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Drug Class Update with New Drug Evaluation: Oral Antifungals

Date of Review: February 2022

Generic Name: ibrexafungerp citrate

Date of Last Review: November 2019
Dates of Literature Search: 08/01/2019 - 11/08/2021
Brand Name (Manufacturer): Brexafemme® (Scynexis, Inc)
Dossier Received: yes

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose of this class update is to review the literature for new comparative evidence since the last class update and evaluate the data for the use of the new antifungal ibrexafungerp.

Research Questions:
1) Is there new comparative evidence related to efficacy for the oral antifungals for important outcomes (e.g., clinical cure or mortality)?
2) Is there new comparative evidence for harms for the oral antifungals?
3) Are there any subpopulations which would receive more benefit or suffer more harm from specific oral antifungals?
4) What is the comparative evidence for efficacy and harms for ibrexafungerp?

Conclusions:
- There was limited new evidence identified since the last antifungal class update in 2019. There was one systematic review and meta-analysis and 2 new randomized controlled trials (RCTs) included in this review.
- A Cochrane review found clinical cure rates to be similar between oral and intra-vaginal antifungals in women with acute, uncomplicated vulvovaginal candidiasis (VVC) based on moderate quality evidence.[1] Moderate quality evidence found short- and long-term mycological cure rates to be higher with oral therapy compared to intra-vaginal therapy.[1]
- The Food and Drug Administration (FDA) approved a new treatment indication and prophylactic indication for posaconazole in 2021. Posaconazole was approved for the treatment of invasive aspergillosis in patients 13 years and older.[2,3] Prophylactic use of posaconazole was broadened to include pediatric patients 2 years and older for prophylaxis against invasive *Aspergillus* and *Candida* infections in severely immunocompromised patients at high risk of developing these infections.[2]
- Secnidazole received an expanded FDA-approved indication for the treatment of trichomoniasis caused by *Trichomonas vaginalis* in adults in June 2021.[4,5]

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- There were 2 updated safety warnings for severe cutaneous reactions with voriconazole and risk during pregnancy for isavuconazonium sulfate (**Table 1**).[6,7]
- In June of 2021, ibrexafungerp was approved for treatment of adult and post-menarchal pediatric females with VVC. There is low quality of evidence from two published studies which demonstrated a clinical cure of 50.5% to 63.3% with ibrexafungerp compared to 28.6% to 44% for placebo (number needed to treat [NNT] 5-6).[8, 9]
- There was insufficient evidence for specific subgroup populations to direct oral antifungal therapy.

Recommendations:
- Maintain ibrexafungerp as non-preferred on the preferred drug list (PDL).
- No changes to the PDL are recommended based on review of recently published evidence.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy
- Presentation of the evidence in the 2019 antifungal class update resulted in no changes to the PDL.
- There is insufficient evidence to strongly support superior efficacy or safety of one oral antifungal over another, with the exception of ketoconazole which is associated with hepatotoxicity, adrenal insufficiency and drug interactions.
- Clotrimazole, fluconazole and nystatin are preferred drugs on the PDL. Griseofulvin, itraconazole, and terbinafine require a prior authorization (PA) due to limited use beyond onychomycosis, which is an unfunded condition.
- Voriconazole and posaconazole are indicated for the treatment of invasive aspergillosis requiring PA approval by a hematologist, oncologist or infectious disease specialist. Approval authorizes use without restriction.
- Oregon Health Plan (OHP) does not fund the treatment of candidiasis of the mouth, skin, nails or dermatophytosis of nail, groin, scalp, and other dematophytosis in immune competent hosts.
- Quarterly expenditures are modest for the antifungal class. Ninety-eight percent of claims are for preferred therapies.

Background:
The antifungal drugs cover a wide spectrum of infections. Serious fungal infections are usually seen in individuals with compromised immune systems, such as prolonged neutropenia, allogenic hematopoietic stem cell transplant and acquired immunodeficiencies requiring oral or intravenous antifungal therapy.[10] Important outcomes to determine antifungal efficacy include: symptom improvement, clinical cure (clinical symptoms), mycological cure (negative mycological test) and mortality. The FDA recommends that drugs studied for VCC should be evaluated with a primary endpoint of complete absence of all signs and symptoms of VCC.[11] The vulvovaginal signs and symptom (VSS) score is a commonly used tool for determining the severity of VVC. The VSS score is used to access the signs and symptoms of VCC by a standardized, predefined scale, in which a numerical rating is assigned (absent = 0; mild = 1, moderate = 2, severe = 3). Scores are calculated to determine a composite score, ranging from 0-18. Clinical cure is defined as a VSS score of 0 without additional antifungal treatment and clinical improvement is defined as a score of 1 or less.[12]

Antifungals can be categorized as azoles, echinocandins, polyenes, allylamines or nucleoside analogs.[13] Choice of antifungal depends on indication, causative organism and resistance patterns. Caspofungin, anidulafungin and micafungin are echinocandins with similar spectrum of action but differing dosing and drug interaction profiles. Echinocandins are most commonly used for serious fungal infections such as invasive candidiasis and as empiric therapy in patients with neutropenic fever.[14] Additionally, echinocandins have been used for salvage therapy in patients with invasive aspergillosis. Amphotericin deoxycholate, liposomal

amphotericin and nystatin are polyene antifungals. Because high risk of nephrotoxicity is associated with systemic formulations of polyenes, these therapies are therefore designated as second-line options for invasive aspergillosis and candidiasis infections. Allylamine antifungals consist of naftifine and terbinafine. Flucytosine works by a different mechanism of action that allows for use in combination with amphotericin B for severe cryptococcal pneumonia and meningocephalitis, with a limited role in select invasive candidiasis infections. Due to high levels of resistance, flucytosine is not commonly used as monotherapy.[15] Drug interactions are common with antifungals and concomitant medications should be considered upon initiation.

Azole antifungals are categorized as either triazoles or imidazoles (e.g., fluconazole, itraconazole, voriconazole, posaconazole, isavuconazole and ketoconazole). The azole antifungals are effective in treating several types of fungal infections: candidiasis, aspergillosis, cryptococcosis, histoplasmosis, blastomycosis, and coccidioidomycosis. Fluconazole is most commonly recommended first-line for a majority of fungal infections due to efficacy and tolerability. Of the azole antifungals, posaconazole and isavuconazole have the broadest spectrum of action and are not associated with nephrotoxicity. There is wide variability in the bioavailability and types of drug interactions (highly metabolized via cytochrome P450 enzyme system) between the different antifungals. Gastrointestinal issues are the most common adverse reactions associated with antifungal therapy and hepatic manifestations from mild elevations to hepatic failure have been demonstrated. For these reasons, transaminase monitoring is recommended for patients receiving extended treatment with antifungal therapy. Drug monitoring is a recommended for itraconazole, voriconazole, and posaconazole to ensure efficacy and avoid toxicity. For the initial treatment and salvage therapy triazole antifungals, such as voriconazole and posaconazole, are recommended for the treatment of aspergillosis.[10]

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, 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 drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
Cochrane – Oral versus Intra-vaginal Imidazole and Triazole Antifungal Treatment of Uncomplicated Vulvovaginal Candidiasis (Thrush)
A 2020 Cochrane review evaluated the comparative efficacy of oral versus intra-vaginal triazole anti-fungal treatment for uncomplicated VVC.[1] Twenty-six trials (n=5007 participants) were included in the review. The following antifungals were included (intra-vaginal unless noted): fluconazole (oral), itraconazole (oral), butoconazole, clotrimazole, econazole, miconazole, sertaconazole, and terconazole.[1] Females 16 years and older with a mycological diagnosis (e.g., positive culture or microscopy for yeast) were included. Patients were excluded if they had a history of diabetes, human immunodeficiency virus (HIV), or were currently immunocompromised, pregnant or breast feeding. Main outcomes of interest were mycological cure, adverse reactions, patient preference and symptom relief.

Overall findings suggest no difference in efficacy between oral and intra-vaginal antifungals. Short-term clinical cure (5-15 days) was reported for all trials. Oral versus intra-vaginal treatments were found to have similar efficacy (odd ratio [OR] 1.14; 95% confidence interval [CI], 0.91 to 1.43) based on moderate quality evidence.[1] Long-term clinical cure (2 to 12 weeks) was also found to be similar between treatments (OR 1.07; 95% CI, 0.77 to 1.50; moderate quality evidence).[1]

Moderate quality evidence found short-term mycological cure to be higher with oral antifungals with an estimated incidence of 796 per 1000 patients treated with intra-vaginal treatment compared to 829 per 1000 patients treated with oral antifungals (OR 1.24; 95% CI, 1.03 to 1.50).[1] Long-term mycological cure was also found to be more effective for oral antifungals compared to intra-vaginal antifungals (OR 1.29; 95% CI, 1.05 to 1.60) based on moderate quality evidence. The risk of withdrawing from the trials due to adverse reactions was low in both groups.

All trials were found to be at high risk of blinding of participants, mostly due to route of administration. Most other risk domains were of low risk of bias for a majority of the trials. Evidence on adverse events was considered low quality due to lack of reporting.

After review, 15 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[16–31]

New Guidelines:
High Quality Guidelines: none identified

Additional Guidelines for Clinical Context: none identified

After review, 2 guidelines were excluded due to poor quality.[16,32]

New Indications:

Posaconazole (Noxafil)® – In June of 2021 posaconazole injection and delayed-release tablets received an indication for the treatment of invasive aspergillosis in patients 13 years of age and older (**Table 2**).[2,3]

Additional expanded indications allow for the prophylactic use of posaconazole delayed-release oral suspension, posaconazole delayed-release tablets and posaconazole injection for broadened age groups. One expanded indication is for those patients 2 years and older, weighing 40 kg or less, who are at high risk of *Aspergillus* and *Candida* infections due to being severely immunocompromised (e.g., hematopoietic stem cell transplant (HSCT), those with graft-versus-host disease (GVHD) or those with hematological malignancies with prolonged neutropenia from chemotherapy). Additional expanded indications are for prophylactic use against invasive *Aspergillus* and *Candida* in pediatric patients 2 years or older, weighing 40 kg or more at high risk of developing these infections due to severe immunocompromising disease (e.g., HSCT, those with GVHD or those with hematological malignancies with prolonged neutropenia from chemotherapy, including pediatric populations 2 years and older).[2]

Secnidazole (Solosec®) – In June of 2021 secnidazole was approved for the treatment of trichomoniasis caused by *Trichomonas vaginalis* in adults.[4] Evidence for approval was based off a multi-center, placebo-controlled, double-blind trial using a single 2-gram oral dose of secnidazole (**Table 2**).[4] Four open-label trials conducted in males and females found a single dose of secnidazole demonstrated efficacy with reported cure rates of 91.7% to 100% at follow up time points of 2 to 20 days.[4] Untreated men had a spontaneous cure rate of 36% (95% CI, 12.8% to 64.9%) at a mean follow-up of 16 days.[4]

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Voriconazole[6]	Vfend®	September 2020	Warnings and Precautions	Severe cutaneous reactions (SCARS) (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reactions with eosinophilia and systemic symptoms) have been reported which can be life threatening or fatal. If SCARS occur then VFEND should be discontinued.
Isavuconazonium sulfate[7]	Cresemba®	May 2021	Warnings and Precautions	Animal reproduction studies demonstrated dose-related increases in multiple skeletal abnormalities in rodents. Isavuconazonium may cause fetal harm and pregnant women should be advised to the potential risk to the fetus.

Randomized Controlled Trials:

A total of 87 citations were manually reviewed from the initial literature search. After further review, 86 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Maertens, et al[3] DB, DD, NI, Phase 3, RCT	Posaconazole IV or oral 300 mg twice on day 1, 300 mg once daily for days 2-84 Vs. Voriconazole 6 mg/kg IV or 300 mg oral twice on day 1 followed by 4 mg/kg IV or 200 mg orally	Patients 13 years and older with proven, probable, or possible invasive aspergillosis N=653	Cumulative all-cause mortality up until day 42 in the ITT population (non-inferiority margin was set at 10%)	Posaconazole: 44 (15%) Voriconazole: 59 (21%) TD -5.3% (95% CI, -11.6 to 1.0) P<0.0001	Posaconazole was non-inferior to voriconazole for all-cause mortality. High attrition in both groups due to death, 32% with posaconazole and 38% with voriconazole. Results most applicable to middle aged, white patients with lower respiratory infection. Analysis of per protocol population is preferred for NI trials. Trial was manufacturer funded.

	twice daily for days 2-84 Treatment was for 12 weeks or less				
Muzny, et al[5] Phase 3, DB, PC, RCT	Secnidazole 2 g orally X 1 dose Vs. Placebo X 1 dose	Females 12 years or older with trichomoniasis (confirmed by positive *T. vaginalis* culture) N=131	Microbiological test of cure (TOC) by culture 6-12 days post dose	Secnidazole: 59 (92.2%) (95% CI, 82.70 to 97.41) Placebo: 1 (1.5%) (95% CI, 0.04 to 8.04) P<0.001 ARR 90.7% / NNT 2	Seconidazole was more effective than placebo for the treatment of trichomoniasis. Results are predominately applicable to women in their thirties who are Black/African American (91% of enrolled patients).

Abbreviations: ARR – absolute risk reduction; DB – double blind; DD – double dummy; ITT – intention to treat; IV – intravenous; NI – non-inferiority; NNT – number needed to treat; PC – placebo controlled; RCT – randomized controlled trial; TD = treatment difference

NEW DRUG EVALUATION:

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Ibrexafungerp is a triterpenoid antifungal therapy that disrupts fungal cell formation.[33] Ibrexafungerp is indicated for treatment of adult and post-menarchal pediatric females with VVC. Ibrexafungerp is given orally as a two tablets, totaling 300 mg, twice daily for one day.[33]

Ibrexafungerp was studied in two phase 3 clinical trials to determine efficacy and safety in the treatment of VVC in women (**Table 3**).[33] Women enrolled had a diagnosis of acute VVC with a median baseline composite VSS score of 9.0 in VANISH 303 and 10.0 in VANISH 306 (total score range of 0-18). Both trials compared ibrexafungerp, 300 mg twice daily for one day, to placebo. The primary endpoint was percentage of patients with clinical cure at test-of-cure (TOC), and key secondary endpoints were patients with mycological irradiation and overall success (clinical cure and mycological eradication). TOC was measured at 11 days (±3 days) and symptom assessment (via VSS scale) at day 1 and 25 (±4 days). VSS scores were recorded in a patient diary from day 1 to TOC visit. Rescue therapy was provided to patients with persistent or worsening symptoms and they were considered to early terminators due to lack of efficacy. In VANISH 303, 376 patients were randomly assigned to ibrexafungerp (n=249) or placebo (n=127). Patients were a mean age of 34 years, 54% were white and 41% were Black.[8] Nine percent of study participants were diabetic. In VANISH 306 (n=449) the mean age was 31 years, 81% were Black and 5% were diabetic.[9] In both trials *C. albicans* was the most common species identified, which is consistent with the most common pathogen associated with VVC.[12]

Trial attrition was high in both trials. In VANISH 303 attrition was >20% in both groups due to lack of follow up treatment of cure test.[8] VANISH 306 had attrition rates of 37% for ibrexafungerp and 44% for placebo.[9] Ibrexafungerp demonstrated clinical cure in 50.5% of patients compared to 28.6% of patients taking placebo (relative risk [RR] 1.71; 95% CI, 1.205 to 2.431; p = 0.001; absolute risk reduction [ARR] 21.9%/NNT 5) in VANISH 303. Similar clinical cure rates were

documented in VANISH 306 (66.3% for ibrexafungerp and 44% for placebo; RR 1.38; 95% CI, 1.073 to 1.783; P=0.007; ARR 19.3%/NNT 6).[8,9] The number of patients with mycological irradiation ranged from 49.5% to 58.5% in patients taking ibrexafungerp compared to 19.4% to 29.8% of patients taking placebo. Overall success (clinical cure and mycological eradication) was higher with ibrexafungerp compared to placebo in VANISH 303 (ARR 23.4%/NNT 5) and VANISH 306 (ARR 28.7%/NNT4).[8,9]

Limitations to the evidence include data from two small, single treatment studies to determine treatment efficacy and safety. High dropout rates in both trials resulted in a high degree of attrition bias. Lack of details on outcome assessment could introduce detection bias. The results are most applicable to women with a VSS score around 9-10 who are white, in their thirties and infected with *C. albicans*. There is insufficient evidence for the use of ibrexafungerp in patients with recurrent VVC, in which there are no FDA-approved therapies. Indirect comparisons would suggest similar efficacy to single-dose fluconazole, which is the only other approved oral antifungal for VVC.[9,12]

Clinical Safety:
The most common adverse events experienced in clinical trials at an incidence rate of 2% or more were diarrhea, nausea, abdominal pain, dizziness and vomiting. Ibrexafungerp is contraindicated in pregnancy as it may cause fetal harm, and females of reproductive potential should use effective contraception while taking ibrexafungerp.

Ibexafungerp is metabolized by the CYP3A4 enzyme system and concomitant use with strong CYP3A4 inhibitors increases the concentration and exposure to ibrexafungerp. The dose of ibrexafungerp should be reduced to 150 mg twice daily if given with a strong CYP3A4 inhibitor. Use of ibrexafungerp with strong to moderate CYP3A4 inducers may reduce the exposure and concomitant use should be avoided.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Mycological cure
2) Vulvovaginal signs and symptoms
3) Adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Clinical cure rates

Table 3. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Ibrexafungerp is a triterpenoid antifungal which inhibits glucan synthase and prevents fungal cell wall formation
Oral Bioavailability	Increased with a high fat meal compared to fasting; not considered clinically significant
Distribution and Protein Binding	Distribution is 600 L 99% protein bound, primarily to albumin
Elimination	Biliary excretion is the primary metabolic pathway
Half-Life	20 hours
Metabolism	Hydroxylation via CYP3A4 followed by glucuronidation and sulfation of a hydroxylated inactive metabolite

Abbreviations: CYP – cytochrome P450 Isoenzymes; L - liters

Table 4. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Schwebke, et al[8] (VANISH 303) DB, MC, PC, Phase 3, RCT	1. Ibrexafungerp 300 mg twice daily X 1 day 2. Placebo X 1 day	Demographics: Mean age: 35 years White: 54% Black: 41% Hispanic ethnicity: 24% Diabetic: 9.0% Median composite VSS score: 9.0 Key Inclusion Criteria: - Ages 12 years and older - Diagnosis of acute VVC* - Positive microscopic examination revealing yeast forms and normal vaginal pH (≤4.5) - Use of contraception in patients of reproductive potential Key Exclusion Criteria: - Any condition interfering with diagnosis or evaluation of response - Mixed infections - Systemic or topical vaginal antifungal treatments within 28 days of baseline	ITT: 1. 249 2. 127 mITT: 1. 188 2. 98 Attrition: 1. 61 (24%) 2. 29 (23%)	Primary Endpoint: Percentage of patients with clinical cure† at test-of-cure: Ibrexafungerp: 95 (50.5%) Placebo: 28 (28.6%) RR 1.71 (95% CI, 1.205 to 2.431) P=0.001 Secondary Endpoints: Patients with mycological eradication: Ibrexafungerp: 93 (49.5%) Placebo: 19 (19.4%) RR 2.87 (95% CI, 1.799 to 4.574) P < 0.001 Overall success (clinical cure and mycological eradication): Ibrexafungerp: 64 (36%) Placebo: 12 (12.6%) RR 3.19 (95% CI, 1.772 to 5.756) P < 0.001	ARR 21.9/ NNT 5 ARR 30.1/ NNT 4 ARR 23.4/ NNT 5	Diarrhea: Ibrexafungerp: 55 (22.3%) Placebo: 5 (4.0%) Nausea: Ibrexafungerp: 27 (10.9%) Placebo: 5 (4.0%)	N/A	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients randomized 2:1 via an interactive response system. Baseline characteristics were similar between groups except for a higher percentage of black patients in the placebo group and a higher percent of Hispanic/Latino in the ibrexafungerp group. Performance Bias: High. All site and sponsor personnel blinded to treatment assignment. Difference in diarrhea adverse event rates may lead to unblinding of treatment assignment. Members responsible for drug distribution logistics were unblinded. Detection Bias: Unclear. Lab samples assessed via a central lab. No additional details were given on outcome assessment. Attrition Bias: High. Each group had greater than 10% attrition bias. Groups were analyzed via mITT. High attrition was due to lack of positive culture for *Candida* species at baseline. Reporting Bias: Low. Trial protocol was followed. Other Bias: High. Manufacturer funded. **Applicability**: Patient: Results are most applicable to patients infected with the *C. albicans*, which accounted for over 90% of positive cultures. Intervention: Ibrexafungerp dose appropriately determined from a phase 2 study. Comparator: Active treatment comparison would be helpful to determine comparative efficacy. Outcomes: Clinical cure rates and mycological cure are appropriate outcomes to determine efficacy. Setting: 27 study sites in the United States.

		- Pregnant or lactating - HIV infection - Compromised immune system - Cervical/vaginal cancer						
2) Sobel, et al[9] (VANISH 306) DB, MC, PC, Phase 3, RCT	1. Ibrexafungerp 300 mg twice daily X 1 day 2. Placebo X 1 day	Demographics: Mean age: 33 years White: 81% Black: 18% Hispanic ethnicity: 9% Diabetic: 5.0% Median composite VSS score: 10.0 Key Inclusion Criteria: - Same as above Key Exclusion Criteria: - Any condition interfering with diagnosis or evaluation of response - Mixed infections - Systemic or topical vaginal antifungal treatments within 28 days of baseline - Pregnant or lactating - HIV infection - Compromised immune system - Cervical/vaginal cancer	ITT: 1. 298 2. 188 mITT: 1. 151 2. 84 Attrition: 1. 110 (37%) 2. 67 (44%)	Primary Endpoint: Percentage of patients with clinical cure† at test-of-cure: Ibrexafungerp: 119 (63.3%) Placebo: 37 (44.0%) RR 1.38 (95% CI, 1.073 to 1.783) P=0.007 Secondary Endpoints: Patients with mycological eradication: Ibrexafungerp: 110 (58.5%) Placebo: 25 (29.8%) RR 1.85 (95% CI, 1.329 to 2.583) P < 0.001 Overall success (clinical cure and mycological eradication): Ibrexafungerp: 82 (46.1%) Placebo: 23 (28.4%) RR 1.48 (95% CI, 1.038 to 2.113) P = 0.022	ARR 19.3/ NNT 6 ARR 28.7/ NNT 4 ARR 17.7/ NNT 6	Diarrhea: Ibrexafungerp: (6.7%) Placebo: 0 (0%) Nausea: Ibrexafungerp: (7%) Placebo: 0 (0%)	N/A	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients randomized 2:1 via an interactive voice or web-based response system. Baseline characteristics were similar between groups except for a higher percentage of Hispanic or Latino patients and patient from Bulgaria in the ibrexafungerp group. Performance Bias: Low. All site and sponsor personnel blinded to treatment assignment. Members responsible for drug distribution logistics were unblinded. Double-dummy design was used to prevent study drug identification. Detection Bias: Unclear. No details were given on outcome assessment. Attrition Bias: High. Each group had greater than 10% attrition bias. A large number of patients (45-48) withdrew before the TOC visit. Groups were analyzed via mITT. Reporting Bias: Low. Trial protocol was followed. Other Bias: High. Manufacturer funded. **Applicability**: Patient: Results are most applicable to white patients infected with the *C. albicans*, which accounted for 89% of positive cultures. Intervention: Ibrexafungerp dose appropriately determined from a phase 2 study. Comparator: Active treatment comparison would be helpful to determine comparative efficacy. Outcomes: Clinical cure rates and mycological cure are appropriate outcomes to determine efficacy. Setting: Nineteen US study sites and 18 sites in Bulgaria

Key: * Defined as a minimum composite vulvovaginal signs and symptoms of 4 or greater with at least 2 signs or symptoms having a score of 2 or more; † VSS score of 0 at test-of-cure visit
Abbreviations [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; ITT = intention to treat; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PP = per protocol; TOC = test of cure; VSS = vulvovaginal signs and symptoms score; VVC = vulvovaginal candidiasis

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
clotrimazole	CLOTRIMAZOLE	TROCHE	Y
fluconazole	DIFLUCAN	SUSP RECON	Y
fluconazole	FLUCONAZOLE	SUSP RECON	Y
fluconazole	DIFLUCAN	TABLET	Y
fluconazole	FLUCONAZOLE	TABLET	Y
nystatin	MYCOSTATIN	ORAL SUSP	Y
nystatin	NYSTATIN	ORAL SUSP	Y
nystatin	NYSTATIN	TABLET	Y
flucytosine	ANCOBON	CAPSULE	N
flucytosine	FLUCYTOSINE	CAPSULE	N
griseofulvin ultramicrosize	GRISEOFULVIN ULTRAMICROSIZE	TABLET	N
griseofulvin, microsize	GRISEOFULVIN	ORAL SUSP	N
griseofulvin, microsize	GRISEOFULVIN	TABLET	N
ibrexafungerp citrate	BREXAFEMME	TABLET	N
isavuconazonium sulfate	CRESEMBA	CAPSULE	N
itraconazole	TOLSURA	CAP SD DSP	N
itraconazole	ITRACONAZOLE	CAPSULE	N
itraconazole	SPORANOX	CAPSULE	N
itraconazole	ITRACONAZOLE	SOLUTION	N
itraconazole	SPORANOX	SOLUTION	N
ketoconazole	KETOCONAZOLE	TABLET	N
posaconazole	NOXAFIL	ORAL SUSP	N
posaconazole	POSACONAZOLE	ORAL SUSP	N
posaconazole	NOXAFIL	TABLET DR	N
posaconazole	POSACONAZOLE	TABLET DR	N
terbinafine HCl	TERBINAFINE HCL	TABLET	N
voriconazole	VFEND	SUSP RECON	N
voriconazole	VORICONAZOLE	SUSP RECON	N
voriconazole	VFEND	TABLET	N
voriconazole	VORICONAZOLE	TABLET	N

Appendix 2: Abstracts of Comparative Clinical Trials

Ibrexafungerp versus placebo for vulvovaginal candidiasis treatment: a phase 3, randomized, controlled superiority trial (VANISH 303)
Schwebke JR, Sobel R, Gersten JK, Sussman SA, et al. Clinical infectious diseases. 2021; issue 10. [30]

Abstract
BACKGROUND: Current treatment of vulvovaginal candidiasis (VVC) is largely limited to azole therapy. Ibrexafungerp is a first-in-class triterpenoid antifungal with broad-spectrum anti-Candida fungicidal activity. The objective of this study was to evaluate the efficacy and safety of ibrexafungerp compared with placebo in patients with acute VVC. STUDY DESIGN: Patients were randomly assigned 2:1 to receive ibrexafungerp (300 mg twice for 1 day) or placebo. The primary endpoint was the percentage of patients with a clinical cure (complete resolution of vulvovaginal signs and symptoms [VSS]=0) at test-of-cure (day 11). Secondary endpoints included the percentage of patients with mycological eradication, overall success (clinical cure and mycological eradication), clinical improvement (VSS?1) at test-of-cure, and symptom resolution at follow-up (day 25). RESULTS: Patients receiving ibrexafungerp had significantly higher rates of clinical cure (50.5% [95/188] vs 28.6% [28/98]; P=0.001), mycological eradication (49.5% [93/188] vs 19.4% [19/98]; P<0.001), and overall success (36.0% [64/178] vs 12.6% [12/95]; P<0.001) compared with placebo. Symptom resolution was sustained and further increased with ibrexafungerp compared with placebo (59.6% [112/188] vs 44.9% [44/98]; P=0.009) at follow-up. Post hoc analysis showed similar rates of clinical cure and clinical improvement at test-of-cure for African American patients (54.8% [40/73] and 63.4% [47/73], respectively) and patients with a body mass index >35 (54.5% [24/44] and 68.2% [30/44], respectively) compared with overall rates. Ibrexafungerp was well tolerated. Adverse events were primarily gastrointestinal and mild in severity.
CONCLUSION: Ibrexafungerp provides a promising safe and efficacious oral treatment that mechanistically differs from current azole treatment options for acute VVC.

Efficacy and Safety of Single Oral Dosing of Secnidazole for Trichomoniasis in Women: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled, Delayed-Treatment Study
Christina A Muzny, Jane R Schwebke, Paul Nyirjesy, et al.

Background: Trichomonas vaginalis is the most prevalent nonviral sexually transmitted infection. We evaluated the efficacy and safety of secnidazole vs placebo in women with trichomoniasis.
Methods: Women with trichomoniasis, confirmed by a positive T. vaginalis culture, were randomized to single-dose oral secnidazole 2 g or placebo. The primary endpoint was microbiological test of cure (TOC) by culture 6-12 days after dosing. At the TOC visit, participants were given the opposite treatment. They were followed for resolution of infection afterward and offered treatment at subsequent visits, if needed. Fifty patients per group (N = 100) provided approximately 95% power to detect a statistically significant difference between treatment groups.
Results: Between April 2019 and March 2020, 147 women enrolled at 10 sites in the United States. The modified intention-to-treat (mITT) population included 131 randomized patients (secnidazole, n = 64; placebo, n = 67). Cure rates were significantly higher in the secnidazole vs placebo group for the mITT population (92.2% [95% confidence interval {CI}: 82.7%-97.4%] vs 1.5% [95% CI: .0%-8.0%]) and for the per-protocol population (94.9% [95% CI: 85.9%-98.9%] vs 1.7% [95% CI: .0%-8.9%]). Cure rates were 100% (4/4) in women with human immunodeficiency virus (HIV) and 95.2% (20/21) in women with bacterial vaginosis (BV). Secnidazole was generally well tolerated. The most frequently reported treatment-emergent adverse events (TEAEs) were vulvovaginal candidiasis and nausea (each 2.7%). No serious TEAEs were observed.
Conclusions: A single oral 2 g dose of secnidazole was associated with significantly higher microbiological cure rates vs placebo, supporting a role for secnidazole in treating women with trichomoniasis, including those with HIV and/or BV.

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to November 08, 2021
Search Strategy:

#	Searches	Results
1	clotrimazole.mp. or Clotrimazole/	3111
2	fluconazole.mp. or Fluconazole/	14874
3	nystatin.mp. or Nystatin/	5323
4	flucytosine.mp. or Flucytosine/	3824
5	griseofulvin.mp. or Griseofulvin/	3961
6	ibrexafungerp.mp.	64
7	isavuconazonium.mp.	70
8	Itraconazole/ or itraconazole.mp.	10895
9	ketoconazole.mp. or Ketoconazole/	9485
10	posaconazole.mp.	3043
11	terbinafine.mp. or Terbinafine/	3161
12	voriconazole.mp. or Voriconazole/	7547
13	vaginal candidiasis.mp.	964
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 12	48959
15	limit 14 to (english language and humans and yr="2019 -Current")	2808
16	limit 15 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	87

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BREXAFEMME® safely and effectively. See full prescribing information for BREXAFEMME®.

BREXAFEMME® (ibrexafungerp tablets), for oral use
Initial US Approval: 2021

----------INDICATIONS AND USAGE----------
BREXAFEMME is a triterpenoid antifungal indicated for the treatment of adult and post-menarchal pediatric females with vulvovaginal candidiasis (VVC). (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended dosage of BREXAFEMME in adult and post-menarchal pediatric females is 300 mg (two tablets of 150 mg) twice a day for one day, for a total treatment dosage of 600 mg. (2.1)
- BREXAFEMME may be taken with or without food. (2.1)
- Prior to initiating treatment, verify pregnancy status in females of reproductive potential. (2.3)

----------DOSAGE FORMS AND STRENGTHS---------
Tablets: 150 mg of ibrexafungerp (3)

----------CONTRAINDICATIONS----------
- Pregnancy (4)
- Hypersensitivity to ibrexafungerp. (4)

----------WARNINGS AND PRECAUTIONS----------
Risk of Fetal Toxicity: May cause fetal harm based on animal studies. Advise females of reproductive potential to use effective contraception during treatment. (2.3, 5.1, 8.1, 8.3)

----------ADVERSE REACTIONS----------
The most frequent adverse reactions (≥ 2%) reported with BREXAFEMME in clinical trials of vulvovaginal candidiasis treatment were diarrhea, nausea, abdominal pain, dizziness, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact SCYNEXIS, Inc. at 1-888-982-7299 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Concomitant use of strong CYP3A inhibitors increases the exposure of ibrexafungerp. Reduce BREXAFEMME dose with concomitant use of a strong CYP3A inhibitor to 150 mg twice daily for one day. (2.2, 7)
- Concomitant use of strong and moderate CYP3A inducers may significantly reduce the exposure of ibrexafungerp. Avoid concomitant administration of BREXAFEMME with strong or moderate CYP3A inducers. (7)

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

Revised: 6/2021

Appendix 5: Key Inclusion Criteria

Population	Patients with an indication for antifungal therapy
Intervention	Oral antifungal
Comparator	Other antifungals or placebo
Outcomes	Mortality, clinical cure, mycological cure, symptom resolution
Timing	Onset of infection
Setting	Outpatient or inpatient

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:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1: Examples of FUNDED indications (12/16/21)

ICD-10	Description
B37.3	Candidiasis of vulva and vagina
B37.1	Candidiasis of the lung
B37.7	Disseminated Candidiasis
B37.5-37.6, B37.81-37.84, B37.89-37.90	Candidiasis of other specified sites
B38.0-B38.4, B38.7, B38.9	Coccidiomycosis various sites
B39.0-39.5, B39.9, G02, I32, I39, J17	Histoplasmosis
B40.9,B41.0, B41.9, B48.0	Blastomycosis
B42.0-42.9,, B43.9, B44.9-45.0, B45.7, B45.9, B46.9, B48.1-48.2, B48.8, B49	Rhinosporidiosis, Sporotrichosis, Chromoblastomycosis, Aspergillosis, Mycosis Mycetomas, Cryptococcosis, Allescheriosis, Zygomycosis, Dematiacious Fungal Infection, Mycoses Nec and Nos
B48.8	Mycosis, Opportunistic
B44.81	Bronchopulmonary Aspergillus, Allergic
N73.9-75.1, N75.9, N76.0-N77.1	Inflammatory disease of cervix vagina and vulva

L03.019,L03.029, L03.039, L03.049	Cellulitis and abscess of finger and toe
P37.5	Neonatal Candida infection
B37.42,B37.49	Candidiasis of other urogenital sites

Table 2: Examples of NON-FUNDED indications (12/16/21)

ICD-10	Description
L2.083, L2.10-2.11, L21.8-21.9,	Erythematosquamous dermatosis
L22	Diaper or napkin rash
L20.0-20.84, L20.89-20.9	Other atopic dermatitis and related conditions
L24.0-24.2, L25.1-25.5, L57.8, L57.9, L23.0, L23.81, L24.81, L25.0, L25.2, L25.8-25.9, L55.1-55.2 , L56.8, L58.9	Contact dermatitis and other eczema
L53.0-53.2, L51.0, L51.8-51.9, L52, L71.0-71.1, L71.8, L93.0, L93.2, L49.0-L49.9, L26, L30.4, L53.8, L92.0, L95.1, L98.2, L53.9	Erythematous conditions
L43.8,L44.1-44.3, L44.9,L66.1	Lichen Planus
L70.0-70.2, L70.8	Rosacea or acne
B35.1	Tinea unguium (onychomycosis)
B36.0	Pityriasis versicolor
B36.2	Tinea blanca
B36.3	Black piedra
B36.8, B36.9	Mycoses, superficial
B37.2	Cutaneous candidiasis
B37.9	Candidiasis, unspecified
R21	Rash and other nonspecific skin eruption

Table 3: Criteria driven diagnoses (12/16/21)

ICD-10	Description
B35.0	Dermatophytosis of scalp and beard (tinea capitis/ tinea barbae)
B35.2	Dermatophytosis of hand (tinea manuum)
B35.6	Dermatophytosis of groin and perianal area (tinea cruris)

B353	Dermatophytosis of foot (tinea pedis)
B35.5	Dermatophytosis of body (tinea corporis / tinea imbricate)
B35.8	Deep seated dermatophytosis
B35.8-B35.9	Dermatophytosis of other specified sites - unspecified site
B36.1	Tinea nigra
,B37.83	Candidiasis of mouth

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 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 prescriber 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 or posaconazole?	**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

Approval Criteria		
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.	**Yes:** Record ICD-10 code. Approve as follows: (immunocompromised patient) ORAL & TOPICAL • Course of treatment. • If length of therapy is unknown, approve for 3 months.	**No:** Go to #8

Approval Criteria		
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: azathioprine, basiliximab, cyclophosphamide, cyclosporine, etanercept, everolimus, hydroxychloroquine, infliximab, leflunomide, mercaptopurine, methotrexate, mycophenolate, rituximab, sirolimus, tacrolimus	**Yes:** Approve as follows: (immunocompromised patient) ORAL & TOPICAL • Course of treatment. • If length of therapy is unknown, approve for 3 months.	**No:** Pass to RPh. Deny; not funded by the OHP

9. RPh only: All other indications need to be evaluated to see if it is an OHP-funded diagnosis:
 	
• If funded: may approve for treatment course with PRN renewals. If length of therapy is unknown, approve for 3-month intervals only.
• If not funded: Deny; not funded by the OHP.
  ○ Deny non-fungal diagnosis (medical appropriateness)
  ○ Deny fungal ICD-10 codes that do not appear on the OHP list pending a more specific diagnosis code (not funded by the OHP).
  ○ Forward any fungal ICD-10 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 Review: *2/22 (KS); 11/19 (KS); 7/15; 09/10; 2/06; 11/05; 9/05; 5/05*
Implemented: *4/1/22; 5/1/16; 8/15; 1/1/11; 7/1/06; 11/1/0; 9/1/0*