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Drug Class Update with New Drug Evaluation: Antifungals

Date of Review: December 2023

Date of Last Review: February 2022 (oral); November 2019 (topical)
Dates of Literature Search: 09/01/2019 - 10/01/2023
Generic Name: oteseconazole
Brand Name (Manufacturer): Vivjoa (Mycovia Pharmaceuticals, Inc)
Dossier Received: no

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

Purpose for Class Update:
To evaluate new literature since the last reviews on oral and topical antifungal therapies. Evidence for the newly approved therapy for recurrent vulvovaginal candidiasis (RVVC), oteseconazole, will be critically evaluated and changes to the preferred drug list (PDL) will be updated if appropriate.

Plain Language Summary:
- Providers prescribe antifungal medicines to treat infections that are caused by fungus. Antifungals can be applied on the skin or taken by mouth.
- A high quality review looked at treatments for fungal infections in the vagina. Antifungals taken by mouth and antifungals applied topically into the vagina were similar in the short term (5 to 15 days) for improving symptoms of the infection.
- The Centers for Disease Control and Prevention (CDC) recommends either topical or oral antifungals to treat vaginal fungal infections.
- The Food and Drug Administration (FDA) approved a new medicine called oteseconazole to treat fungal infections in the vagina. The FDA approved oteseconazole for people that have 3 or more vaginal infections per year. Compared to a sugar pill (placebo), oteseconazole cured more vaginal infections.
- The Oregon Health Authority will pay for antifungals to treat serious fungal infections. Antifungals can be covered for minor fungal infections if people have conditions that could lead to complications. The Drug Use Research and Management group does not recommend any changes to this policy. We recommend that the Oregon Health Authority only pay for oteseconazole for patients who cannot get pregnant because of safety concerns. This process is called prior authorization.

Research Questions:
1. Is there new comparative evidence related to efficacy for the oral and topical antifungals for important outcomes (e.g., clinical cure or mycological cure)?
2. Is there new comparative evidence for harms for oral and topical antifungals?
3. What is the comparative evidence for efficacy and harms for oteseconazole?
4. Are there any subpopulations, such as people living in a congregate setting, who have more benefit or suffer more harm from antifungal therapy?

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Conclusions:

- There was one systematic review, one new guideline, one new drug, and 8 new safety warnings included in this review.
- A Cochrane review of the efficacy and safety of antifungals for the treatment of vulvovaginal candidiasis (VCC) found moderate quality of evidence that oral and intravaginal antifungal therapies had similar clinical cure rates in the short term (odds ratio [OR] 0.91; 95% confidence interval [CI], 0.91 to 1.43).[1] Oral therapies had higher mycological cure rates compared to intravaginal treatments in the short term (5-15 days) (OR 1.24; 95% CI, 1.03 to 1.50) and in the long term (OR 1.29; 95% CI, 1.05 to 1.60) (moderate quality evidence). All data for adverse events (AE) was considered to be of low quality.
- In 2021, the Centers for Disease Control and Prevention (CDC) published guidance for the treatment of VCC infections and RVVC infections.[2] Azole antifungals were recommended for acute treatment; however, there was no preference for one therapy over another.
- Since the last review, there have been 8 new FDA-issued safety warnings, detailed below, for the following drugs: fluconazole, flucytosine, ibrexafungerp, isavuconazonium, itraconazole, posaconazole, tinidazole, metronidazole, fexinidazole and voriconazole.
- Oteseconazole is a new therapy approved by the FDA for RVVC. There is moderate strength of evidence from 2 trials that oteseconazole is more effective than placebo to resolve symptoms of RVVC with a number to treat (NNT) of 3.[3,4] The most common adverse events (AEs) were nausea and headache.
- There was insufficient evidence on the use of antifungals in people living in congregate settings. Topical therapies are recommended for women who are pregnant.[2]

Recommendations:

- No changes to the preferred drug list (PDL) for oral and topical antifungals are recommended based on review of the evidence.
- Recommend renaming the topical antifungal class to reflect the inclusion of vaginal antifungal agents.
- Maintain oteseconazole as non-preferred and subject to prior authorization (PA) criteria.
- After evaluation of costs in executive session, make vaginal formulations terconazole, butoconazole, miconazole kits, miconazole 3 vaginal suppositories be non-preferred. Make other vaginal formulations preferred.

Summary of Prior Reviews and Current Policy

- Presentation of the evidence in the 2022 oral antifungal class update and in the 2019 topical antifungal class update resulted in no changes to the PDL.
- Clotrimazole, fluconazole and nystatin are preferred oral antifungals on the PDL and miconazole and nystatin are preferred topical agents (see **Appendix 1**).
- Griseofulvin, itraconazole, and terbinafine require a PA due to limited use beyond onychomycosis, which is an unfunded condition (see **Appendix 5**).
- Voriconazole and posaconazole are indicated for the treatment of invasive aspergillosis and require PA approval by a hematologist, oncologist or infectious disease specialist.
- 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 patients.
- Quarterly expenditures are modest for the antifungal class. Ninety-eight percent of claims were for preferred oral therapies and 78% claims for topical therapies were for preferred products.

Background:

Oral and topical antifungal drugs are used to treat 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. Serious fungal infections typically require oral or intravenous antifungal therapy.[5]

Antifungals can be categorized as azoles, echinocandins, polyenes, allylamines or nucleoside analogs.[6] 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.[7] 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 designated as second-line options for invasive aspergillosis and candidiasis infections. Allylamine antifungals consist of antofine 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.[8] 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 between the different antifungals in their bioavailability and types of drug interactions (due to metabolism via the cytochrome P450 enzyme system).

Gastrointestinal issues are the most common adverse reactions associated with antifungal therapy. Hepatic manifestations from mild elevations in liver enzymes to hepatic failure have occurred. 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 and salvage treatment of aspergillosis, triazole antifungals (e.g, voriconazole and posaconazole) are recommended.[5]

Antifungals are used for the treatment of VVC, which occurs in up to 75% of women in their lifetime.[9] *C. albicans* is the most common organism implicated in VVC infections, in which 80%-90% of resolve with the use of an azole antifungal.[9] Acute treatment recommendations include topical clotrimazole, miconazole, tioconazole, butoconazole and terconazole. Fluconazole is the only oral therapy for VVC. One of the components of this review is an evaluation of the efficacy and safety of a new drug for the treatment of RVVC, oteseconazole. Currently, there are no approved therapies for the treatment of RVVC. Recurrent VVC is defined as 3 or more infections within the previous 12 months. Guideline recommendations from the 2006 American College of Obstetricians and Gynecologists (ACOG) and the 2016 Infectious Disease Society of America (IDSA) (published prior to oteseconazole approval) for RVVC include using 2 therapies divided into induction regimens and longer maintenance regimens.[10] However, even maintenance regimens lasting up to 6 months do not guarantee a cure in the subsequent 6 months.

Important outcomes to determine antifungal efficacy include: symptom improvement, clinical cure (clinical symptoms), mycological cure (negative mycological test) and mortality. The FDA recommends that studies for VVC use a primary endpoint of complete absence of all signs and symptoms of VVC.[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 VVC by a standardized, predefined scale, in which a numerical rating is assigned (absent = 0; mild = 1, moderate = 2, severe = 3). Vulvovaginal signs are edema, erythema, and excoriation and symptoms are defined as burning, itching, and irritation. 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. Clinical improvement is defined as a score of 1 or less.[12]

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (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 2**, 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
A 2020 Cochrane review evaluated the use of antifungals in the treatment of VVC administered topically and vaginally. Women 16 years old and older with uncomplicated VVC with a mycological diagnosis (e.g., positive culture, microscopy for yeast, or both) were included.[1] Women with a diagnosis of HIV, or who were immunocompromised, pregnant, breast feeding or diabetic were excluded. Twenty-six trials were included (n=5007) with 23 trials evaluating acute VVC and 3 trials evaluating chronic VVC.[1] Follow-up ranged from 5 to 15 days (short term) for most trials. Two oral treatments were included, fluconazole and itraconazole, and six intravaginal treatments (butoconazole, clotrimazole, econazole, miconazole, sertaconazole, and terconazole) were studied. Main outcomes of interest were clinical cure (disappearance of symptoms either upon examination or by self-report), mycological cure (laboratory test determining no presence of VVC by mycological culture or microscopy), symptom reduction and side effects.

Clinical cure rate of candidiasis for oral compared to intra-vaginal therapy were no different in short term cure, 790 per 1000 versus 767 per 1000 (OR 0.91; 95% CI, 0.91 to 1.43) based on moderate quality evidence.[1] Long term (2 to 12 weeks) cure rates were also similar between oral and intravaginal treatments; OR 1.07 (95% CI, 0.77 to 1.50; moderate evidence). [1] There was moderate-quality evidence that mycological cure rates were higher in those treated with oral therapies compared to intravaginal treatments in the short term (OR 1.24; 95% CI, 1.03 to 1.50) and long term (OR 1.29; 95% CI, 1.05 to 1.60).[1] Withdrawals due to adverse events were reported by 3 trials, 2 withdrawals for intravaginal treatments and one for oral treatments (high quality of evidence). There was low-quality evidence of no difference for the number of AEs and preference to route of treatment.

After review, 3 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).[13–16]

New Guidelines:
Centers for Disease Control - Sexually Transmitted Infections Treatment Guidelines
In 2021 the CDC updated guidance for the treatment of sexually transmitted infections (STIs), which included recommendations for the treatment of VVC.[2] The guidelines separate VVC into 2 severities; uncomplicated and complicated. Uncomplicated VVC is characterized by sporadic or infrequent VVC which is associated with mild to moderate symptoms most likely due to *C. albicans* in women who are non-immunocompromised. Complicated VVC is due to recurrent VVC (3 or more episodes of symptomatic VVC in less than 1 year) or severe VVC symptoms or due to an organism other than non-albicans candidiasis or women

with diabetes, immunocompromising conditions, underlying immunodeficiency or immunosuppressive therapy.[2] Treatment options are outlined in **Table 1**. Treatment recommendations for uncomplicated VVC include topical formulations, given as a single dose or 1-3 day regimens. Severe VVC should be diagnosed by vaginal culture or polymerase chain reaction (PCR) to determine organism and confirm diagnosis. Recurrent VVC caused by *C. albicans* should be treated with short-duration oral or topical azole therapy.[2] Initial therapy lasting 7-14 days for topicals or oral fluconazole 100 mg, 150 mg, or 200 mg every third dose for a total of 3 doses for recurrent VVC is recommended. Maintenance therapy, which may be indicated in some women, is typically oral fluconazole 100 mg, 150 mg or 200 mg weekly for 6 months. Severe VVC can be treated with 7-14 days of topical azoles or oral fluconazole 150 mg in 2 sequential oral doses (second dose 72 hours after initial dose).[2] Infections thought to be caused by non-albicans VVC should be treated with non-fluconazole azole (e.g., miconozole) regimens of 7-14 days (oral or topical).[2] If infection reoccurs then boric acid 600 mg administered vaginally daily for 3 weeks is recommended.

In women who are immunocompromised, treatment with a more prolonged course may be needed for acute VVC (7-14 days).[2] Women who are pregnant should be treated with topical azole therapy for 7 days.[2] Fluconazole is not recommended due to possible increase in spontaneous abortion.

Table 1. Centers for Disease Control and Prevention Recommended Treatments for Vulvovaginal Candidiasis[2]

Drug	Dose	Prescription status
Clotrimazole 1% cream	5 gm intravaginally daily for 7-14 days	OTC
Clotrimazole 2% cream	5 gm intravaginally daily for 3 days	OTC
Miconazole 2% cream	5 gm intravaginally daily for 7 days	OTC
Miconazole 4% cream	5 gm intravaginally daily for 3 days	OTC
Miconazole 100 mg vaginal suppository	1 suppository daily for 7 days	OTC
Miconazole 200 mg vaginal suppository	1 suppository daily for 3 days	OTC
Miconazole 1,200 mg vaginal suppository	1 suppository for 1 day	OTC
Tioconazole 6.5% ointment	5 gm intravaginally in a single application	OTC
Butoconazole 2% cream	5 gm intravaginally in a single application (single-dose bioadhesive product)	Prescription
Terconazole 0.4% cream	5 gm intravaginally daily for 7 days	Prescription
Terconazole 0.8% cream	5 gm intravaginally daily for 3 days	Prescription
Terconazole 80 mg vaginal suppository	1 suppository daily for 3 days	Prescription
Fluconazole 150 mg orally	1 tablet for 1 dose	Prescription
Abbreviations: OTC =over thee counter		

Adverse events experienced with topical treatments include itching and burning. Oral therapy can cause nausea, abdominal pain and headache. Liver enzyme elevations have been associated with oral azoles, unrelated to dose or duration of therapy. Topical products may weaken latex condoms and diaphragms and patients should refer to manufacturer recommendations on use.

New Formulations or Indications:
No new formulations or indications.

New FDA Safety Alerts:

Table 2. 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)
Fluconazole[17]	DIFLUCAN	7/2023	Drug Interactions	Use with ivacaftor causes a 3-fold increase in ivacaftor. Reduction in ivacaftor dose is recommended. Use with lurasidone may increase lurasidone concentrations. Reduce dose of lurasidone if concomitant use cannot be avoided.
Flucytosine[18]	ANCOBON	2/2022	Contraindications	Use is contraindicated in people with complete dihydropyrimidine dehydrogenase (DPD) enzyme deficiency.
Ibrexafungerp[19]	BREXAFEMME	11/2022	Boxed Warning	There is a new boxed warning of the risk of embryo-fetal toxicity with ibrexafungerp use. It is contraindicated in pregnancy due to fetal harm demonstrated in animal studies. Contraception should be used during treatment and 4 days after discontinuation.
Isavuconazonium[20]	CRESEMBA	12/2021	Warnings and Precautions	Anaphylaxis with fatal outcomes have been reported with the use of isavuconazonium and use should be discontinued if symptoms (e.g., hypotension, generalized erythema and flushing and urticaria) are reported.
Itraconazole[21]	SPORANOX	12/2022	Boxed Warning	Administration of itraconazole with venetoclax is contraindicated in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) during the dose initiation and ramp-up phase of venetoclax.
Posaconazole[22]	NOXAFIL	1/2022	Contraindications	Posaconazole should not be used with venetoclax at initiation and during ramp-up phase in patients with CLL or SLL due to increase in risk of tumor lysis syndrome.
Tinidazole[23] Metronidazole[24] Fexinidazole[25]	TINDAMAX FLAGYL	12/2021	Warnings and Precautions	Warnings against use in people with Cockayne Syndrome which can cause severe irreversible hepatotoxicity/acute liver failure and death.
Voriconazole[26]	VFEND	10/2022	Warnings and Precautions	Photosensitivity skin reactions have been reported. Direct sun exposure should be avoided. Reactions have ranged from premalignant conditions to cutaneous lupus erythematosus with a higher incidence in pediatric populations. An increased risk of skin toxicity with concomitant use of methotrexate has also been reported.

Randomized Controlled Trials:
A total of 204 citations were manually reviewed from the initial literature search. After further review, all 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).

NEW DRUG EVALUATION: Oteseconazole (VIVJOA)

See **Appendix 3** 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:
Oteseconazole is a selective inhibitor of fungal lanosterol demethylase, the enzyme required for fungal growth.[27] Oteseconazole is FDA-approved to reduce the incidence of recurrent VVC in females with a history of RVVC and are not of reproductive potential.[27] Oteseconazole can be used as induction therapy and maintenance therapy or in combination with fluconazole (as induction therapy). As monotherapy, oteseconazole is given as a single 600 mg dose on day 1 followed by a 450 mg dose on day 2.[27] Starting on day 14, oteseconazole 150 mg should be given once weekly for 11 weeks. If oteseconazole is given with fluconazole, the regimen should be the following: fluconazole 150 mg orally on day 1, day 4 and day 7; on days 14 thru 20 oteseconazole 150 mg once daily for 7 days then on day 28 give oteseconazole 150 mg once a week for 11 weeks.[27] Approval was based on 2 identical trials comparing oteseconazole to placebo (after fluconazole induction) and a third study comparing oteseconazole to placebo after either oteseconazole or fluconazole induction, specific trial details are provide in **Table 3**. Induction treatment is used to clear the acute VVC infection.

The VIOLET studies (n=656) were 2 identical phase 3, multi-center, double-blind, placebo-controlled randomized trials.[3] The majority of participants were generally healthy White women (89%), with a mean age of 34 years, that responded to treatment of an acute VVC episode with fluconazole (induction phase) who had a history of RVVC (defined as ≥3 episodes of VVC in a 12-month period).[3] Oteseconazole is contraindicated in females of reproductive potential due to the risk of embryo-fetal toxicity; however some females of reproductive potential were included in the trials. Participants were given 150 mg of oteseconazole daily for 7 days and then once weekly for 11 weeks or matching placebo for 12 weeks using the same dosing protocol. Participants that did not have resolution of infection during the induction phase did not enter the maintenance phase but were included in the intention to treat (ITT) analysis. The primary endpoint was the averaged percentage of patients with one or more RVVC episode through week 48.

Results from both trials included in VIOLET found oteseconazole to be superior to placebo for the primary endpoint at week 48. In study 1 there were 6.7% (n= 15) of participants that had one or more episodes of RVVC compared to 42.8% (n=93) of placebo treated patients (P<0.001)(CI not provided).[3] In the second study, 3.9% (n=9) of patients in the oteseconazole groups experienced one or more episodes of RVVC compared to 39.4% (n=86) of those treated with placebo (P<0.001).[3] In 87% of women with RVVC, the primary causative organism was *C. albicans*.

A third study evaluated the safety and efficacy of oteseconazole in the treatment of RVVC in a randomized, double-blind, multicenter trial. Patients were a mean age of 35 years old, 59% were White and 7% had diabetes. Patients were randomized to oteseconazole induction/oteseconazole maintenance phase or fluconazole induction/placebo maintenance phase. For the primary endpoint of the proportion of patients with 1 or greater culture-verified acute VVC episode

through week 50, oteseconazole was superior to placebo (absolute risk reduction [ARR] 37.1%/NNT 3). A key secondary endpoint was the proportion of patients with a resolved acute VVC in the induction phase, which oteseconazole was non-inferior to fluconazole, 93.2% versus 95.8%, respectively (p-value not reported).

Trial limitations include insufficient evidence on repeat cycles of oteseconazole and use in women that have underlying disease states such as diabetes or HIV that are predisposed to developing VVC. The use of fluconazole 150 mg for induction could underestimate the treatment effect since a dose of 200 mg fluconazole is also appropriate.

Clinical Safety:
The most common adverse reactions experienced during clinical trials were headache and nausea.[27] Other AEs that occurred in 2% or less of people treated with oteseconazole included increased blood creatinine phosphokinase, dyspepsia, hot flush, dysuria, menorrhagia, and vulvovaginal irritation.[27] Oteseconazole may cause fetal harm based on animal studies and is contraindicated in people who are of reproductive age and if they are pregnant or lactating.[27] Oteseconazole has a half-life of 138 days and women should be informed of these implications before using. There were similar numbers of patients treated with oteseconazole and placebo that withdrew from RCTs due to treatment emergent adverse events (TEAE) and those with serious AEs.[27]

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Clinical cure
2) Mycological cure
3) Recurrent infections
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Proportion of patients with ≥1 culture-verified acute VVC episode (positive fungal culture for Candida species associated with a clinical signs and symptoms score of ≥3)

Table 3. Pharmacology and Pharmacokinetic Properties.[27]

Parameter	
Mechanism of Action	Azole metalloenzyme inhibitor targeting the fungal sterol, 14α demethylase (CYP51) with a lower affinity for human CYP enzymes
Oral Bioavailability	73% - 100% (with food)
Distribution and Protein Binding	423 L 99.5 to 99.7% bound to plasma proteins
Elimination	56% in the feces and 26% in the urine
Half-Life	138 days
Metabolism	Not significantly metabolized

Abbreviations: CYP = cytochrome; L = liter

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. Martens, et al[4] (ultraVIOLET) DB, MC, Phase 3, RCT	1. Oteseconazole 600 mg on day 1 and 450 mg on day 2 then oteseconazole 150 mg weekly for 11 weeks† 2. Fluconazole 150 mg every 72 hours for 3 doses then placebo weekly for 11 weeks Treatment: 2-week induction phase followed by maintenance phase for 11 weeks* † Maintenance dose of oteseconazole 150 mg or placebo weekly Follow-up: 37 weeks	Demographics: Age: 35 years White: 59% Black: 34% Hispanic or Latino: 26% Diabetes: 7% Acute VVC in past 12 months:5 Candida Albicans at baseline: 40% Key Inclusion Criteria: - Women and girls 12 years and older - History of RVVC (defined as 3 or more episodes of acute VVC in the past 12 months) - Active vulvovaginal candidiasis infection (at least 1 episode documented positive by culture, PCR, Affirm test, KOH test, positive vaginal smear or other approved diagnostic test; confirmation of acute VCC defined by total score of 3 or greater for vulvovaginal signs and symptoms; positive KOH wet mount preparation from vaginal smear with hyphae or pseudohyphae and/or budding yeast cells) - Negative pregnancy test Key Exclusion Criteria: - Vaginal infection other than acute VVC - use of systemic antifungal therapy 7 or less days before screening	ITT: 1. 147 2. 72 PP: 1. 103 2. 51 Attrition: 1. 44 (30%) 2. 21 (29%)	Primary Endpoint: Proportion of participants with 1 or greater culture-verified acute VVC episode through week 50: Oteseconazole: 8 (5.1%) Fluconazole: 31 (42.2%) (CI not provided) P<0.001 Secondary Endpoints: Resolved acute VVC infection at day 14 : Oteseconazole: 93.1% (n=96) Fluconazole: 50 98.3% (n=50) MD 5.2% (95% CI, -10.7 to 0.2) Lower limit of non-inferiority margin was above -12.5; non-inferiority achieved	ARR 37.1%/ NNT 3 NA	Serious TEAE: 1. 3 (2%) 2. 1 (1%) Discontinuations due to TEAE: 1. 1 (<1%) 2. 0 Urinary tract infections: 1. 18 (12%) 2. 12 (17%) Bacterial vaginosis: 1. 16 (11%) 2. 11 (15%) Skin and subcutaneous tissue disorders: 1. 10 (7%) 2. 3 (4%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized 2:1 by interactive web response system. Baseline characteristics were similar between groups. Performance Bias: (Low) Blinded with use of matching placebo. Same number of capsules provided per group. Detection Bias: (Unclear) Not described. Attrition Bias: (High) High attrition in both groups due to induction failure (14%) and lost to follow-up (5%). Missing values were imputed by multiple imputation. Primary analysis was done on the ITT population and secondary analysis was done on the per protocol population to determine non-inferiority. Reporting Bias: (High) Trial conducted as stated. Lack of CI limits ability to interpret results. Other Bias: (Unclear) Manufacturer funded. **Applicability**: Patient: Results are most applicable to women with recurrent VVC and in their 30's without diabetes. Seventy-six percent of RVVC isolates were *C albicans*. Intervention: Oteseconazole dose was appropriate based on other trials and FDA labeling. Comparator: Active treatment comparison to fluconazole in induction phase was appropriate; however a 200 mg dose is also appropriate. There were a high number of non-albicans Candida at baseline, in which optimal treatment is unknown however a non-fluconazole regimen is recommended. Placebo comparison in the maintenance phase was appropriate since fluconazole is not approved for RVVC. Outcomes: Outcomes are appropriate to determine efficacy of antifungal treatment. Setting: Thirty-eight US sites.

		immunosuppressive therapy - Major organ disease - Absence of contraception						
2. Sobel, et al‡[3] VIOLET (2 trials with same design) DB, MC, PC, Phase 3, RCT	1. Oteseconazole 150 mg daily for 7 days and then once weekly for 11 weeks* 2. Matching placebo for 12 weeks* * All patients entered an induction phase of fluconazole 150 mg every 72 hours for 3 doses (with matching placebo capsules) Follow up: 48 weeks	Demographics (pooled): Age: 34 years White: 80.5% Black: 11.5% Hispanic or Latino: 11.5% Diabetes: 2.5% Acute VVC episodes in past 12 months: 4 Candida Albicans: 51% Key Inclusion Criteria: - Women 12 and older with 3 or more symptomatic acute VCC within the previous 12 months (recurrent VVC) presenting with acute VVC - screening episode cleared with fluconazole induction therapy Key Exclusion Criteria: - Vaginal infection other than acute VVC - Use of systemic antifungal therapy 7 or less days before screening - Renal or hepatic impairment	ITT: 1. 435 2. 217 PP: 1. 324 2. 162 Attrition: 1. 111 (25.5%) 2. 55 (25.3%)	Study 1: Primary Endpoint: Averaged percentage of participants with 1 or greater culture-verified acute VVC episode through week 48. 1. 15 (6.7%) 2. 47 (42.8%) CI not reported P<0.001 Study 2: Primary Endpoint: Averaged percentage of participants with 1 or greater culture-verified acute VVC episode through week 48. 1. 9 (3.9%) 2. 43 (39.4%) CI not reported P<0.001 Secondary Endpoints: Study 1: Time to first recurrence of culture-verified VVC through week 48: 1. 45.7 weeks 2. 27.8 weeks HR 0.11 95% CI, 0.06 to 0.21 P<0.001 Study 2: Time to first recurrence of culture-verified VVC through week 48: 1. 47.2 weeks 2. 33.1 weeks HR 0.08 95% CI, 0.04 to 0.17	ARR 36%/ NNT 3 ARR 36%/ NNT 3	Serious TEAE: 1. 10 (2.3%) 2. 8 (3.6%) Discontinuations due to TEAE: 1. 3 (<1%) 2. 1 (<1%) Urinary tract infections: 1. 24 (5.5%) 2. 11 (5.0%) Bacterial vaginosis: 1. 28 (6.5%) 2. 17 (7.8%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized design through an IWRS used to assign subjects in a 2:1 ratio to the dose regimen of oteseconazole or placebo. Baseline characteristics were well matched. Performance Bias: (Low) Participants and trial personnel were blinded to treatment assignment. Placebo and oteseconazole were identical in appearance. Detection Bias: (Unclear) Not described. Attrition Bias: (High) More than 10% attrition in both groups. Primary endpoint was analyzed via ITT. Missing values were imputed by multiple imputation. Reporting Bias: (Low) Trial was conducted as reported. Other Bias: (Unclear) Manufacturer funded. **Applicability**: Patient: Applies mostly to patients with RVVC who are White that responded to initial fluconazole therapy. Intervention: Dose of oteseconazole was appropriate based on data from phase 2 studies. Comparator: Placebo comparison appropriate since there are no other approved treatments for RVVC. Outcomes: Recurrent VVC episode is an appropriate primary endpoint. Setting: In one study 97 sites were in North America, Japan and Europe and in the second study 84 centers were in North America and Europe. Thirty-eight percent of participants in the first trial and 36% of participants in the second trial were from the US.

				P<0.001				

Key: * Only participants with resolved acute VC infection (clinical signs and symptoms score of <3) entered the maintenance phase; ‡ Pooled results from 2 identical trials
Abbreviations [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; ITT = intention to treat; IWRS = interactive web response system; MD = mean difference; 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; RVVC = recurrent vulvovaginal candidiasis; VVC = vulvovaginal candidiasis

References:

1. Denison HJ, Worswick J, Bond CM, et al. Oral versus intra-vaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush). *Cochrane Database of Systematic Reviews*. 2020;(8). doi:10.1002/14651858.CD002845.pub3

2. Workowski KA, Bachmann LH, Chan PA, et al. Sexually Transmitted Infections Treatment Guidelines, 2021. *MMWR Recomm Rep*. 2021;70(4):1-187. doi:10.15585/mmwr.rr7004a1

3. Sobel JD, Donders G, Degenhardt T, et al. Efficacy and Safety of Oteseconazole in Recurrent Vulvovaginal Candidiasis. *NEJM Evidence*. 2022;1(8):EVIDoa2100055. doi:10.1056/EVIDoa2100055

4. Martens MG, Maximos B, Degenhardt T, et al. Phase 3 study evaluating the safety and efficacy of oteseconazole in the treatment of recurrent vulvovaginal candidiasis and acute vulvovaginal candidiasis infections. *Am J Obstet Gynecol*. 2022;227(6):880.e1-880.e11. doi:10.1016/j.ajog.2022.07.023

5. Patterson TF, Thompson GR, Denning DW, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;63(4):e1-e60. doi:10.1093/cid/ciw326

6. Pappas P, Kauffman C, Andes D, et al. Clinical practice guidelines for the managment of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infec Dis*.2016;62:e1-50.

7. Lewis R. Pharmacology of echinocandins. UpToDate. 2019. Accessed August 24, 2019.

8. Drew R, Perfect J. Pharmacology of flucytosine (5-FC). UpToDate. 2019. Accessed August 24, 2019.

9. Workowski KA. Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines. *Clinical Infectious Diseases*. 2015;61(suppl 8):S759-S762. doi:10.1093/cid/civ771

10. Food and Drug Administration. Oteseconazole Integrated Review. Center for Drug Evaluation and Research. April 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215888Orig1s000IntegratedR.pdf. Accessed October 10, 2023.

11. Food and Drug Administration. Vulvovaginal Candidiasis: Developing Drugs for Treatment - Guidance for Industry. Centers for Drug Evaluation and Research. August 2019.

12. Food and Drug Administration. Multi-discipline Review - NDA 214900 Brexafemme (ibrexafungerp). Center for Drug Evaluation and Research. October 12, 2018.

13. Tang BHE, Bay JW, Yeong FM, Samuel M. Efficacy and safety of echinocandin monotherapy and combination therapy for immunocompromised patients with systemic candidiasis: A systematic review and meta-analysis. *Journal of Medical Mycology*. 2023;33(2):101362. doi:10.1016/j.mycmed.2023.101362

14. Mwassi HA, Yahav D, Ayada G, et al. Systemic antifungal therapy for oesophageal candidiasis – systematic review and meta-analysis of randomized controlled trials. *International Journal of Antimicrobial Agents*. 2022;59(6):106590. doi:10.1016/j.ijantimicag.2022.106590

15. Fávero MLD, Bonetti AF, Domingos EL, Tonin FS, Pontarolo R. Oral antifungal therapies for toenail onychomycosis: a systematic review with network meta-analysis toenail mycosis: network meta-analysis. *Journal of Dermatological Treatment*. 2022;33(1):121-130. doi:10.1080/09546634.2020.1729336

16. Foley K, Gupta AK, Versteeg S, et al. Topical and Device-based Treatments for Fungal Infections of the Toenails. Cochrane Database of Systematic Reviews. 2020; Issue 1. Art. No.:CD012093.

17. Food and Drug Administration. Drug Safety-related Labeling Changes - Fluconazole. July 2023. Available at: https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchResult.page. Accessed October 3, 2023.

18. Food and Drug Administration. Drug Safety-related Labeling Changes - Flucytosine. February 2022. Available at: https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchResult.page Accessed October 3, 2023.

19. Food and Drug Administration. Drug Safety-related Labeling Changes - Ibrexafungerp. October 2022. Available at: https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchResult.page. Accessed October 3, 2023.

20. Food and Drug Administration. Drug Safety-related Labeling Changes - Isavuconazonium. December 2021. Available at: https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchResult.page. Accessed October 3, 2023.

21. Food and Drug Administration. Drug Safety-related Labeling Changes - Itraconazole. December 2022. Available at: https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchResult.page. Accessed October 3, 2023.

22. Food and Drug Administration. Drug Safety-related Labeling Changes - Posaconazole. January 2022. Available at: https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchResult.page. Accessed October 3, 2023.

23. Food and Drug Administration. Drug Safety-related Labeling Changes - Tinidazole. December 2021. Available at: https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchResult.page. Accessed October 3, 2023.

24. Food and Drug Administration. Drug Safety-related Labeling Changes - Metronidazole.December 2021. Available at:https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=1506. Accessed October 3, 2023.

25. Food and Drug Administration. Drug Safety-related Labeling Changes - Fexinidazole. December 2021. Available at: https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchResult.page Accessed October 3, 2023.

26. Food and Drug Administration. Drug Safety-related Labeling Changes - Voriconazole. October 2022. Available at: https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchResult.page. Accessed October 3, 2023.

27. Vivjoa (oteseconazole) [prescribing information]. Durham, NC 27703; Mycovia Pharmaceuticals, Inc. April 2022.

Appendix 1: Current Preferred Drug List

Antifungals, Oral

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
miconazole	ORAVIG	MA BUC TAB	N
oteseconazole	VIVJOA	CAPSULE	N
posaconazole	NOXAFIL	ORAL SUSP	N
posaconazole	POSACONAZOLE	ORAL SUSP	N
posaconazole	NOXAFIL	SUSPDR PKT	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

Antifungals, Topical

Generic	Brand	Form	PDL
miconazole nitrate	MICONAZOLE NITRATE	CREAM (G)	Y
nystatin	NYSTATIN	CREAM (G)	Y
nystatin	NYSTATIN	OINT. (G)	Y
acetic ac/resorcino/salicyl ac	ANTIFUNGAL NAIL	TINCTURE	N
butenafine HCl	BUTENAFINE HCL	CREAM (G)	N
butenafine HCl	MENTAX	CREAM (G)	N
ciclopirox	CICLOPIROX	GEL (GRAM)	N
ciclopirox	CICLOPIROX	SHAMPOO	N
ciclopirox	LOPROX	SHAMPOO	N
ciclopirox	CICLODAN	SOLUTION	N
ciclopirox	CICLOPIROX	SOLUTION	N
ciclopirox olamine	CICLODAN	CREAM (G)	N
ciclopirox olamine	CICLOPIROX	CREAM (G)	N
ciclopirox olamine	LOPROX	CREAM (G)	N
ciclopirox olamine	CICLOPIROX	SUSPENSION	N
ciclopirox olamine	LOPROX	SUSPENSION	N
ciclopirox/skin cleanser no.28	CICLODAN	COMBO. PKG	N
ciclopirox/skin cleanser no.40	LOPROX	COMBO. PKG	N
ciclopirox/skin cleanser no.40	LOPROX	KIT SS-CLN	N
ciclopirox/urea/camph/men/euc	CICLODAN	SOLUTION	N
ciclopirox/urea/camph/men/euc	CICLOPIROX	SOLUTION	N
clotrimazole	ANTIFUNGAL	CREAM (G)	N
clotrimazole	ATHLETE'S FOOT	CREAM (G)	N
clotrimazole	CLOTRIMAZOLE	CREAM (G)	N
clotrimazole	FUNGOID	CREAM (G)	N
clotrimazole	LOTRIMIN AF	CREAM (G)	N
clotrimazole	MICOTRIN AC	CREAM (G)	N
clotrimazole	MYCOZYL AC	CREAM (G)	N
clotrimazole	ALEVAZOL	OINT. (G)	N
clotrimazole	CLOTRIMAZOLE	SOLUTION	N
clotrimazole	FUNGOID	SOLUTION	N
clotrimazole/betamethasone dip	CLOTRIMAZOLE-BETAMETHASONE	CREAM (G)	N
clotrimazole/betamethasone dip	CLOTRIMAZOLE-BETAMETHASONE	LOTION	N
econazole nitrate	ECONAZOLE NITRATE	CREAM (G)	N
efinaconazole	JUBLIA	SOL W/APPL	N
ketoconazole	KETOCONAZOLE	CREAM (G)	N
ketoconazole	EXTINA	FOAM	N

ketoconazole	KETOCONAZOLE	FOAM	N
ketoconazole	KETODAN	FOAM	N
ketoconazole	KETOCONAZOLE	SHAMPOO	N
ketoconazole/skin cleanser 28	KETODAN	COMBO. PKG	N
luliconazole	LULICONAZOLE	CREAM (G)	N
luliconazole	LUZU	CREAM (G)	N
miconazole nitrate	ATHLETE'S FOOT SPRAY	AERO POWD	N
miconazole nitrate	THERA ANTIFUNGAL	CREAM(ML)	N
miconazole nitrate	ALOE VESTA	OINT.(ML)	N
miconazole nitrate	ANTIFUNGAL POWDER	POWDER	N
miconazole nitrate	MICONAZORB AF	POWDER	N
miconazole nitrate	MICOTRIN AP	POWDER	N
miconazole nitrate	MYCOZYL AP	POWDER	N
miconazole nitrate	THERA ANTIFUNGAL	POWDER	N
miconazole nitrate	MICONAZOLE NITRATE	SOL W/APPL	N
miconazole nitrate	FUNGOID TINCTURE	TINCTURE	N
miconazole nitrate/zinc ox/pet	MICONAZOLE-ZINC OXIDE-PETROLTM	OINT. (G)	N
miconazole nitrate/zinc ox/pet	VUSION	OINT. (G)	N
naftifine HCl	NAFTIFINE HCL	CREAM (G)	N
naftifine HCl	NAFTIFINE HCL	GEL (GRAM)	N
naftifine HCl	NAFTIN	GEL (GRAM)	N
nystatin	NYAMYC	POWDER	N
nystatin	NYSTATIN	POWDER	N
nystatin	NYSTOP	POWDER	N
nystatin/triamcinolone acet	MYCONEL	CREAM (G)	N
nystatin/triamcinolone acet	MYTREX	CREAM (G)	N
nystatin/triamcinolone acet	N.T.A.	CREAM (G)	N
nystatin/triamcinolone acet	NYSTATIN-TRIAMCINOLONE	CREAM (G)	N
nystatin/triamcinolone acet	MYTREX	OINT. (G)	N
nystatin/triamcinolone acet	N.T.A.	OINT. (G)	N
nystatin/triamcinolone acet	NYSTATIN-TRIAMCINOLONE	OINT. (G)	N
oxiconazole nitrate	OXICONAZOLE NITRATE	CREAM (G)	N
oxiconazole nitrate	OXISTAT	LOTION	N
sertaconazole nitrate	ERTACZO	CREAM (G)	N
sulconazole nitrate	EXELDERM	CREAM (G)	N
sulconazole nitrate	EXELDERM	SOLUTION	N
tavaborole	KERYDIN	SOL W/APPL	N
tavaborole	TAVABOROLE	SOL W/APPL	N
terbinafine HCl	ATHLETE'S FOOT	CREAM (G)	N
terbinafine HCl	ATHLETE'S FOOT AF	CREAM (G)	N

terbinafine HCl	TERBINAFINE	CREAM (G)	N
tolnaftate	ATHLETE'S FOOT	AERO POWD	N
tolnaftate	TOLNAFTATE	AERO POWD	N
tolnaftate	ANTIFUNGAL CREAM	CREAM (G)	N
tolnaftate	FUNGOID-D	CREAM (G)	N
tolnaftate	TOLNAFTATE	CREAM (G)	N
tolnaftate	TOLNAFTATE	POWDER	N
tolnaftate	ANTIFUNGAL	SOLUTION	N
tolnaftate	MICOTRIN AL	SOLUTION	N
tolnaftate	MYCOZYL AL	SOLUTION	N
tolnaftate	TOLNAFTATE	SOLUTION	N
undecylenic ac/zinc undecylena	ANTIFUNGAL CREAM	CREAM (G)	N
undecylenic ac/zinc undecylena	UNDEX-25	OINT. (G)	N
clotrimazole	VOTRIZA-AL	LOTION	
econazole/triamcinolone	TRIAMAZOLE	CMB ONT CR	
gentian violet/brgreen/proflav	TRIPLE DYE	MED. SWAB	
gentian violet/brilliant green	TRIPLE DYE	LIQUID	

Antifungals, Vaginal

Generic	Brand	Form
butoconazole nitrate	GYNAZOLE 1	CRM/PF APP
clotrimazole	VAGINAL 3-DAY	COMBO. PKG
clotrimazole	3-DAY VAGINAL CREAM	CREAM/APPL
clotrimazole	CLOTRIMAZOLE	CREAM/APPL
clotrimazole	CLOTRIMAZOLE-3	CREAM/APPL
clotrimazole	CLOTRIMAZOLE	TABLET
miconazole nitrate	MICONAZOLE 3	CMB PF CRM
miconazole nitrate	MICONAZOLE 7	CREAM/APPL
miconazole nitrate	MICONAZOLE NITRATE	CREAM/APPL
miconazole nitrate	MICONAZOLE-7	CREAM/APPL
miconazole nitrate	YEAST-X	CREAM/APPL
miconazole nitrate	MICONAZOLE 1	KIT
miconazole nitrate	MICONAZOLE 3	KIT
miconazole nitrate	MICONAZOLE 3	SUPP.VAG
miconazole nitrate	MICONAZOLE 7	SUPP.VAG
miconazole nitrate	MICONAZOLE NITRATE	SUPP.VAG
terconazole	TERCONAZOLE	CREAM/APPL
terconazole	TERCONAZOLE	SUPP.VAG
tioconazole	TIOCONAZOLE-1	OIN/PF APP

Appendix 2: Medline Search Strategy

#	Searches	Results
1	clotrimazole.mp. or Clotrimazole/	3272
2	fluconazole.mp. or Fluconazole/	16337
3	Nystatin/ or nystatin.mp.	5543
4	flucytosine.mp. or Flucytosine/	4010
5	griseofulvin.mp. or Griseofulvin/	4059
6	ibrexafungerp.mp.	111
7	isavuconazonium.mp.	91
8	Itraconazole/ or itraconazole.mp.	11838
9	ketoconazole.mp. or Ketoconazole/	9831
10	miconazole.mp. or Miconazole/	3480
11	oteseconazole.mp.	32
12	posaconazole.mp.	3503
13	terbinafine.mp. or Terbinafine/	3490
14	voriconazole.mp. or Voriconazole/	8632
15	Nystatin/ or nystatin.mp.	5543
16	acetic.mp.	59749
17	butenafine.mp.	109
18	ciclopirox.mp. or Ciclopirox/	704
19	econazole.mp. or Econazole/	1053
20	efinaconazole.mp.	240
21	luliconazole.mp.	194
22	naftifine.mp.	220
23	oxiconazole.mp.	122
24	sertaconazole.mp.	164
25	sulconazole.mp.	99
26	tavaborole.mp.	145
27	tolnaftate.mp. or Tolnaftate/	304
28	undecylenic.mp.	394
29	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28	116475
30	limit 29 to (english language and humans and yr="2019 -Current")	6996
31	limit 30 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	204

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

VIVJOA™ (oteseconazole) capsules, for oral use
Initial U.S. Approval: 2022

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

VIVJOA™ is an azole antifungal indicated to reduce the incidence of recurrent vulvovaginal candidiasis (RVVC) in females with a history of RVVC who are NOT of reproductive potential. (1)

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

- There are two recommended VIVJOA dosage regimens: a VIVJOA-only regimen and a Fluconazole/VIVJOA regimen. Use one of these two dosage regimens. (2.1)
  - Administer VIVJOA orally with food. (2.1)
- For the *VIVJOA-only Dosage Regimen*: (2.2)
  - **On Day 1:** Administer VIVJOA 600 mg (as a single dose), then
  - **On Day 2:** Administer VIVJOA 450 mg (as a single dose), then
  - **Beginning on Day 14**: Administer VIVJOA 150 mg once a week (every 7 days) for 11 weeks (Weeks 2 through 12).
- For the *Fluconazole/VIVJOA Dosage Regimen*, prescribe fluconazole and: (2.3)
  - **On Day 1**, **Day 4**, and **Day 7**: Administer fluconazole 150 mg orally, then
  - **On Days 14 through 20**: Administer VIVJOA 150 mg once daily for 7 days, then
  - **Beginning on Day 28**: Administer VIVJOA 150 mg once a week (every 7 days) for 11 weeks (Weeks 4 through 14).

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

Capsules: 150 mg of oteseconazole (fluconazole is not supplied in the carton). (3)

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

- Females of Reproductive Potential (4), (5.1), (8.3)
- Pregnant and Lactating women (4), (8.1), (8.2)
- Hypersensitivity to oteseconazole (4)

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

Embryo-Fetal Toxicity: Based on animal studies, VIVJOA may cause fetal harm. The drug exposure window of approximately 690 days (based on 5 times the half-life of oteseconazole) precludes adequate mitigation of the embryo-fetal toxicity risks. Advise patients that VIVJOA is contraindicated in females of reproductive potential, and in pregnant and lactating women because of potential risks to a fetus or breastfed infant. (5.1, 8.1, 8.2, 8.3)

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

The most frequently reported adverse reactions (incidence > 2%) were headache and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mycovia Pharmaceuticals, Inc. at 1-855-299-0637 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

BCRP (Breast Cancer Resistance Protein) Substrates: Concomitant use of VIVJOA with BCRP substrates may increase the exposure of drugs that are BCRP substrates, which may increase the risk of adverse reactions associated with these drugs. Use the lowest possible starting dose of the BCRP substrate or consider reducing the dose of the substrate drugs and monitor for adverse reactions. (7.1)

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

- Renal Impairment: Not recommended in severe renal impairment or ESRD (with or without dialysis). (8.6)
- Hepatic Impairment: Not recommended in moderate or severe hepatic impairment. (8.7)

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

Revised: 4/2022

Appendix 4: Key Inclusion Criteria

Population	Patients with active fungal infection
Intervention	Antifungals
Comparator	Placebo or active treatment
Outcomes	Mycological cure
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

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.
- Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:

- See criteria

Requires PA:

- Non-preferred drugs

Covered Alternatives:

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

Table 1: Examples of FUNDED indications (10/19/23)

ICD-10	Description
B37.3	Candidiasis of vulva and vagina (vaginitis and cervicitis)
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, subacute meningitis, acute bacterial meningitis

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, 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, N76.0-N77.1	Acute inflammatory pelvic disease
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
L30.4	Severe intertrigo (see HERC guideline note 21 for definition of severe inflammatory skin disease)

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
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 (1/1/24)

ICD-10	Description
B35.0	Dermatophytosis of scalp and beard (tinea capitis/ tinea barbae)
B35.1	Tinea unguium (onychomycosis)
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 #8
3. Is the request for oteseconazole?	**Yes:** Go to #4	**No:** Go to #7
4. Does the patient have a diagnosis of recurrent vulvovaginal candidiasis (RVVC) defined as a history of 3 or more episodes of acute vulvovaginal candidiasis (VCC) in the previous 12 months?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Has the patient failed to have benefit with, or have contraindications or intolerance to, a course of oral fluconazole for recurrent vulvovaginal candidiasis?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
6. Is the patient of reproductive potential?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve up to 18 capsules for 12 months
7. 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.
8. 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 #9
9. Is the diagnosis not funded by OHP? (see examples in Table 2).	**Yes:** Current age ≥ 21 years: Pass to RPh. Deny; not funded by OHP Current age < 21 years: Go to #10	**No:** Go to #10
10. Is the diagnosis funded by OHP if criteria are met? (see examples in Table 3).	**Yes:** Go to #11	**No:** Current age ≥ 21 years: Go to #16 Current age < 21 years: Go to #16

Approval Criteria		
11. 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 #12

Approval Criteria		
12. 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 / leflunomide basiliximab / mercaptopurine cyclophosphamide / methotrexate cyclosporine / mycophenolate etanercept / rituximab everolimus / sirolimus hydroxychloroquine / tacrolimus infliximab	**Yes:** Approve as follows: (immunocompromised patient) ORAL & TOPICAL • Course of treatment. • If length of therapy is unknown, approve for 3 months.	**No:** Go to #13

Approval Criteria		
13. Is the request for treatment of a foot condition and does the member meet criteria for high-risk foot care? Antifungals are funded when all of the following criteria are met: 1) The patient is at high risk for nail/foot complications due to severe circulatory insufficiency and/or areas of desensitization OR resides in an institutional setting (e.g., skilled nursing/rehabilitation facility, group home, etc) AND 2) There is clinical evidence of mycosis of the toenail; AND 3) The patient has documented marked limitation of ambulation, pain, and/or secondary bacterial infection resulting from the thickening and dystrophy of the infected toenail plate.	**Yes:** Approve as follows: ORAL & TOPICAL • Course of treatment. • If length of therapy is unknown, approve for 3 months.	Current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP Current age < 21 years: Go to #14
14. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #15	**No:** Pass to RPh. Deny; medical necessity.

Approval Criteria		
15. Is the request for a preferred product OR has the patient failed to have benefit with, or have contraindications or intolerance to, at least 2 preferred products? Message: Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Approve for 12 months.	**No:** Pass to RPh. Deny; medical appropriateness. Inform prescriber of covered alternatives in class and process appropriate PA.

16. 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:
    - If current age< 21 years; Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?
        - Is yes, may approve for treatment course with PRN renewals. If length of therapy is unknown, approve for 3-month intervals only.
        - If No, Deny (medical appropriateness)
    - If current age ≥ 21 years, 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: *12/23 (KS);12/22; 2/22; 11/19; 7/15; 09/10; 2/06; 11/05; 9/05; 5/05*
Implemented: *1/1/24; 1/1/23; 4/1/22; 5/1/16; 8/15; 1/1/11; 7/1/06; 11/1/0; 9/1/0*