NEW DRUG APPROVAL

Brand Name	Vivjoa™
Generic Name	oteseconazole
Drug Manufacturer	Mycovia Pharmaceuticals, Inc.

New Drug Approval

FDA approval date: April 26, 2022

Review designation: Priority

Type of review: Type 1 - New Molecular Entity; New Drug Application (NDA): 215888

Dispensing restriction: Open distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Vulvovaginal candidiasis (VVC) is a widespread vaginal infection primarily caused by Candida albicans commonly characterized by vulvar itching, burning, pain while urinating, and vaginal discharge. Candida is a dimorphic fungus from the phyla Ascomycota that inhabits the respiratory, gastrointestinal, and genitourinary tracts of more than 30% of healthy individuals during their lifetime. VVC affects up to 75% of women of childbearing age once in their life, and up to 9% of women in different populations experience more than three episodes per year, which is defined as recurrent vulvovaginal candidiasis (RVVC). RVVC results in diminished quality of life as well as increased associated healthcare costs. For a long time, VVC has been considered the outcome of inadequate host defense against Candida colonization, as in the case of primary immunodeficiencies associated with persistent fungal infections and insufficient clearance.

Epidemiological studies from 1985 to 2016 and, basing their study on the 6000 online surveys from five Western European countries and the United States documented a global annual prevalence of 3871 RVVC cases per 100,000 women, with the highest frequency (9%) in patients aged between 25 and 34 years old. It has emerged that the incidence of Candida infections is also species related. Distribution and epidemiological studies carried out on cohorts in the United States, Europe and Australia identified C. albicans as the main occurring species, isolated in 75–90% of the positive cultures for VVC. As far as the non-albicans Candida (NAC) infections are concerned, the highest frequency rates have been reported for C. glabrata—around 10–20% of cases, followed by C. parapsilosis, C. tropicalis, C. krusei and C. Africana. This has been reported in Tunisia, Nigeria, Middle Eastern countries and Asia, where C. glabrata is the most frequently isolated NAC (30–50%). In addition, it is believed that NAC species are more likely to favor recurrent infections in VVC patients, perhaps because of their refractoriness to the current azole drug treatment. In addition, clinical reports showed that African Americans are more prone to fungal infections in comparison to European or Hispanic women, thus suggesting a variation in frequency among ethnic groups.

Efficacy

VIOLENT TRIALS: The VIOLET trials (Trial 1 and Trial 2) were both randomized, placebo-controlled trials evaluating the efficacy and safety of Vivjoa™ in the reduction of RVVC. Both trials consisted of two phases: an open-label induction phase and a maintenance phase. Patients received three doses of 150 mg of fluconazole (every 72 hours) on Days 1, 4, and 7 during the induction phase. Patients returned 14 days after the first dose of fluconazole and, if the acute VVC episode was resolved (vulvovaginal signs and symptoms score <3), they were randomized (2:1) to receive either 150 mg of Vivjoa™ or placebo for 7 days followed by 11 weekly doses in the maintenance phase.

Table 1 summarizes the study design of the VIOLET trials.

Table 1. VIOLET Trials: Study Design Summary		
	Trial 1 (NCT03562156) (N = 483)	**Trial 2 (NCT03561701) (N = 425)**
Study Description	Phase 3 randomized, placebo-controlled trial evaluating the efficacy and safety of Vivjoa™ in the reduction of RVVC.	
Study Population	• Mean age: 34 years (range, 17–78 years). ○ Patients aged 18–44 years: 85% ○ Patients aged 45 years and above: 15%. • White, 72%; Black or African American, 13%; Asian, 14%; Hispanic or Latino, 8%.	• Mean age: 34 years (range, 18–73 years) ○ Patients aged 18–44 years: 85%. ○ Patients aged 45 years and older: 15%. • White, 89%; Black or African American, 10%; Hispanic or Latino, 15%.
Inclusion Criteria	• Three or more episodes of acute VVC in the past 12 months. • Positive KOH or Gram stain. • Total vulvovaginal signs and symptoms score of ≥3 at screening visit and <3 at baseline visit.	
Key Exclusion Criteria	• Presence or a history of another vaginal or vulvar condition(s) • Evidence of major organ system disease • History of cervical cancer • Poorly controlled diabetes mellitus • Pregnancy	
Interventions	**Open-label induction phase:** • Patients were administered three sequential doses of fluconazole 150 mg (every 72 hours) on Days 1, 4, and 7. **Maintenance phase:** • Patients with vulvovaginal signs and symptoms score <3 were randomized (2:1) to receive either of the following regimens once daily for 7 days, followed by once weekly for 11 weeks:	
	Trial 1: ○ Vivjoa™ 150 mg (n = 217) ○ Placebo (n = 109)	**Trial 2:** ○ Vivjoa™ 150 mg (n = 220) ○ Placebo (n = 110)
Primary Endpoint	Proportion of patients with ≥1 culture-verified acute VVC episode (Day 1 through Week 48) in the ITT population.	

Abbreviations: ITT, intent-to-treat (population); KOH, potassium hydroxide; RVVC, recurrent vulvovaginal candidiasis; VVC, vulvovaginal candidiasis.

Efficacy of Vivjoa™ in VIOLET Trials

In the two global VIOLET studies, 93.3% and 96.1% of women with RVVC who received Vivjoa™ did not have a recurrence for the 48-week maintenance period compared to 57.2% and 60.6% of patients who received placebo (P < 0.001). For both VIOLET trials, efficacy was assessed by the 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)

during the maintenance phase through Week 48. Treatment for acute VVC was permitted if it was deemed to be clinically necessary when the patient had a signs and symptoms score ≥3 and a positive KOH test (but not a positive culture). The proportion of patients with ≥1 culture verified acute VVC episode or who took medication known to treat VVC during the maintenance phase through Week 48 is also included in the Vivjoa™ label.

Table 2 summarizes key efficacy endpoints in the VIOLET studies.

Table 2. VIOLET Trials Efficacy Endpoints: ITT Population

	Trial 1		Trial 2	
	Vivjoa™ (n=217)	**Placebo (n = 109)**	**Vivjoa™ (n=218)**	**Placebo (n = 108)**
Proportion of patients with ≥1 culture-verified acute VVC episode (Day 1 through Week 48) *	6.7%	42.8%	3.9%	39.4%
Treatment difference *P* value**	<0.001		<0.001	
Proportion of patients with ≥1 culture-verified acute VVC episode or received VVC medication (Day 1 through Week 48) *	27.3%	50.8%	21.3%	49.7%
Treatment difference *P* value**	<0.001		<0.001	

Abbreviations: ITT, intent-to-treat (population); VVC, vulvovaginal candidiasis. *Average %. Missing values were imputed with multiple imputation using the following auxiliary information: region, treatment, baseline body mass index, baseline age, ethnicity, and visit. **The P value was obtained using a Chi-square test comparing Vivjoa™ with placebo.

UltraVIOLET Trial: The UltraVIOLET trial (Trial 3) was a randomized, double-blind trial evaluating the efficacy and safety of Vivjoa™ versus fluconazole and placebo in adults and postmenarchal pediatric females with RVVC. The trial consisted of two phases: induction and maintenance. During the induction phase, patients received 1050 mg of Vivjoa™ over 2 days or three sequential doses of 150 mg of fluconazole (every 72 hours) on Days, 1, 4, and 7. Patients returned 14 days after the first dose and moved to the maintenance phase if the acute VVC episode was resolved. During the maintenance phase, patients received 150 mg Vivjoa™ weekly or placebo weekly for 11 weeks.

Table 3 summarizes the UltraVIOLET study design.

Table 3. UltraVIOLET Clinical Trial (NCT03840616): Study Design Summary

Study Description	Randomized, double-blind trial evaluating the efficacy and safety of Vivjoa™ versus fluconazole and placebo in adult and postmenarchal pediatric females with RVVC.

Study Population (N = 219)	• Mean age: 35 years (range, 16–78 years)
	  ○ 18–44 years of age: 80%
	  ○ ≥45 years of age: 19%
	• White, 59%; Black or African American, 34%; Asian, 1%; Hispanic or Latino, 26%.

Inclusion Criteria	• Three or more episodes of acute VVC in the past 12 months. • Positive KOH test. • Total vulvovaginal signs and symptoms score of ≥3 at screening visit and <3 at Day 14.
Key Exclusion Criteria	• Presence or a history of other vaginal or vulvar condition(s) • Evidence of major organ system disease • History of cervical cancer • Poorly controlled diabetes mellitus • Pregnancy
Interventions	**Patients were randomized (2:1) to one of the following regimens for induction:** • Vivjoa™ 600 mg (4 × 150 mg) on Day 1 and 450 mg (3 × 150 mg) on Day 2 (n = 146). • Three sequential doses of 150 mg of fluconazole (every 72 hours) on Days, 1, 4, and 7 (n = 72). **If the acute episode of VVC was resolved 14 days after the first induction dose, patients continued to the maintenance phase:** • Patients receiving Vivjoa™ for induction were treated with Vivjoa™ 150 mg weekly × 11 weeks. • Patients receiving fluconazole for induction received placebo weekly × 11 weeks.
Primary Endpoint	Percentage of patients with ≥1 culture verified acute VVC episode during the maintenance phase of the study in the ITT population.

Abbreviations: ITT, intent-to-treat (population); KOH, potassium hydroxide; RVVC, recurrent vulvovaginal candidiasis; VVC, vulvovaginal candidiasis.

Efficacy of Vivjoa™ in UltraVIOLET Trial

Efficacy was assessed by the proportion of patients with ≥1 culture verified acute VVC episode during the maintenance phase (post-randomization through Week 50) or who failed to clear their infection during the induction phase. Evaluation of clinical signs and symptoms included erythema (redness), edema (swelling), excoriation (skin picking), itching, burning, and irritation.

In the UltraVIOLET trial, 89.7% of women with RVVC who received Vivjoa™ cleared their initial yeast infection and did not have a recurrence for the 50-week maintenance period compared to 57.1% of those who received fluconazole followed by placebo (P < 0.001). Table 4 represents key efficacy endpoints in the UltraVIOLET trial.

Table 4. UltraVIOLET Trial Efficacy Endpoints: ITT Population

	Vivjoa™ (n = 147)	Fluconazole/Placebo (n = 72)	Treatment Difference *P* value**
Proportion of patients with ≥1 culture-verified acute VVC episode through Week 50 or who had unresolved VVC during the induction phase*	10.3%	42.9%	<0.001

Proportion of patients with ≥1 culture-verified acute VVC episode or who took VVC medication through Week 50 or had unresolved VVC during the induction phase*	43.5%	59.0%	0.039

Abbreviations: ITT, intent-to-treat (population); VVC, vulvovaginal candidiasis. *Average %. Missing values were imputed with multiple imputation using the following auxiliary information: treatment, baseline body mass index, baseline age, ethnicity, and visit. **The P value was obtained using a Chi-square test comparing Vivjoa™ with fluconazole/placebo.

Safety: The most frequently reported adverse reactions among Vivjoa™-treated patients in Trial 1, Trial 2, and Trial 3 were headache (includes headache, migraines, sinus headaches) (7.4%) and nausea (3.6%). Other adverse reactions occurred in <2% of patients receiving Vivjoa™ and included increased serum creatine phosphokinase ≤10 times the upper limit of normal, dyspepsia, hot flush, dysuria, menorrhagia, metrorrhagia, and vulvovaginal irritation.

The adverse reaction that led to discontinuation in 1 of 580 (0.2%) Vivjoa™-treated patients was allergic dermatitis. Overall, similar percentages of serious adverse reactions and adverse reactions leading to drug discontinuation were reported across the Vivjoa™ and comparator patient dosing groups.

Safety

ADVERSE EVENTS

The adverse reaction that led to discontinuation in 1 of 580 (0.2 %) Vivjoa™-treated patients was allergic dermatitis. Overall, similar percentages of serious adverse reactions and adverse reactions leading to drug discontinuation were reported across the Vivjoa™ and comparator patient dosing groups.

The most frequently reported adverse reactions (incidence >2%) among Vivjoa™-treated patients in Trial 1, Trial 2 and Trial 3 were headache (includes headache, migraines, sinus headaches) (7.4%) and nausea (3.6%).

The following selected adverse reactions occurred in < 2% of patients receiving Vivjoa™ in Trial 1, Trial 2 and Trial 3 were increased blood creatine phosphokinase, dyspepsia, hot flush, dysuria, menorrhagia (includes genital hemorrhage, menorrhagia; menometrorrhagia; uterine hemorrhage, vaginal hemorrhage) metrorrhagia; vulvovaginal irritation (includes vulvovaginal burning sensation, vulvovaginal discomfort, and vulvovaginal pain).

WARNINGS & PRECAUTIONS

Embryo-Fetal Toxicity Contraindicated in females of reproductive potential, and in pregnant and lactating women. 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. Ocular abnormalities occurred at doses about 3.5 times the steady state clinical exposure seen with patients being treated for RVVC. 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.

CONTRAINDICATIONS

- Females of reproductive potential.
- Pregnant and lactating women.
- Patients with known hypersensitivity to oteseconazole.

Clinical Pharmacology

MECHANISMS OF ACTION

NEW DRUG APPROVAL

Oteseconazole is an azole metalloenzyme inhibitor targeting the fungal sterol, 14α demethylase (CYP51), an enzyme that catalyzes an early step in the biosynthetic pathway of ergosterol, a sterol required for fungal cell membrane formation and integrity. Inhibition of CYP51 results in the accumulation of 14-methylated sterols, some of which are toxic to fungi. Through the inclusion of a tetrazole metal-binding group, oteseconazole has a lower affinity for human CYP enzymes.

Dose & Administration

ADULTS

There are two recommended Vivjoa™ dosage regimens: Vivjoa™-only regimen and a Fluconazole/ Vivjoa™ regimen.

Vivjoa™-only Dosage Regimen:

- On Day 1: Administer Vivjoa™ 600 mg (as a single dose).
- On Day 2: Administer Vivjoa™ 450 mg (as a single dose).
- Beginning on Day 14: Administer Vivjoa™ 150 mg once a week (every 7 days) for 11 weeks (Weeks 2 through 12).

Fluconazole/ Vivjoa™ Dosage Regimen:

- On Day 1, Day 4, and Day 7: Administer fluconazole 150 mg orally.
- On Days 14 through 20: Administer Vivjoa™ 150 mg once daily for 7 days.
- Beginning on Day 28: Administer Vivjoa™ 150 mg once a week (every 7 days) for 11 weeks (Weeks 4 through 14).

PEDIATRICS

Refer to adult dosing.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

None

HEPATIC IMPAIRMENT

None

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Capsules: 150 mg of oteseconazole