde.12064 EXCLUDED - INTERVENTION

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50. Benjamin DK Jr, Hudak ML, Duara S, et al. Effect of fluconazole prophylaxis on candidiasis and mortality in premature infants: a randomized clinical trial. *JAMA.* 2014;311(17):1742-9. doi:10.1001/jama.2014.2624 EXCLUDED - COMPARISON

Database(s): Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to May Week 1 2015
Search Strategy:

#	Searches	Results
1	isavuconazole.mp.	78
2	BAL4815.mp.	11
3	1 or 2	82
4	limit 3 to (english language and humans)	61
5	limit 4 to (clinical trial, all or controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews)	6

1. Howard SJ, Lass-Florl C, Cuenca-Estrella M, Gomez-Lopez A, Arendrup MC. Determination of isavuconazole susceptibility of Aspergillus and Candida species by the EUCAST method. *Antimicrob Agents Chemother.* 2013;57(11):5426-31. doi:10.1128/AAC.01111-13
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Antifungals

Goal(s):

- Approve use of antifungals only for OHP-funded diagnoses. Minor fungal infections of skin, such as dermatophytosis and candidiasis are only funded when complicated by an immunocompromised host.

Length of Authorization:

See criteria

Requires PA:

- Non-preferred drugs

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org/drugs/

Table 1: Examples of FUNDED indications (1/1/15)

ICD-9	Description
112.1	Candidiasis of vulva and vagina
112.4	Candidiasis of the lung
112.5	Disseminated Candidiasis
112.8x	Candidiasis of other specified sites
114.0-114.9	Coccidiomycosis various sites
115.00-115.99	Histoplamosis
116.0-116.2	Blastomycosis
117.xx	Rhinosporidosis, Sporotrichosis, Chromoblastomycosis, Aspergillosis, Mycotis Mycetomas, Cryptococcosis, Allescheriosis, Zygomycosis, Dematiacious Fungal Infection, Mycoses Nec and Nos
118.xx	Mycosis, Opportinistic
518.6	Bronchopulmonary Aspergillus, Allergic
616.xx (except 616.0)	Inflammatory disease of cervix vagina and vulva
681.xx	Cellulitis and abscess of finger and toe
771.7	Neonatal Candida infection

Table 2: Examples of NON-FUNDED indications (1/1/15)

ICD-9	Description
690.10 – 690.8	Erythematosquamous dermatosis
691.0	Diaper or napkin rash
691.8	Other atopic dermatitis and related conditions
692.0 – 692.70, 692.74, 692.79-692.9	Contact dermatitis and other eczema
695.0,695.10, 695.11, 695.19, 695.2-695.4, 695.50-695.59, 695.89-695.9	ERYTHEMATOUS CONDITIONS
697.0-697.9	Lichen Planus
706.0,706.1	ROSACEA; ACNE
110.1	Dermatophytosis of nail (onychomycosis)
111.0	Pityriasis versicolor
111.2	Tinea blanca
111.3	Black piedra
111.8	Dermatomycoses nec
111.9	Dermatomycosis nos
112.3	Cutaneous candidiasis
112.9	Candidiasis site nos
782.1	Nonspecif skin erupt nec

Table 3: Criteria driven diagnoses (1/1/15)

ICD-9	Description
110.0	Dermatophytosis of scalp and beard (tinea capitis/ tinea barbae)
110.2	Dermatophytosis of hand (tinea manuum)
110.3	Dermatophytosis of groin and perianal area (tinea cruris)
110.4	Dermatophytosis of foot (tinea pedis)
110.5	Dermatophytosis of body (tinea corporis / tinea imbricate)
110.6	Deep seated dermatophytosis
110.8-110.9	Dermatophytosis of other specified sites - unspecified site

111.1	Tinea nigra	
112.0	Candidiasis of mouth	
112.2	Candidiasis of other urogenital sites	
Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the diagnosis funded by OHP? (See examples in Table 1).	Yes: Go to #3	No: Go to #4
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety.	Yes: Inform provider of preferred alternatives.	No: Approve for 3 months or course of treatment.
4. Is the prescriber a hematology, oncology or infectious disease specialty prescriber requesting voriconazole?	Yes: Approve for 3 months or course of treatment.	No: Go to #5
5. Is the diagnosis not funded by OHP? (see examples in Table 2).	Yes: Pass to RPH: Deny (Not Funded by OHP).	No: Got to #6
6. Is the diagnosis funded by OHP if criteria are met? (see examples in Table 3).	Yes: Go to #7	No: Go to #9

<table>
<tr>
<td>7. Is the patient immunocompromised (examples below)?
• Does the patient have a current (not history of) diagnosis of cancer AND is currently undergoing Chemotherapy or Radiation? Document therapy and length of treatment. OR
• Does the patient have a diagnosis of HIV/AIDS? OR
• Does the patient have sickle cell anemia?
• Poor nutrition, elderly or chronically ill?
• Other conditions as determined and documented by a RPh.</td>
<td>Yes: Record ICD-9 code. Approve as follows: (Immunocompromised patient)

ORAL & TOPICAL
• Course of treatment.
• If length of therapy is unknown, approve for 3 months.</td>
<td>No: Go to #8</td>
</tr>
<tr>
<td>8. Is the patient currently taking an immunosuppressive drug? Document drug.

Pass to RPH for evaluation if drug not in list.

Immunosuppressive drugs include but are not limited to:
<table>
<tr><td>azathioprine</td><td>leflunomide</td></tr>
<tr><td>basiliximab</td><td>mercaptopurine</td></tr>
<tr><td>cyclophosphamide</td><td>methotrexate</td></tr>
<tr><td>cyclosporine</td><td>mycophenolate</td></tr>
<tr><td>etanercept</td><td>rituximab</td></tr>
<tr><td>everolimus</td><td>sirolimus</td></tr>
<tr><td>hydroxychloroquine</td><td rowspan="2">tacrolimus</td></tr>
<tr><td>infliximab</td></tr>
</table>
</td>
<td>Yes: Approve as follows: (Immunocompromised patient)

ORAL & TOPICAL
• Course of treatment.
• If length of therapy is unknown, approve for 3 months.</td>
<td>No: Pass to RPH; Deny (Not Funded by the OHP)</td>
</tr>
</table>

9. RPH only: All other indications need to be evaluated to see if it is an OHP-funded diagnosis:

   - If above the line, then may be approved for treatment course with PRN renewals. If length of therapy is unknown, approve for 3-month intervals only.

   - If below the line: Deny (Not Funded by the OHP).
     - Deny Non-fungal diagnosis (Medical Appropriateness)
     - Deny Fungal ICD-9 codes that do not appear on the OHP list pending a more specific diagnosis code (Not Funded by the OHP).
     - Forward any fungal ICD-9 codes not found in the Tables 1, 2, or 3 to the Lead Pharmacist. These codes will be forwarded to DMAP to be added to the Tables for future requests.

P&T / DUR Review: *7/15 (kk); 09/10; 2/06; 11/05; 9/05; 5/05*
Implemented *TBA; 1/1/11; 7/1/06; 11/1/0; 9/1/0*