Oteseconazole (VIVJOA)
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Oteseconazole (OTE) is an azole metalloenzyme inhibitor of fungal enzyme CYP51 which catalyzes an early step in conversion of lanosterol to ergosterol, which inhibits cell-wall synthesis and fungal cell growth.

Indication(s) Under Review in This Document

- OTE is indicated in females who are not of reproductive potential to reduce the incidence of recurrent vulvovaginal candidiasis (RVVC)
- OTE was approved by the FDA on 4/26/2022.

Dosage Form(s) Under Review

- Oral: 150 mg tablet
    - **Monotherapy dose:**
        - OTE 600 mg on day 1, 450 mg on day 2, then 150 mg weekly for 11 weeks starting day 14.
    - **Sequential therapy with fluconazole:**
        - Fluconazole (FLU) 150 mg as a single dose on days 1, 4, and 7 during induction
        - OTE 150 mg once daily days 14-20, then 150 mg once weekly for 11 weeks starting day 28.

Clinical Evidence Summary

Efficacy Considerations

- Efficacy data for OTE comes from 3 multicenter, double-blind, placebo-controlled, Phase 3 randomized clinical trials in the treatment and prevention of recurrent vulvovaginal candidiasis.
    - Two identical phase 3 trials enrolled patients aged 12 and older with RVVC who successfully were treated with 3 doses of FLU to OTE daily for 7 days, then weekly for 11 weeks.
    - The third phase 3 trial randomized patients with RVVC to 2 days of OTE or 3 days of FLU, followed by weekly OTE or placebo for 11 weeks.
- Efficacy data are summarized in Table 1

Table 1: Efficacy results from clinical trials

Study and Intervention	Design	Demographics	Efficacy Results
VIOLET Trial CL-011 Randomized, multicenter, multinational double-blind, placebo-controlled trial	**Step 1:** open-label induction phase with 3 doses of fluconazole 150 mg on days 1, 4, and 7 **Step 2:** if acute VVC resolved on day 14, randomized 2:1 to either placebo or OTE 150 mg x7 days then 11 weekly doses in maintenance phase **Key inclusion:** • ≥3 acute VVC episodes in 12 mos. • positive KOH or Gram stain • total vulvovaginal signs/symptoms score of <3 at baseline visit and ≥3 at screening **Exclusion:** • Other vaginal/vulvar condition • pregnancy or breastfeeding • Uncontrolled diabetes, major organ disease, cervical cancer • recent use of immunosuppressive or systemic corticosteroid, antifungal, or antibacterial drugs **Primary endpoint:** • % subjects with ≥1 culture-verified acute VVC episodes (post-randomization through week 48)	**ITT population:** • OTE: n=217 • Placebo: n=109 **Median age:** 33 years (range 17-78 years) **Race:** 72% White, 13% Black/African-American, 14% Asian, 8% Hispanic/Latino **≥ 4 acute VVC episodes in past 12 months:** OTE: 45% Placebo: 50% >80% did NOT grow *Candida* at baseline Of those who did grow *Candida spp*, *C.albicans* and *C.glabrata* most common	**% with ≥1 RVVC episode through week 48:** • OTE: 7% • Placebo: 43% • P<0.001 **Mean time to recurrence:** • OTE: 46 weeks • Placebo: 28 weeks HR 0.11 (95% CI 0.06, 0.21)
VIOLET Trial CLL-012 Randomized (2:1), multicenter, double-blind, placebo-controlled trial	**Dosing as in CLL-011** **Key inclusion:** • Same as CLL-011 **Exclusion:** • Same as CLL-011 **Primary endpoint:** • Same as CLL-011	**ITT population:** • OTE: n=218 • Placebo: n=108 **Median age:** 33 yrs. (range 18-73) **Race:** 89% White, 10% Black/AA, 15% Hispanic **≥ 4 acute VVC episodes in past 12 months:** OTE: 51% Placebo: 56% 85% did NOT grow *Candida*	**Avg % with ≥1 RVVC episode through week 48:** • OTE: 4% • Placebo: 36% • P<0.001 **Mean time to recurrence:** • OTE: 46 weeks • Placebo: 33 weeks
ultraVIOLET Trial CL-017 Randomized (2:1), multicenter, DB, PC trial	**Step 1:** induction with OTE 600 mg on day 1 and 450 mg on day 2 OR three doses of fluconazole 150 mg on days 1, 4, and 7 **Step 2:** if acute VVC was resolved on day 14, OTE 150 mg weekly or placebo weekly for 11 wks. **Key inclusion:** • Same as Cl-011 **Exclusion:** • Same as CL-011 **Primary endpoint:** • % with ≥1 culture-verified acute VVC episodes through week 50)	**ITT population:** • OTE: n=147 • Fluconazole/placebo: n=72 **Median age:** 34 years (range 16-78 years) **Race:** 59% White, 34% Black/African-American, 26% Hispanic/Latino, 1% Asian	**% failure or recurrence through week 50:** • OTE: 10% • FLU/placebo: 38% • P<0.001 ***Induction failure:*** • ***7% OTE vs. 4% FLU*** ***RVVC*** • ***3% vs. 33%***

Efficacy summary:

- The VIOLET and ultraVIOLET trials (CLL-011, CLL-012 and CL-017) found oral OTE maintenance, given two weeks after FLU induction, was superior in preventing RVVC by 35-37% over placebo for up to 48 weeks after treatment initiation.
- In ultraVIOLET, oral OTE was noninferior to standard-of-care FLU in treatment of acute VVC.
- While women of childbearing age were allowed into the trial, and the median age was 34 years, the drug is currently only indicated for use in women who are NOT of childbearing potential. Only 16% of trial participants were > 44 yrs.

Safety Considerations

Safety Results from Clinical Trials:

- Safety data for OTE comes from Phase 3 trials, CLL-011, CLL-012, ultraVIOLET, with support from phase 2 trials
- In all 3 Phase 3 trials, adverse events (AE), serious AEs (SAE) and treatment-emergent AEs (TEAE) were similar between OTE and placebo

Contraindications:

- Pregnancy or lactation
- Persons of reproductive potential
  - Defined as biological females who DO NOT have a reason for permanent infertility (e.g. age ≥ 47 years tubal ligation, hysterectomy, salpingo-oophorectomy)
- Previous hypersensitivity to OTE

Other warnings / precautions:

- **Embryo and fetal toxicity**
  - Based on animal studies, OTE may cause embryo-fetal ocular abnormalities
  - Observed abnormalities include cataracts, opacities, exophthalmos/buphthalmos, optic nerve/retinal atrophy, lens degeneration, and hemorrhage
  - Due to a drug exposure window of approximately 690 days (5x its half-life) and limited human data in pregnant women during clinical trials to exclude a potential risk to human infants, OTE is therefore contraindicated in females of reproductive potential and in pregnant/lactating women

Adverse reactions

- **Common (≥ 3% in trials)**
  - Headache (7.4%)
  - Nausea (3.6%)
  - Infections (nasopharyngitis, UTI, URTI, bacterial vaginosis, sinusitis, cystitis, etc.)
- **Laboratory abnormalities:**
  - Transient elevations in serum creatine phosphokinase ≥10x ULN
- **Impact on QT interval:** OTE at approximately 5 times maximum exposures does not prolong the QT
- **Special populations:**
  - **Pregnant or lactating**
    - OTE is contraindicated in females of reproductive potential and in women who are pregnant/lactating due to embryo-fetal ocular abnormalities in animal studies.
      - Ocular abnormalities were observed in a pre/postnatal study in rats at doses 3.5 times the recommended human dose, including cataracts, opacities, exophthalmos/buphthalmos, optic nerve/retinal atrophy, lens degeneration and hemorrhage
    - There are no data on the presence of OTE in human or animal milk and no reported adverse effects in breastfed infants following maternal exposure to OTE during lactation. However, due to limited duration of follow-up during the post-natal period and ocular abnormalities are often

not noticed until 12-36 months after the administration of a drug product, no conclusions were drawn from these data.

- **Geriatric**
  - Very limited data in patients 65 years of age and older and unable to determine whether they respond differently from younger patients.
- **Renal impairment**
  - No dosage adjustment necessary in mild-moderate renal impairment (eGFR 30-89 mL/min)
  - Not recommended in patients with severe renal impairment (eGFR <30 mL/min) or end-stage renal disease as clinical studies did not include a sufficient number of patients
- **Hepatic impairment**
  - No dosage adjustment necessary with mild hepatic impairment (Child-Pugh A)
  - Insufficient information to determine safety with moderate-severe hepatic impairment (Child-Pugh B-C); use is not recommended

Other Considerations

- **Antimicrobial activity:**
  - *Candida albicans, Candida glabrata, Candida krusei, Candida parapsilosis, Candida tropicalis, Candida lusitaniae, Candida dubliniensis*
  - Some evidence suggests elevated MIC_{50} and MIC_{90} values in fluconazole-resistant *Candida spp*. versus fluconazole-susceptible isolates, but the clinical significance of these higher MICs on clinical efficacy is unknown. This suggests at least partial cross-resistance between OTE and other azoles, due to upregulation of efflux pumps CDR1, MDR1 and lanosterol 14-alpha-demethylase.
  - However against some fluconazole-resistant *Candida spp*, OTE may maintain meaningful in vitro activity against some FLU resistant isolates.

- **Pharmacokinetics**
  - **Absorption**
    - T_{max} = 5-10 hours
    - Administration of OTE with a high-fat, high-calorie meal increased C_{max} by 45% and AUC by 36%
  - **Distribution**
    - V_d = 423 L with animal studies indicating OTE exposures in vaginal tissue similar to plasma
    - 99% protein-bound
  - **Metabolism**
    - OTE does not undergo significant metabolism
  - **Excretion**
    - **Half-life = 138 days**
    - 56% eliminated in feces via biliary excretion
    - 26% eliminated in urine

- **Drug-Drug Interactions**
  - OTE is an inhibitor of BCRP
    - Rosuvastatin – increases concentrations of rosuvastatin with an increase in the AUC of 114%
    - Use the lowest possible starting dose of rosuvastatin or consider reducing the dose and monitoring for adverse events
  - Through inclusion of a tetrazole meta-binding group, OTE has a lower affinity for human CYP enzymes

Other Therapeutic Options

Table 2: Treatment Alternatives

Drug	Formulary status	Clinical Guidance	Other Considerations
OTE (VIVJOA)	**NF**	Indicated for prevention of RVVC either as monotherapy or in conjunction with fluconazole in women with multiple symptomatic episodes (3 over a 12-month period) Long half-life allows for weekly dosing after initial treatment for VVC, or oral OTE load	**Contraindicated in women of childbearing potential and women who are pregnant/lactating given potential embryo-fetal toxicity in animals and very long-half life** Not recommended in moderate-severe hepatic impairment or with an eGFR < 30
FLU	F	No official indication for RVVC, but maintenance treatment (weekly dose for 6 months) is recommended first-line in CDC sexually transmitted infection guidelines and improves quality of life in 96% of women Available in a low-cost generic	Not recommended during pregnancy as epidemiologic studies suggested a single 150mg dose might be associated with spontaneous abortion and congenital abnormalities (CDC 2021 STI guidelines) Rarely curative and > 60% of those who complete maintenance therapy continued to have ongoing infections
Topical azole (cream or suppository)	F	Recommended as first line options for acute VVC but not for RVVC, although intermittent treatment can be considered. Multiple different drugs and formulations (cream, suppository) Is available in a low-cost generic formulation	Only recommended treatment in pregnancy
Ibrexafungerp (BREXAFEMME)	NF	In November 2022, added an indication for reduction in the incidence of RVVC at a dose of 600mg monthly for 6 months – 13% reduction of RVVC over placebo at 24 weeks and 12% reduction at 36 weeks Retains activity against azole-resistant *Candida* isolates Given as a 2-dose oral regimen	Contraindicated in pregnancy Cannot be given with CYP3A inducers and requires dose adjustment with CYP3A inhibitors Clinical trials for prevention of RVVC ongoing

Projected Place in Therapy

- Approximately 75% of females will experience vulvovaginal candidiasis at least once in their lifetime, with up to 8% also experiencing recurrent vulvovaginal candidiasis. Uncomplicated vulvovaginal candidiasis is often treated with a short-course of an oral or topical azole.

- In the 2021 CDC guidelines for Sexually Transmitted Infections, recommendations for the treatment of RVVC included combined induction/maintenance regimens of up to six months to achieve and maintain remission. The

induction phase includes 7-14 days of topical agents or three doses of fluconazole 150 mg given every 72 hours, followed by at least 6 months of fluconazole 150 mg given weekly. Treatment guidelines from the American College of Obstetricians and Gynecologists (ACOG) and Infectious Diseases Society of America (IDSA) also recommended two agents (topical and oral) given in a similar fashion.

- In 3 double-blind, placebo-controlled RCTs, OTE was superior to placebo for reduction of RVVC episodes, and noninferior to FLU for the treatment of acute RVVC.

- Sustained remission of RVVC is not always successful suppressive therapy was discontinued, with 50% of patients having a recurrent episode within 6 months of treatment completion. Additional concerns include possible emergence of azole-resistant strains of *Candida spp.* that prevent the use of FLU for other infections and the many drug interactions and adverse effects. OTE appears to maintain activity against some FLU-resistant *Candida spp.,* but in vitro data does suggest a potential for cross-resistance with higher OTE MICs (up to 4-fold) in FLU-resistant isolates. The clinical significance of the higher MICs is unknown as such patients were rare in the phase 3 trials.

- In contrast, ibrexafungerp is a newer antifungal which has several advantages over oteseconazole for prevention of rVVC in adults. It is also approved as treatment of VVC and prevention of rVVC in adult and post-menarchal pediatric females. Given the differing mechanism of action, this agent may be particularly valuable in patients who have RVVC due to azole-resistant *Candida spp.* In addition, although, ibrexafungerp is also contraindicated in pregnancy, it is not in all persons of childbearing potential, providing a broader population who would be eligible for treatment.

- One of the biggest limitations to implementation of OTE maintenance therapy is potential for fetal-embryo toxicity, and because of the long half-life, is contraindicated in women of childbearing potential. Given RVVC is most common in young women, the potential use is likely to be low. The ideal place in therapy for OTE is likely to be in post-menopausal women who have RVVC (at least 3 symptomatic episodes in 12 months) and for whom ibrexafungerp is not clinically appropriate or available.

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