

# VIVJOA™ (OTESECONAZOLE) CLINICAL MONOGRAPH

NOW APPROVED FOR RVVC

Prior to the approval of VIVJOA™ (oteseconazole) in April 2022, no therapies were approved by the US Food and Drug Administration (FDA) to treat recurrent vulvovaginal candidiasis (RVVC).<sup>1,2</sup>

VIVJOA is the first labeled medication to reduce the incidence of RVVC in females with a history of RVVC who are not of reproductive potential.

In clinical trials, VIVJOA was generally well-tolerated and demonstrated significant reductions in rates of acute vulvovaginal candidiasis (VVC) episodes versus comparators.

VIVJOA is notably contraindicated in females of reproductive potential, in pregnant and lactating women, and in patients with known hypersensitivity to oteseconazole.<sup>3</sup>

## VIVJOA™ (OTESECONAZOLE)

### *Indications and Usage*<sup>3</sup>

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

Females who are NOT of reproductive potential are defined as: persons who are biological females who are postmenopausal or have another reason for permanent infertility (e.g., tubal ligation, hysterectomy, salpingo-oophorectomy).

## IMPORTANT SAFETY INFORMATION

### *CONTRAINDICATIONS*<sup>3</sup>

VIVJOA is contraindicated in females of reproductive potential.

VIVJOA is contraindicated in pregnant and lactating women.

VIVJOA is contraindicated in patients with known hypersensitivity to oteseconazole.

## DISCLAIMER

This publication is intended for payers, formulary committees, or other similar entities with knowledge and expertise in the area of healthcare economics making decisions regarding access, coverage, and reimbursement for VIVJOA.

**This publication of *The American Journal of Managed Care*® was developed in collaboration with and with support from Mycovia Pharmaceuticals, Inc.**

## VIVJOA™ IMPORTANT SAFETY INFORMATION

### INDICATION

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**Females of Reproductive Potential:** VIVJOA is contraindicated in females of reproductive potential. Females who are NOT of reproductive potential are defined as: persons who are biological females who are postmenopausal or have another reason for permanent infertility (e.g., tubal ligation, hysterectomy, salpingo-oophorectomy).

**Pregnant and Lactating Women:** VIVJOA is contraindicated in pregnant and lactating women.

**Hypersensitivity:** VIVJOA is contraindicated in patients with known hypersensitivity to oteseconazole.

Please see INDICATION and IMPORTANT SAFETY INFORMATION and accompanying FULL PRESCRIBING INFORMATION.

## VIVJOA™ (OTESECONAZOLE) CLINICAL MONOGRAPH

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This Clinical Monograph provides Pharmacy and Therapeutics (P&T) Committee members with current, detailed information about a specific therapeutic agent to help them manage their formularies and establish medication-related policies. The monograph supplies information about pharmacology, clinical studies, FDA-approved indications, safety, efficacy, acquisition costs, and other pharmaco-economic variables, along with additional P&T committee considerations, in a convenient package.

### ABOUT THE AUTHORS

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### DISCLOSURES

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Mycovia Pharmaceuticals, Inc. provided funding for this publication. Heather Magsarili and Larisa Vulakh report they have no financial arrangement or affiliation with Mycovia Pharmaceuticals, Inc. that might constitute a conflict of interest with respect to this publication.

This publication is intended for use by payers, formulary committees, and other multidisciplinary entities making drug selection, access, coverage, and reimbursement decisions on a population basis.

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## IMPORTANT SAFETY INFORMATION (CON'T)

### 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.

### ADVERSE REACTIONS

The most frequently reported adverse reactions among VIVJOA-treated patients in clinical studies included headache (7.4%) and nausea (3.6%).

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## IMPORTANT SAFETY INFORMATION (CON'T)

### DRUG INTERACTIONS

**Effect of VIVJOA on Other Drugs:** Oteseconazole is a Breast Cancer Resistance Protein (BCRP) inhibitor. Concomitant use of VIVJOA with BCRP substrates (e.g., rosuvastatin) may increase the exposure of BCRP substrates (e.g., rosuvastatin), 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 drug and monitor for adverse reactions.

# FORMULARY CONSIDERATIONS IN THE MANAGEMENT OF RECURRENT VULVOVAGINAL CANDIDIASIS FOR LONG-TERM REDUCTION OF RECURRENCE

## INTRODUCTION

This Clinical Monograph introduces VIVJOA™ (oteseconazole) capsules, 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.<sup>3</sup> VIVJOA was approved by the US Food and Drug Administration (FDA) on April 26, 2022.<sup>2</sup>

Recurrent vulvovaginal candidiasis (RVVC), also frequently referred to as a recurrent yeast infection, is a distinct subtype of vulvovaginal candidiasis (VVC).<sup>1,4-6</sup> The 2021 Centers for Disease Control and Prevention (CDC) *Guidelines* define RVVC as 3 or more symptomatic acute episodes within 12 months.<sup>7</sup>

The following presents an overview of the disease state of RVVC and the efficacy and safety considerations for the use of VIVJOA.

## DISEASE STATE OVERVIEW

### Prevalence and Classification

Vulvovaginal candidiasis (VVC) is a common infection involving acute inflammation of the vulva and vaginal mucosa and is associated with overgrowth of many types of *Candida* yeast, most often *Candida albicans*.<sup>4,8,9</sup> It is estimated that up to 75% of adult women will have at

least 1 acute VVC infection during their lifetime, and roughly 50% will experience a recurrence.<sup>7,10</sup> RVVC—which has been defined by the CDC as 3 or more symptomatic acute VVC episodes within 12 months<sup>7</sup>—occurs in up to 9% of women (Table 1).<sup>7,10,11</sup> About 6 million women in the US and 138 million women worldwide are affected annually; 372 million women are impacted by RVVC over their lifetime. The global population of women with RVVC is estimated to increase to 158 million by 2030.<sup>11</sup>

VVC is categorized as uncomplicated or complicated. The majority (90%) of cases are considered uncomplicated, while the remaining 10% of complicated cases are characterized by severe or recurrent disease (RVVC), non-*albicans* candidiasis, and/or infection in an abnormal host.<sup>7,12</sup>

### Estimates of Females of Nonreproductive Potential

While the highest prevalence of RVVC is among women ages 25 to 34 years, substantial numbers of postmenopausal women are affected, especially those on hormone replacement therapy.<sup>11</sup> Approximately 57 million women in the US are at least 45 years of age, with roughly 6,000 women reaching menopause every day.<sup>13</sup>

Typical onset of menopause is between ages 40 to 58 years, occurring at a median age of 51 to 52 years.<sup>14,15</sup> Based on real-world data of women with RVVC, an estimated 44% of women are aged 45 years and older, and those between the ages of 45 and 54 years have the second highest prevalence of RVVC (18%) after women ages 25 to 34 years (22%) and those ages 35 to 44 years (22%).<sup>16</sup>

Regarding nonreproductive potential in other demographics, certain procedures may cause fertility loss among younger women.<sup>17-19</sup> In 2021, approximately 750,000 women aged 18 to 44 years had the following conditions that cause permanent infertility: hysterectomy (n ≈ 200,000), salpingo-oophorectomy (n ≈ 225,000), and tubal ligation (n ≈ 325,000).<sup>20</sup>

**Table 1.** VVC and RVVC Statistics<sup>7,10,11</sup>

Proportion of women who will experience at least 1 acute VVC infection	75% <sup>7</sup>
Proportion of women who will experience recurrent infection	40%-50% <sup>10</sup>
Proportion of women who will develop RVVC	Up to 9% <sup>11</sup>

RVVC, recurrent vulvovaginal candidiasis; VVC, vulvovaginal candidiasis.

## IMPORTANT SAFETY INFORMATION (CON'T)

### USE IN SPECIFIC POPULATIONS

**Pregnancy:** VIVJOA is contraindicated in females of reproductive potential and in pregnant women. Based on animal studies, VIVJOA may cause fetal harm when administered to pregnant women. In addition, 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.

**Lactation:** VIVJOA is contraindicated in lactating women and females of reproductive potential. There are no data on the presence of oteseconazole in human or animal milk or data on the effects of oteseconazole on milk production. There were no reported adverse effects in breastfed infants following maternal exposure to oteseconazole during lactation; however, given the limited duration of follow-up of the oteseconazole-exposed infants during the post-natal period, no conclusions can be drawn from these data.

### Burden of Disease: Focus on RVVC

VVC is associated with a significant clinical and economic burden. Of roughly 3.6 million outpatient visits (\$2.1 billion) for noninvasive candidiasis in 2014, VVC accounted for 37% of these visits (\$368 million).<sup>21</sup> In terms of RVVC, annual lost productivity has been estimated at \$14.4 billion in high-income countries (2010 data).<sup>11</sup> In the United States, about 7 hours of work are missed for each episode of RVVC, or roughly 5 workdays per year, resulting in lost productivity costs.<sup>22</sup>

Among 536 women with RVVC across 5 European countries and the US, while a majority (60%) reported RVVC lasting less than 3 years, 6% reported symptoms exceeding 10 years.<sup>23</sup>

As a chronic condition, RVVC has a negative impact on quality of life for many women.<sup>11</sup> In a prospective study of 200 women with chronic vaginal symptoms, 20.5% were diagnosed with RVVC. Of these patients with RVVC, 42% had concomitant psychiatric diagnoses. The same proportion also reported a moderate to severe impact on their social and professional lives, as well as decreased sexual desire.<sup>24</sup> In addition, women with RVVC report reduced confidence and self-esteem,<sup>11</sup> and many suffer from decreased mental health. In a global survey of 620 women with RVVC in the US and Europe, 68% experienced anxiety/depression during an acute infectious episode, and 54% reported having these symptoms outside of an acute event. Of US respondents with RVVC (N = 102), nearly 56% reported anxiety and depression, and around 60% complained that RVVC impacted their activities of daily living.<sup>22</sup>

**RVVC has a negative impact on quality of life for many women.<sup>11</sup>**

### Etiology and Risk Factors

RVVC may be idiopathic in nature or secondary to underlying host factors (e.g., frequent antibiotic use, presence of diabetes), but the majority of patients have no apparent predisposing conditions.<sup>7</sup> Although *Candida* species are considered normal vaginal flora, acute VVC is presumed to be a result of triggered overgrowth and/or altered

host defense mechanisms. *C. albicans*, an opportunistic fungus found in upwards of 90% of acute cases of VVC, is also the primary causative pathogen in RVVC.<sup>4,5</sup> Non-*albicans Candida* species occur in 10% to 20% of RVVC. Conventional antifungal treatments are not as effective against non-*albicans* yeasts.<sup>7</sup> Risk factors for infection with *C. glabrata*—the most commonly isolated non-*albicans Candida* species—include older age, type 2 diabetes and relevant glycosuria-inducing drug treatments (SGLT2 inhibitors), and postmenopausal status (Table 2).<sup>4,10,11,25-27</sup>

In the postmenopausal population, studies have shown an association between VVC/RVVC and hormone replacement therapy. Estrogen levels are thought to play an important role in disease pathology, with multiple effects on both the host and *Candida* pathogens (e.g., estrogen promotes *Candida* adherence to vaginal epithelial cells).<sup>4,5,11</sup>

### Clinical Presentation

Common symptoms of acute VVC include pruritus, irritation, vaginal soreness, dysuria, dyspareunia, and abnormal vaginal discharge.<sup>4,7</sup>

**Table 2.** Selected Risk Factors for RVVC<sup>10,26,27</sup>

<b>Host factors</b>	<ul style="list-style-type: none"> <li>• Uncontrolled diabetes</li> <li>• HIV</li> <li>• Medications (e.g., corticosteroids, antibiotics, hormone replacement therapy)</li> <li>• Pregnancy</li> <li>• Immunosuppression</li> </ul>
<b>Genetic factors</b>	<ul style="list-style-type: none"> <li>• Familial history</li> <li>• African American heritage</li> <li>• Polymorphisms in immunity genes</li> </ul>
<b>Behavioral factors</b>	<ul style="list-style-type: none"> <li>• Oral contraceptive use</li> <li>• Sponge/intrauterine device use</li> <li>• Intercourse frequency/type</li> <li>• Poor personal hygiene</li> <li>• Use of feminine hygiene products</li> <li>• Clothing</li> </ul>

RVVC, recurrent vulvovaginal candidiasis.

## IMPORTANT SAFETY INFORMATION (CON'T)

**Females of Reproductive Potential:** VIVJOA is contraindicated in females of reproductive potential based on data from rat studies.

**Pediatric Use:** The safety and effectiveness of VIVJOA have not been established in pre-menarchal pediatric females.

**Geriatric Use:** Clinical studies of VIVJOA did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients.

Because of the chronic nature of RVVC, affected women may also report mental symptoms, such as depression and anxiety.<sup>4</sup>

**Figure 1** presents the frequency of clinical characteristics of VVC.<sup>26</sup>

Women affected by RVVC frequently report feelings of depression and anxiety.<sup>22</sup>

### Treatment Guidelines

Prior to the approval of VIVJOA in April 2022, there were no FDA-approved therapies for RVVC.<sup>1,2</sup> While uncomplicated VVC can be effectively treated with several short-course topical or oral azole treatment options, RVVC requires a different treatment approach.<sup>7,12</sup>

The Infectious Diseases Society of America (IDSA), American College of Obstetricians and Gynecologists (ACOG), and CDC recognize RVVC as distinct from uncomplicated VVC, and their guidelines (2016, 2020, and 2021, respectively) reflect this clinical differentiation.<sup>7,12,28</sup> While the older guidelines define RVVC as at least 4 symptomatic

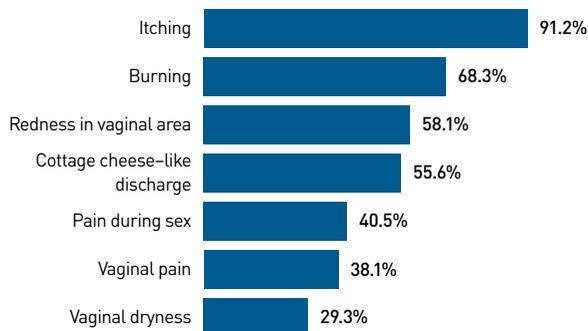
acute VVC episodes within 12 months, the most recently updated guideline from the CDC defines RVVC as at least 3 episodes within a year. All guidelines distinguish between treatment of uncomplicated VVC and RVVC—due to the chronicity of infection, RVVC warrants longer-term treatment than uncomplicated VVC to maintain clinical and mycological control. Unlike the short-term (over 1 to 14 days depending on route of administration) treatment recommended for uncomplicated VVC, guidelines advise treating RVVC with up to 14 days of induction therapy with either a topical agent or oral fluconazole, followed by a 6-month maintenance azole regimen (**Table 3**).<sup>7,12,28</sup>

### Maintenance Fluconazole Therapy for RVVC

Although most cases of RVVC are caused by azole-susceptible *C. albicans*, cure is rarely achieved, and recurrence occurs in up to 50% of women following discontinuation of maintenance fluconazole therapy.<sup>7,12,29</sup> In a randomized, placebo-controlled study that evaluated the effect of maintenance fluconazole on the frequency of clinical episodes of RVVC, 387 women with RVVC were randomized to weekly fluconazole or placebo for 6 months. **Figure 2** presents RVVC recurrence rates at the end of maintenance, 3 months post maintenance, and 6 months post maintenance following 6 months of fluconazole versus placebo among the 343 women included in the efficacy analysis.<sup>29</sup> Although patients who received placebo experienced significantly higher rates of clinical recurrence at all 3 time points compared with fluconazole ( $P < 0.001$ ), relapse rates among patients in the fluconazole arm progressively increased after cessation of fluconazole.<sup>29</sup> In a retrospective chart review (N = 120) of women with RVVC, the mean length of follow-up after discontinuing maintenance fluconazole was 39.9 months; the majority (63.3%) of women experienced ongoing disease following completion of maintenance treatment (duration of therapy ranged from 1 to 12 months, with a mean of 6.38 months), whereas only 19.2% achieved resolution of disease (duration of therapy ranged from 3 to 26 months, with a mean of 8.22 months).<sup>30</sup>

Studies have found that women with fluconazole-resistant *C. albicans* have had substantial prior exposure to fluconazole.<sup>4</sup> Additionally, suppressive fluconazole therapy is typically less effective in those with RVVC caused by non-*albicans* species. Repeat rounds

**Figure 1.** Clinical Features of VVC by Reported Frequency<sup>26,a</sup>



VVC, vulvovaginal candidiasis.

<sup>a</sup>Based on an online survey of 284 nonpregnant women attending US obstetrics/gynecology clinics.

## IMPORTANT SAFETY INFORMATION (CON'T)

**Renal Impairment:** No dosage adjustment of VIVJOA is recommended in patients with mild to moderate renal impairment. VIVJOA is not recommended for use in patients with severe renal impairment or end-stage renal disease, as clinical studies did not include sufficient numbers of these patients.

**Hepatic Impairment:** No dosage adjustment of VIVJOA is recommended in patients with mild hepatic impairment. VIVJOA is not recommended for use in patients with moderate or severe hepatic impairment, as there is insufficient information in these patients.

**Table 3.** Definition and Treatment of RVVC by Guidelines<sup>7,12,28</sup>

	Infectious Diseases Society of America <sup>12</sup> (Last Updated: 2016)	Centers for Disease Control and Prevention <sup>7</sup> (Last Updated: 2021)	American College of Obstetricians and Gynecologists <sup>28</sup> (Last Updated: 2020)
<b>Definition of RVVC</b>	≥ 4 episodes of symptomatic VVC within 1 year	≥ 3 episodes of symptomatic VVC within 1 year	≥ 4 episodes of symptomatic VVC within 1 year
<b>Induction</b>	Topical agent <b>OR</b> Oral fluconazole for 10-14 days	Short duration oral or topical azole <b>OR</b> Longer duration (e.g., 7-14 days of topical therapy or 100 mg, 150 mg, or 200 mg fluconazole on Days 1, 4, 7)	Oral or topical azole
<b>Maintenance</b>	150 mg fluconazole weekly for 6 months	Oral fluconazole (100 mg, 150 mg, or 200 mg) weekly for 6 months <b>Second-line:</b> Intermittent topical treatment	150 mg fluconazole weekly for 6 months <b>Second-line:</b> Intermittent topical agents (e.g., clotrimazole 500 mg weekly or 200 mg twice weekly)

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of induction and maintenance treatment may be necessary as some women experience episodes of RVVC over a prolonged duration.<sup>1</sup>

### Disclaimers

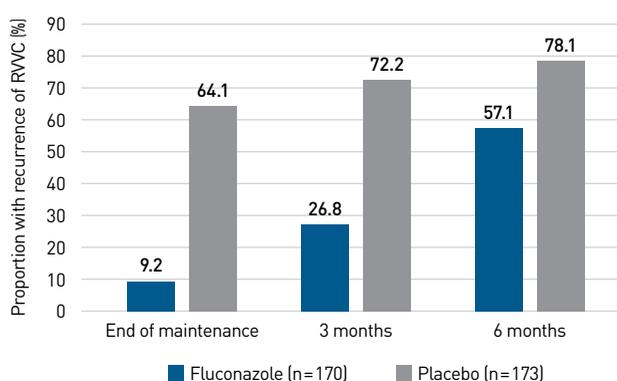
The aforementioned disease state information refers to women in the general population, not specifically the VIVJOA™ patient population or patients who may be prescribed VIVJOA. VIVJOA has not been shown to impact Quality of Life (QOL) indicators in all clinical subjects. Not all products approved for RVVC are appropriate for all patients. Please refer to the VIVJOA Full Prescribing Information for more information.

## INDICATION

### Indication and Usage<sup>3</sup>

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

If specimens for fungal culture are obtained prior to therapy, antifungal therapy may be instituted before the results of the cultures

**Figure 2.** RVC Recurrence Rates After 6 Months of Maintenance Fluconazole<sup>29</sup>

RVC, recurrent vulvovaginal candidiasis.

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**Pregnant and Lactating Women:** VIVJOA is contraindicated in pregnant and lactating women.

**Hypersensitivity:** VIVJOA is contraindicated in patients with known hypersensitivity to oteseconazole.

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are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

## MICROBIOLOGY<sup>3</sup>

### Mechanism of Action:

Oteseconazole is an azole metalloenzyme inhibitor targeting the fungal sterol, 14 $\alpha$  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.

### Resistance:

The potential for increases in minimum inhibitory concentrations (MIC) to oteseconazole has been evaluated *in vitro* including specific mechanisms of resistance. Increases in oteseconazole MIC were associated with upregulation of the efflux pumps CDR1, MDR1, and the azole target, lanosterol 14- $\alpha$ -demethylase (CYP51). Against certain *Candida* spp. oteseconazole maintained meaningful *in vitro* activity against clinical isolates that were resistant to fluconazole.

### Antimicrobial Activity:

The following *in vitro* data is available, but their clinical significance is unknown. Oteseconazole has been shown to be active against most isolates of the following microorganisms associated with RVVC.

- *Candida albicans*
- *Candida glabrata*
- *Candida krusei*
- *Candida parapsilosis*
- *Candida tropicalis*
- *Candida lusitanae*
- *Candida dubliniensis*

Table 4 presents susceptibility data for viable clinical isolates collected from 3 different phase 3 studies.<sup>31</sup>

## CLINICAL STUDIES

### Clinical Studies<sup>3</sup>

A total of 656 adults and postmenarchal pediatric females with RVVC (defined as  $\geq 3$  episodes of VVC in a 12-month period) were randomized in 2 multicenter, multinational, double-blind, placebo-controlled

**Table 4.** MIC Susceptibility of Clinical Isolates Collected from RVVC Clinical Studies<sup>31</sup>

Clinical isolates	VIVJOA			Fluconazole		
	Range ( $\mu\text{g/mL}$ )	MIC <sub>50</sub> ( $\mu\text{g/mL}$ )	MIC <sub>90</sub> ( $\mu\text{g/mL}$ )	Range ( $\mu\text{g/mL}$ )	MIC <sub>50</sub> ( $\mu\text{g/mL}$ )	MIC <sub>90</sub> ( $\mu\text{g/mL}$ )
All <i>C. albicans</i> (n = 1341)	$\leq 0.0005$ - $> 0.25$	0.002	0.016	$\leq 0.06$ - $> 32$	0.125	2
<i>C. glabrata</i> (n = 249)	0.001 - $> 0.25$	0.03	0.125	$\leq 0.06$ - 32	1	8
<i>C. parapsilosis</i> (n = 66)	$\leq 0.0005$ - 0.125	0.004	0.06	$\leq 0.06$ - $> 32$	0.25	4
<i>C. tropicalis</i> (n = 28)	0.001 - 0.06	0.008	0.06	0.125 - 32	0.5	4
<i>C. lusitanae</i> (n = 20)	0.001 - $> 0.25$	0.03	0.25	$\leq 0.06$ - 16	0.25	8
Other species (n = 116)	$\leq 0.0005$ - $> 0.25$	0.016	0.125	$\leq 0.06$ - $> 32$	1	8

C, *Candida*; MIC, minimum inhibitory concentration; RVVC, recurrent vulvovaginal candidiasis.

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### ADVERSE REACTIONS

The most frequently reported adverse reactions among VIVJOA-treated patients in clinical studies included headache (7.4%) and nausea (3.6%).

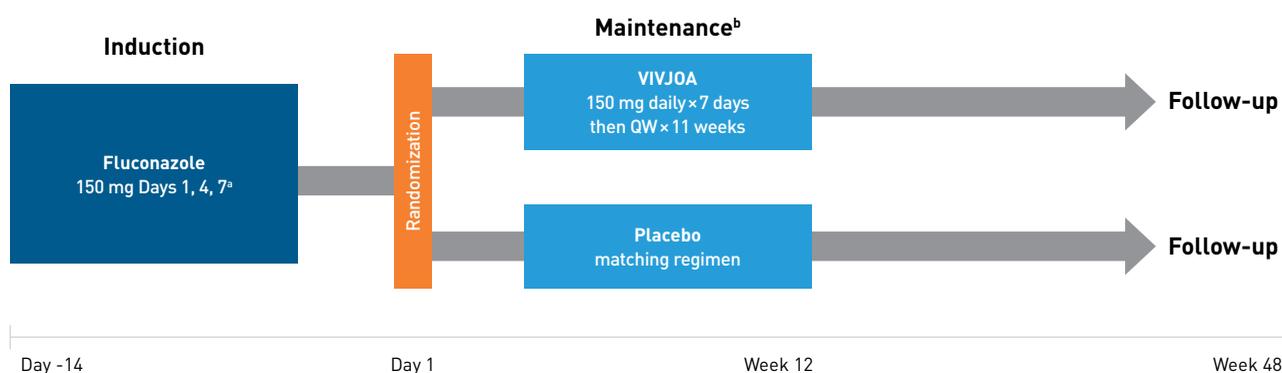
trials: Trial 1 (NCT# 03562156) and Trial 2 (NCT# 03561701), known as the VIOLET trials.<sup>32,33</sup> A total of 219 adults and postmenarchal pediatric females with RVVC were randomized in a multicenter, double-blind trial known as ultraVIOLET (Trial 3 [NCT# 03840616]).<sup>34</sup> Although females of reproductive potential were included in the clinical efficacy data, VIVJOA is contraindicated in females of reproductive potential due to the risk of embryo-fetal toxicity.

The VIOLET trials were both randomized, placebo-controlled trials evaluating the efficacy and safety of VIVJOA in the reduction of RVVC. Both trials consisted of 2 phases: an open-label induction phase and an 11-week maintenance phase. Patients received 3 sequential 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 (Figure 3).<sup>3,32,33</sup>

For both VIOLET trials, efficacy was assessed by the proportion of patients with  $\geq 1$  culture-verified acute VVC episode (positive fungal culture for *Candida* species associated with a clinical signs and symptoms score of  $\geq 3$ ) during the maintenance phase through Week 48. Evaluation of clinical signs and symptoms included erythema (redness), edema (swelling), excoriation (skin picking), itching, burning, and irritation. Since treatment for acute VVC was allowed to be provided to a patient if it was deemed to be clinically needed when the patient had a signs and symptoms score  $\geq 3$  and a positive KOH test, the proportion of patients with  $\geq 1$  culture verified acute VVC episode or who took medication known to treat VVC during the maintenance phase through Week 48 is also presented.

In VIOLET Trial 1, a total of 483 patients were enrolled in the induction phase with 326 patients entering the maintenance phase. Of these 326 patients, 217 patients were randomized to VIVJOA and 109 patients were randomized to placebo. A total of 182 patients (84%) in the VIVJOA group and 91 patients (83%) in the placebo group completed

**Figure 3.** VIOLET Trials Study Design<sup>3,32,33</sup>



QW, once a week; VVC, vulvovaginal candidiasis.

<sup>a</sup>Based on Infectious Diseases Society of America guidelines.

<sup>b</sup>Maintenance phase ensued if acute VVC episode was resolved (vulvovaginal signs and symptoms score < 3).

## IMPORTANT SAFETY INFORMATION (CON'T)

### DRUG INTERACTIONS

**Effect of VIVJOA on Other Drugs:** Oteseconazole is a Breast Cancer Resistance Protein (BCRP) inhibitor. Concomitant use of VIVJOA with BCRP substrates (e.g., rosuvastatin) may increase the exposure of BCRP substrates (e.g., rosuvastatin), 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 drug and monitor for adverse reactions.

the trial. In VIOLET Trial 2, a total of 425 patients were enrolled into the induction phase with 330 patients entering the maintenance phase. Of these 330 patients, 220 were randomized to VIVJOA and 110 were randomized to placebo. A total of 191 patients (87%) in the VIVJOA group and 91 patients (83%) in the placebo group completed the trial. **Table 5** presents demographic information for the VIOLET trials.<sup>3,32,33</sup>

VIVJOA was superior to placebo with reference to the proportion of patients with  $\geq 1$  culture-verified acute VVC episode through Week 48 or the proportion of patients with  $\geq 1$  culture-verified acute VVC episode or who took medication known to treat VVC during the maintenance phase through Week 48. For both trials, the average percentage of patients was lower in the VIVJOA groups compared with the placebo group (**Table 6**).<sup>3,32,33</sup> A total of 6.7% and 3.9% of women with RVVC who received VIVJOA in VIOLET Trial 1 and Trial 2, respectively, experienced a recurrence over the 48-week study period compared with 42.8% and 39.4% of patients who received placebo ( $P < 0.001$ ). In other words, 93.3% and 96.1% of women with

RVVC who received VIVJOA in Trial 1 and Trial 2, respectively, did not have a recurrence for 48 weeks compared with 57.2% and 60.6% of patients who received placebo.

Trial 3, ultraVIOLET, 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 2 phases: induction and maintenance. During the induction phase, patients received 1050 mg of VIVJOA over 2 days (600 mg [4 × 150 mg] on Day 1 and 450 mg [3 × 150 mg] on Day 2) or 3 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 (**Figure 4**).<sup>3,34</sup>

A total of 219 patients were randomized (2:1) into the induction phase: 147 to VIVJOA and 72 to fluconazole/placebo. One patient in the VIVJOA group did not receive drug; therefore, 146 patients

**Table 5.** VIOLET Trials Demographics (ITT population)<sup>3,32,33</sup>

	Trial 1 overall (N=326)	Trial 2 overall (N=330)
<b>Mean age, years (range)</b>	34 [17-78]	34 [18-73]
Aged 18-44 years	85%	85%
Aged $\geq 45$ years	15%	15%
<b>Race</b>		
White	72%	89%
Black or African American	13%	10%
Asian	14%	—
Hispanic or Latino	8%	15%

ITT, intention to treat (population).

**Table 6.** VIOLET Trials Efficacy End Points (ITT population)<sup>3,32,33</sup>

	Trial 1		Trial 2	
	VIVJOA (n=217)	Placebo (n=109)	VIVJOA (n=218)	Placebo (n=108)
<b>Proportion of patients with <math>\geq 1</math> culture-verified acute VVC episode (Day 1 through Week 48)<sup>a</sup></b>	6.7%	42.8%	3.9%	39.4%
<b>Treatment difference P value<sup>b</sup></b>	< 0.001		< 0.001	
<b>Proportion of patients with <math>\geq 1</math> culture-verified acute VVC episode or received VVC medication (Day 1 through Week 48)<sup>a</sup></b>	27.3%	50.8%	21.3%	49.7%
<b>Treatment difference P value<sup>b</sup></b>	< 0.001		< 0.001	

ITT, intention to treat (population); VVC, vulvovaginal candidiasis.

<sup>a</sup>Average %. Missing values were imputed with multiple imputation using the following auxiliary information: region, treatment, baseline body mass index, baseline age, ethnicity, and visit.

<sup>b</sup>The P value was obtained using a Chi-square test comparing VIVJOA with placebo.

## IMPORTANT SAFETY INFORMATION (CON'T)

### USE IN SPECIFIC POPULATIONS

**Pregnancy:** VIVJOA is contraindicated in females of reproductive potential and in pregnant women. Based on animal studies, VIVJOA may cause fetal harm when administered to pregnant women. In addition, 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.

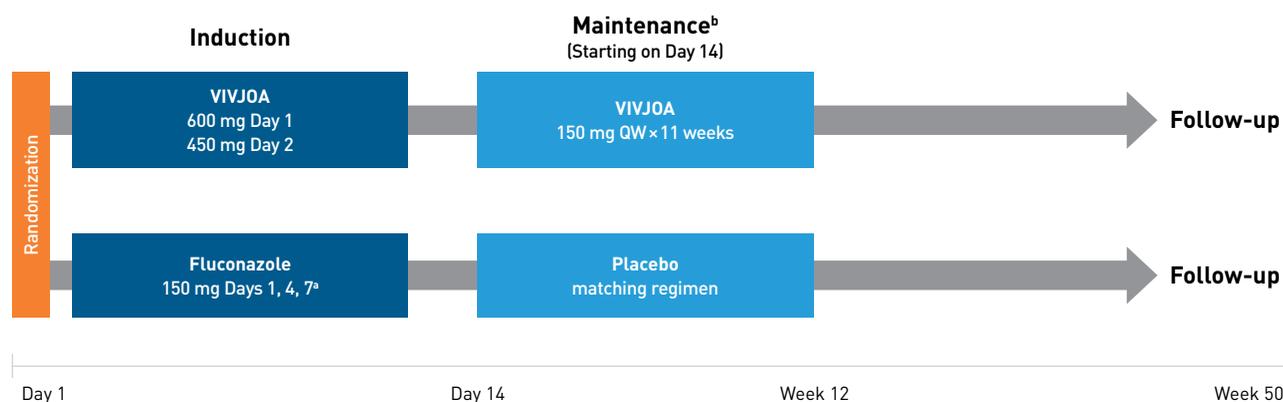
**Lactation:** VIVJOA is contraindicated in lactating women and females of reproductive potential. There are no data on the presence of oteseconazole in human or animal milk or data on the effects of oteseconazole on milk production. There were no reported adverse effects in breastfed infants following maternal exposure to oteseconazole during lactation; however, given the limited duration of follow-up of the oteseconazole-exposed infants during the post-natal period, no conclusions can be drawn from these data.

received VIVJOA. A total of 112 patients (76%) in the VIVJOA group and 55 patients (76%) in the fluconazole/placebo group completed the trial. The trial was conducted completely in the United States. **Table 7** presents demographic information for the ultraVIOLET trial.<sup>3,34</sup>

Efficacy was assessed by the proportion of patients with  $\geq 1$  culture-verified acute VVC episode during the maintenance phase (postrandomization through Week 50) or who failed clearing their infection during the induction phase. A recurring acute VVC episode was defined as a positive culture for *Candida* species and a clinical signs and symptoms score of  $\geq 3$ . Evaluation of clinical signs and symptoms included erythema (redness), edema (swelling), excoriation (skin picking), itching, burning, and irritation. Additionally, the proportion of patients with  $\geq 1$  culture verified acute VVC episode or who took medication known to treat VVC during the maintenance phase (postrandomization through Week 50) or who failed clearing their infection during the induction phase is presented.

VIVJOA was superior to fluconazole/placebo in the proportion of patients with  $\geq 1$  culture-verified recurring acute VVC episode during the maintenance phase (postrandomization through Week 50) or failed clearing their infection during the induction phase, and the proportion of patients with  $\geq 1$  culture-verified recurring acute VVC episode or took VVC medication known to treat VVC during the maintenance phase (postrandomization through Week 50) or who failed clearing their infection during the induction phase (**Table 8**).<sup>3,34</sup> The average percentage of patients was lower in the VIVJOA group compared with the fluconazole/placebo group. A total of 10.3% of women with RVVC who received 12 weeks of VIVJOA experienced a recurrence over the 50-week study period compared with 42.9% of patients who received fluconazole followed by placebo ( $P < 0.001$ ). In other words, 89.7% of women with RVVC who received 12 weeks of VIVJOA did NOT have a recurrence by 50 weeks compared to 57.1% of those who received fluconazole followed by placebo.

**Figure 4.** ultraVIOLET Trial Study Design<sup>3,34</sup>



QW, once a week; VVC, vulvovaginal candidiasis.

<sup>a</sup>Based on Infectious Diseases Society of America guidelines.

<sup>b</sup>Maintenance phase ensued if acute VVC episode was resolved (vulvovaginal signs and symptoms score  $< 3$ ).

## IMPORTANT SAFETY INFORMATION (CON'T)

**Females of Reproductive Potential:** VIVJOA is contraindicated in females of reproductive potential based on data from rat studies.

**Pediatric Use:** The safety and effectiveness of VIVJOA have not been established in pre-menarchal pediatric females.

**Geriatric Use:** Clinical studies of VIVJOA did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients.

**Table 7.** ultraVIOLET Trial Demographics (ITT population)<sup>3,34</sup>

	ultraVIOLET overall (N=219)
<b>Mean age, years (range)</b>	35 (16-78)
Aged 18-44 years	80%
Aged ≥45 years	19%
<b>Race</b>	
White	59%
Black or African American	34%
Asian	1%
Hispanic or Latino	26%

ITT, intention to treat (population).

**Table 8.** ultraVIOLET Trial Efficacy End Points (ITT population)<sup>3,34</sup>

	VIVJOA (n=147)	Fluconazole/ placebo (n=72)	Treatment difference P value <sup>b</sup>
<b>Proportion of patients with ≥ 1 culture-verified acute VVC episode through Week 50 or unresolved VVC episode during induction phase<sup>a</sup></b>	10.3%	42.9%	< 0.001
<b>Proportion of patients with ≥ 1 culture-verified acute VVC episode or took VVC medication through Week 50 or unresolved VVC episode during induction phase<sup>a</sup></b>	43.5%	59.0%	0.039

ITT, intention to treat (population); VVC, vulvovaginal candidiasis.

<sup>a</sup>Average %. Missing values were imputed with multiple imputation using the following auxiliary information: treatment, baseline body mass index, baseline age, ethnicity, and visit.<sup>b</sup>The P value was obtained using a Chi-square test comparing VIVJOA with fluconazole/placebo.

## DOSAGE AND ADMINISTRATION

### Dosage Regimen<sup>3</sup>

The available recommended VIVJOA dosage regimen is as follows:

- VIVJOA-only Dosage Regimen
  - **On Day 1:** Administer 600 mg (as a single dose), then
  - **On Day 2:** Administer 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).

VIVJOA should be administered orally with food. The capsules should be swallowed whole; the capsules should not be chewed, crushed, dissolved, or opened.

### Dosage Form and Strengths<sup>3</sup>

VIVJOA Capsules: 150 mg of oteseconazole in lavender hard gelatin capsules imprinted with OTE 150 in black ink.

Fluconazole is not supplied in the carton.

### How Supplied/Storage and Handling<sup>3</sup>

VIVJOA (oteseconazole capsules) are supplied as lavender hard gelatin capsules. Printed black "OTE 150" on the capsule and contain 150 mg oteseconazole. They are available in an 18-count (NDC 74695-823-18) blister package within a child resistant wallet. There is one blister pack per wallet and one wallet per outer carton.

The fluconazole/VIVJOA dosage regimen is in an 18-count (NDC 74695-945-18) blister package within a child resistant wallet. There is one blister pack of VIVJOA (oteseconazole capsules) per wallet and one wallet per outer carton. The outer carton and wallet contain the following: "fluconazole/VIVJOA dosage regimen" and "fluconazole is prescribed separately".

Fluconazole is not supplied in the carton.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F to 86°F). Protect from light when removed from the outer carton.

## IMPORTANT SAFETY INFORMATION (CON'T)

**Renal Impairment:** No dosage adjustment of VIVJOA is recommended in patients with mild to moderate renal impairment. VIVJOA is not recommended for use in patients with severe renal impairment or end-stage renal disease, as clinical studies did not include sufficient numbers of these patients.

**Hepatic Impairment:** No dosage adjustment of VIVJOA is recommended in patients with mild hepatic impairment. VIVJOA is not recommended for use in patients with moderate or severe hepatic impairment, as there is insufficient information in these patients.

## SAFETY CONSIDERATIONS

### CONTRAINDICATIONS<sup>3</sup>

**Females of Reproductive Potential:** VIVJOA is contraindicated in females of reproductive potential. Females who are NOT of reproductive potential are defined as: persons who are biological females who are postmenopausal or have another reason for permanent infertility (e.g., tubal ligation, hysterectomy, salpingo-oophorectomy).

**Pregnant and Lactating Women:** VIVJOA is contraindicated in pregnant and lactating women.

**Hypersensitivity:** VIVJOA is contraindicated in patients with known hypersensitivity to oteseconazole.

### WARNINGS AND PRECAUTIONS<sup>3</sup>

#### *Embryo-Fetal Toxicity*

VIVJOA is 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 were observed in the offspring of pregnant rats dosed at 7.5 mg/kg/day during organogenesis through lactation in pre and postnatal developmental studies. The observed ocular abnormalities included cataracts, opacities, exophthalmos/buphthalmos, optic nerve/retinal atrophy, lens degeneration and hemorrhage. 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.

### ADVERSE REACTIONS<sup>3</sup>

#### *Clinical Trials Experience*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of one drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 580 patients were treated with VIVJOA in three clinical trials (Trial 1, Trial 2, and Trial 3). Patients in the clinical trials were women with RVVC who received VIVJOA medication for 12 weeks. The mean age of the patient population was 34 years (range: 16-78 years), with 84% of patients aged 18-44 years and 16% of patients aged 45 years and older. Although females of reproductive potential were included in the clinical safety data, VIVJOA is contraindicated in females of reproductive potential due to the risk of embryo-fetal toxicity.

The clinical trials population was 75% (435/580) White, 17% (96/580) Black or African American, 6% (36/580) Asian, and 2% (13/580) Other women. Fifteen percent (86/580) of all women were Hispanic/Latino. Patients enrolled in the induction and maintenance phases of the clinical trials were treated with different VIVJOA dosage regimens versus comparators.

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%).

#### Other Adverse Reactions

The following selected adverse reactions occurred in < 2% of patients receiving VIVJOA in Trial 1, Trial 2 and Trial 3:

- Laboratory investigations: Increased blood creatine phosphokinase
- Gastrointestinal disorders: Dyspepsia
- Vascular disorders: Hot flush
- Renal and urinary disorders: Dysuria
- Reproductive system and breast disorders: Menorrhagia (includes genital hemorrhage, menorrhagia; menometrorrhagia; uterine hemorrhage, vaginal hemorrhage) metrorrhagia; vulvovaginal irritation (includes vulvovaginal burning sensation, vulvovaginal discomfort, and vulvovaginal pain)

## VIVJOA™ IMPORTANT SAFETY INFORMATION

### INDICATION

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

### IMPORTANT SAFETY INFORMATION

#### CONTRAINDICATIONS

**Females of Reproductive Potential:** VIVJOA is contraindicated in females of reproductive potential. Females who are NOT of reproductive potential are defined as: persons who are biological females who are postmenopausal or have another reason for permanent infertility (e.g., tubal ligation, hysterectomy, salpingo-oophorectomy).

**Pregnant and Lactating Women:** VIVJOA is contraindicated in pregnant and lactating women.

**Hypersensitivity:** VIVJOA is contraindicated in patients with known hypersensitivity to oteseconazole.

### Laboratory Findings

#### *Elevations in Creatine Phosphokinase*

Serum creatine phosphokinase (CPK) (an indirect marker of muscle injury/necrosis) elevations greater than or equal to 10 times the upper limit of normal were observed in 11 (1.9%) patients treated with VIVJOA versus 2 (0.7%) patients in the comparator groups during the VIVJOA clinical trials. The elevations were transient.

## DRUG INTERACTIONS<sup>3</sup>

### *Effect of VIVJOA on Other Drugs*

#### BCRP (Breast Cancer Resistance Protein) Transporter Substrates

Oteseconazole is a BCRP inhibitor. Concomitant use of VIVJOA with BCRP substrates (e.g., rosuvastatin) may increase the exposure of BCRP substrates (e.g., rosuvastatin), 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 drug and monitor for adverse reactions.

## USE IN SPECIFIC POPULATIONS<sup>3</sup>

### PREGNANCY

#### Risk Summary

VIVJOA is contraindicated in females of reproductive potential and in pregnant women. Based on animal studies, VIVJOA may cause fetal harm when administered to pregnant women. In addition, 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 were observed in a pre and postnatal animal study in the offspring of rats administered oteseconazole from Gestation Day 6 through Lactation Day 20 at doses about 3.5 times the recommended human dose based on AUC comparisons. The observed ocular abnormalities included cataracts, opacities, exophthalmos/buphthalmos, optic nerve/retinal atrophy, lens degeneration and hemorrhage.

There are limited human data in pregnant women who were exposed to VIVJOA during the clinical trials; these data are insufficient

to exclude a potential risk of cataracts or other eye abnormalities in human infants.

#### Data

##### *Animal Data*

Rat and rabbit embryofetal development was assessed after oral administration of oteseconazole. There was no embryofetal toxicity or malformations at 40 mg/kg/day following administration of oteseconazole during organogenesis in pregnant rats at doses about 10 times the maximum human exposure for RVVC based on AUC comparisons. Abortions occurred in rabbits in the presence of maternal toxicity (reduced bodyweight gain with reduced food consumption) but there were no malformations at 15 mg/kg/day following administration of oteseconazole during organogenesis in pregnant rabbits about 6 times the maximum human exposure for RVVC based on AUC comparisons.

Ocular abnormalities including cataracts, opacities, exophthalmos/buphthalmos, optic nerve/retinal atrophy, lens degeneration and hemorrhage were observed in the offspring of rats administered oteseconazole from Gestation Day 6 through Lactation Day 20 at 7.5 mg/kg/day (about 3.5 times the recommended human dose based on AUC comparisons). There were no effects on pregnancy or parturition in these pre and postnatal studies at any dose.

### LACTATION

#### *Risk Summary*

VIVJOA is contraindicated in lactating women and females of reproductive potential. There are no data on the presence of oteseconazole in human or animal milk or data on the effects of oteseconazole on milk production. There were no reported adverse effects in breastfed infants following maternal exposure to oteseconazole during lactation; however, given the limited duration of follow-up of the oteseconazole-exposed infants during the post-natal period, no conclusions can be drawn from these data.

Ocular abnormalities were observed in a pre and postnatal study in the offspring of rats administered oteseconazole from Gestation Day 6 through Lactation Day 20 at doses approximately 3.5 times

## IMPORTANT SAFETY INFORMATION (CON'T)

### 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.

### ADVERSE REACTIONS

The most frequently reported adverse reactions among VIVJOA-treated patients in clinical studies included headache (7.4%) and nausea (3.6%).

the recommended human dose based on AUC comparisons. The relationship between the observed animal findings and breastfed infants is unknown.

### FEMALES OF REPRODUCTIVE POTENTIAL

VIVJOA is contraindicated in females of reproductive potential based on animal findings. 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.

Females who are NOT of reproductive potential are defined as: persons who are biological females who are postmenopausal or have another reason for permanent infertility (e.g., tubal ligation, hysterectomy, salpingo-oophorectomy).

### PEDIATRIC USE

VIVJOA is contraindicated in females of reproductive potential. Based on animal studies, VIVJOA may cause fetal harm when administered to a pregnant woman or potential harm to the breastfed infant. 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 associated with VIVJOA use.

The safety and effectiveness of VIVJOA have not been established in pre-menarchal pediatric females.

### GERIATRIC USE

Clinical studies of VIVJOA did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients.

### RENAL IMPAIRMENT

No dosage adjustment of VIVJOA is recommended in patients with mild to moderate renal impairment (i.e., estimated glomerular filtration rate (eGFR) by the modification of diet in renal disease (MDRD) equation 30-89 mL/min). Clinical studies of VIVJOA did not include sufficient numbers of patients with severe renal impairment (eGFR 15-29 mL/min) or end-stage renal disease (ESRD), defined as eGFR < 15 mL/min, to determine the safety of

VIVJOA in this population. Therefore, VIVJOA is not recommended for use in patients with severe renal impairment or ESRD (with or without dialysis).

### HEPATIC IMPAIRMENT

No dosage adjustment of VIVJOA is recommended in patients with mild hepatic impairment (Child-Pugh A). There is insufficient information to determine the safety of VIVJOA in patients with moderate or severe hepatic impairment (Child-Pugh B-C). Therefore, VIVJOA is not recommended for use in patients with moderate or severe hepatic impairment.

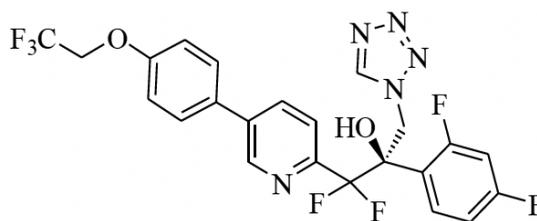
## CHEMISTRY AND CLINICAL PHARMACOLOGY

### CHEMICAL AND PHYSICAL PROPERTIES<sup>3</sup>

VIVJOA (oteseconazole capsules) contains oteseconazole which is an oral azole antifungal agent. The chemical name of oteseconazole is (R)-2-(2,4-difluorophenyl)-1,1-difluoro-3-(1H-tetrazol-1-yl)-1-(5-(4-(2,2,2-trifluoroethoxy)phenyl)pyridin-2-yl)propan-2-ol or 2-Pyridineethanol,  $\alpha$ -(2,4-difluorophenyl)- $\beta$   $\beta$ -difluoro-  $\alpha$ -(1H-tetrazol-1-ylmethyl)-5-(4-(2,2,2-trifluoroethoxy)phenyl)-, ( $\alpha$ R)-. The empirical formula is  $C_{23}H_{16}F_7N_5O_2$ . The molecular weight is 527.39 g/mol.

The structural formula is below (Figure 5).<sup>3</sup>

Figure 5. VIVJOA Structural Formula<sup>3</sup>



## IMPORTANT SAFETY INFORMATION (CON'T)

### DRUG INTERACTIONS

**Effect of VIVJOA on Other Drugs:** Oteseconazole is a Breast Cancer Resistance Protein (BCRP) inhibitor. Concomitant use of VIVJOA with BCRP substrates (e.g., rosuvastatin) may increase the exposure of BCRP substrates (e.g., rosuvastatin), 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 drug and monitor for adverse reactions.

Oteseconazole is a white to off-white crystalline powder and is practically insoluble in water within a pH range of 1 to 9 but is soluble in a variety of organic solvents.

Each oteseconazole capsule, for oral use, contains 150 mg oteseconazole and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose, magnesium stearate, silicified microcrystalline cellulose, and sodium lauryl sulfate. Capsule shell and print constituents: FD&C Blue #1, FD&C Red #3, gelatin, Opacode SW-9008/SW-9009 and titanium dioxide. Contains no ingredient made from a gluten-containing grain (wheat, barley, or rye).

## CLINICAL PHARMACOLOGY<sup>3</sup>

### Pharmacodynamics

Oteseconazole exposure-response relationships and the time course of pharmacodynamic response are unknown.

### Cardiac Electrophysiology

At 5 times the maximum exposures for the recommended dose, VIVJOA does not prolong the QT interval to any clinically relevant extent.

### Pharmacokinetics

The AUC of oteseconazole increased approximately dose proportionally while the  $C_{max}$  increased less than dose proportionally over a dose range of 20 mg (0.13 times the lowest recommended dose) to 320 mg (0.53 times the highest recommended dose). The pharmacokinetic

parameters of oteseconazole associated with the administration of the recommended dosing regimen of VIVJOA are presented in **Table 9**.<sup>3</sup>

### Absorption

The time to peak plasma concentrations of oteseconazole was approximately 5 to 10 hours.

### Effect of Food

Administration of VIVJOA with a high-fat, high-calorie meal (800-1000 Calories; 50% fat) increased  $C_{max}$  and  $AUC_{0-72h}$  by 45% and 36%, but no significant differences were observed with a low-fat, low-calorie meal.

### Distribution

The central volume of distribution of oteseconazole is approximately 423 L. Oteseconazole is 99.5-99.7% bound to plasma proteins. Animal studies indicated that oteseconazole exposures in vaginal tissue are comparable to plasma exposures.

### Elimination

The median terminal half-life of oteseconazole is approximately 138 days.

### Metabolism

Oteseconazole does not undergo significant metabolism.

### Excretion

Following oral administration of radiolabeled oteseconazole, approximately 56% of the radiolabeled dose was recovered in feces primarily through biliary excretion and 26% was recovered in urine.

### Specific Populations

There were no clinically significant differences in the pharmacokinetics of oteseconazole based on sex, race/ethnicity or mild to moderate renal impairment.

### Drug Interaction Studies

BCRP substrates: Oteseconazole increased the  $C_{max}$  and  $AUC_{0-24h}$  of rosuvastatin, a BCRP substrate, by 118% and 114%, respectively.

**Table 9.** Pharmacokinetic Parameters of Oteseconazole<sup>3</sup>

PK parameter*	Mean (± SD)
$C_{max}$ (µg/mL)	2.8 (1.25)
$AUC_{24hr}$ (h × µg/mL)	64.2 (29.4)
$C_{min}$ (µg/mL)	2.5 (1.19)

AUC, area under the curve;  $C_{max}$ , peak serum concentration;  $C_{min}$ , minimum serum concentration; PK, pharmacokinetic.

\*Following repeat dose administration of VIVJOA at the approved recommended dosage for recurrent vulvovaginal candidiasis at the end of treatment.

## IMPORTANT SAFETY INFORMATION (CON'T)

### USE IN SPECIFIC POPULATIONS

**Pregnancy:** VIVJOA is contraindicated in females of reproductive potential and in pregnant women. Based on animal studies, VIVJOA may cause fetal harm when administered to pregnant women. In addition, 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.

**Lactation:** VIVJOA is contraindicated in lactating women and females of reproductive potential. There are no data on the presence of oteseconazole in human or animal milk or data on the effects of oteseconazole on milk production. There were no reported adverse effects in breastfed infants following maternal exposure to oteseconazole during lactation; however, given the limited duration of follow-up of the oteseconazole-exposed infants during the post-natal period, no conclusions can be drawn from these data.

**Other Drugs:** No clinically significant differences in the pharmacokinetics of the following drugs were observed when co-administered with oteseconazole: Midazolam (sensitive CYP3A4 substrate), ethinyl estradiol (CYP3A4 substrate), norethindrone (CYP3A4 substrate), or digoxin (P-gp substrate).

## NONCLINICAL TOXICOLOGY<sup>3</sup>

### CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

#### Carcinogenesis

There was no increase in the incidence of tumors following daily oral administration of oteseconazole to Tg.rasH2 mice for 6 months at doses of 5 mg/kg/day (males) and 15 mg/kg/day (females), which are up to 3 and 10 times, respectively, the maximum human exposure for RVVC based on AUC comparisons.

In an oral carcinogenicity study, Sprague Dawley rats were administered doses of 0.5, 1.5, or 5 mg/kg/day oteseconazole once daily for up to 90 weeks. The high dose was initially reduced from 5 to 3 mg/kg/day due to excess mortality in males and reduced body weight in females. In males, an increase in the incidence in Leydig cell adenomas of the testes and thyroid follicular cell adenomas/carcinomas (combined) were increased at  $\geq 1.5$  mg/kg/day (similar to the maximum human exposure for RVVC based on AUC comparisons). In females, thyroid follicular cell adenomas and carcinomas (combined) were increased at  $\geq 1.5$  mg/kg/day (similar to the maximum human exposure for RVVC based on AUC comparisons) and thyroid carcinomas were increased at 5 to 3 mg/kg/day (5 times the maximum human exposure for RVVC based on AUC comparisons). The Leydig and thyroid findings are of uncertain relevance to humans.

#### Mutagenesis

Oteseconazole was negative in the bacterial reverse mutation assay, *in vitro* chromosomal aberration assay and micronucleus assay in rats.

#### Impairment of Fertility

Male rats were administered daily oral doses of 0, 0.5, 3, or 10 mg/kg/day oteseconazole beginning 42 days prior to pairing with untreated females, through the mating and post-mating period until euthanasia on Day 76 of treatment followed by a 12-week recovery period. There were no effects on reproductive and/or fertility parameters at the time of mating at 10 mg/kg/day (7 times the maximum human exposure for RVVC based on AUC comparisons). Increased incidences of abnormal sperm were observed at 3 mg/kg/day and sperm counts were reduced at 10 mg/kg/day. Although fertility was unaffected, sperm concentration remained reduced at the end of the recovery period.

Female rats were administered daily oral doses of 0, 1.5, 5, or 25 mg/kg/day oteseconazole beginning 28 days prior to cohabitation with untreated males, continuing throughout mating and through gestational day 7. Although there were no effects on estrous cyclicity, effects on reproductive and fertility parameters were observed at 25 mg/kg/day in the presence of maternal toxicity (11 times the maximum human exposure for RVVC based on AUC comparisons).

### ANIMAL TOXICOLOGY AND/OR PHARMACOLOGY

In an oral carcinogenicity study, Sprague Dawley rats were administered doses of 0.5, 1.5, or 5 mg/kg/day oteseconazole once daily for up to 90 weeks. The high dose was initially reduced from 5 to 3 mg/kg/day in males due to excess mortality. Incidences of hemorrhage were increased in the adrenals, brain, coagulating gland, ears, epididymides, head, heart, lung, nose, pancreas, pharynx, prostate, seminal vesicles, spinal cord, testes, thymus and bladder of male Crl:CD®(SD) rats (after 77 weeks of dosing at about 5 times the MRHD based on AUC comparisons). There were no increases in the incidence of hemorrhage in rats after 26 weeks at 5 mg/kg. The clinical relevance of these findings after very high doses (5 to 7 times the MRHD) for the lifetime of the rat remains unclear.

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## IMPORTANT SAFETY INFORMATION (CON'T)

**Females of Reproductive Potential:** VIVJOA is contraindicated in females of reproductive potential based on data from rat studies.

**Pediatric Use:** The safety and effectiveness of VIVJOA have not been established in pre-menarchal pediatric females.

**Geriatric Use:** Clinical studies of VIVJOA did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients.

## P&T COMMITTEE CONSIDERATIONS

P&T committees are tasked with evaluating the efficacy, safety, and cost-effectiveness of new and existing drug products for inclusion in their organizations' drug formularies. This evaluation attempts to assess the relative value of a product through an extensive review of scientific evidence, clinical guidelines, economic studies, and medical publications. Two former medical and pharmacy directors at national health plans were consulted to provide their insights and perspectives on issues P&T committee members may wish to consider in their review of VIVJOA.

**PAYER 1:** Former Vice President of Pharmaceutical Contracting at a national health plan with over 20 years of experience in formulary management and manufacturer relations.

**PAYER 2:** Former Chief Strategy Officer at a national pharmacy benefit manager with more than 30 years of pharmacy management experience in government markets

**Do payers consider recurrent vulvovaginal candidiasis (RVVC) to be a distinct therapeutic condition? Please discuss your thoughts on this condition.**

**PAYER 1:** No. Therapies for the treatment of RVCC will likely be reviewed in the same class as other VVC agents as the only differentiation is the frequency and recurrence of these symptoms.

**PAYER 2:** Agreed. Medicaid will review this as part of the oral antifungal class and not specifically for just VVC or RVVC.

**Are payers aware of other treatments for RVVC? If so, which ones?**

**PAYER 1:** No. Other than VIVJOA, there is nothing indicated for RVVC today, but generic fluconazole is used quite regularly for VVC episodes today.

**PAYER 2:** Agreed.

**The CDC identified RVVC as a distinct condition from VVC in its updated RVVC treatment guidelines (July 2021). Will this impact your decision-making when managing this category?**

**PAYER 1:** Yes. We always reference established guidelines or national entities that help delineate any unique treatment guidelines for a specific condition. This recent update by the CDC will help provide an additional layer of support to move RVVC away from traditional VVC treatment algorithms.

**PAYER 2:** Maybe. Medicaid P&T committees will have all the updated guidelines, but they will likely be cautious and won't consider a treatment for RVVC without a diagnosis of VVC first, and then they will want to ensure patients have documented progression through appropriate VVC treatments.

**What is your perspective on the clinical efficacy of VIVJOA?**

**PAYER 1:** VIVJOA shows very good data that illustrates the proportion of patients with  $\geq 1$  culture-verified acute VVC episode through Week 48 or those who received a VVC medication during this same timeframe. Efficacy seems to confirm that VIVJOA does have a significant reduction in VVC episodes vs placebo.

## IMPORTANT SAFETY INFORMATION (CON'T)

**Renal Impairment:** No dosage adjustment of VIVJOA is recommended in patients with mild to moderate renal impairment. VIVJOA is not recommended for use in patients with severe renal impairment or end-stage renal disease, as clinical studies did not include sufficient numbers of these patients.

**Hepatic Impairment:** No dosage adjustment of VIVJOA is recommended in patients with mild hepatic impairment. VIVJOA is not recommended for use in patients with moderate or severe hepatic impairment, as there is insufficient information in these patients.

**PAYER 2:** Agreed. The results from Trial 1 demonstrated that 93.3% of women with RVVC who received VIVJOA did not have a recurrence versus 57.2% women who received placebo. Additionally, in Trial 2, 96.1% of women receiving VIVJOA did not have a recurrence compared to 60.6% of women receiving placebo in the 48-week maintenance period.

#### Were the clinical end points in the 3 key studies sufficient to justify that VIVJOA is a safe and effective treatment for RVVC?

**PAYER 1:** Yes. The 3 studies confirm that VIVJOA can provide RVVC patients with a significant reduction of culture verified acute VVC episodes through week 50. As for the safety aspect of VIVJOA, there is a contraindication for women of reproductive potential or those who are pregnant and lactating, so this must be monitored by both physicians and payers to help ensure appropriate patient selection.

**PAYER 2:** VIVJOA is safe and effective for the right patient, yes. The challenge for payers will be ensuring that their system (via electronic PA [prior authorization]) or their call center staff (PA process) can identify the appropriate patient and ensure that appropriate safeguards are in place to cover VIVJOA for the right patient.

#### What clinical end points are most important when assessing clinical trials for RVVC?

**PAYER 1:** The long-term (up to 50-week) data that show lower rates of culture-verified acute VVC episodes vs placebo.

**PAYER 2:** Agree. This also helps to justify the cost difference between VIVJOA and fluconazole or the newly approved triterpenoid antifungal drug.

#### What is your perspective on the clinical safety of VIVJOA?

**PAYER 1:** I have some concerns that physicians and patients will recognize the embryo-fetal toxicity warnings and appropriate patient types for VIVJOA. However, it is important to note that fluconazole is also associated with a risk of embryotoxicity. Payers may need to implement a prior authorization asking the prescriber to attest that they are not prescribing the drug to women of reproductive potential or those who are pregnant and lactating.

**PAYER 2:** I completely agree. Physicians and payers may want to ensure, to the extent possible, that the patient is not of child-bearing potential (not just on birth control). Since childbearing potential is not age-specific, an electronic PA is highly unlikely for this product.

#### How will payers likely assess the current treatment options of RVVC?

**PAYER 1:** Payers will likely want to utilize current standards of care, whether prescription-based or OTC, as treatment options for VVC and evaluate the clinical cure rates and cost-effectiveness of these products vs VIVJOA. If VIVJOA can help reduce RVVC OB/GYN, PCP, and/or ER visits due to more effectively treated patients, then payers can link the healthcare cost offsets vs the price of VIVJOA.

**PAYER 2:** Payers will want documentation that current VVC treatments OTC, fluconazole, or the newly approved triterpenoid antifungal drug have failed, which will confirm a diagnosis of RVVC; then they will approve VIVJOA for RVVC for the appropriate patient. •

## VIVJOA™ IMPORTANT SAFETY INFORMATION

### INDICATION

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

### IMPORTANT SAFETY INFORMATION

#### CONTRAINDICATIONS

**Females of Reproductive Potential:** VIVJOA is contraindicated in females of reproductive potential. Females who are NOT of reproductive potential are defined as: persons who are biological females who are postmenopausal or have another reason for permanent infertility (e.g., tubal ligation, hysterectomy, salpingo-oophorectomy).

**Pregnant and Lactating Women:** VIVJOA is contraindicated in pregnant and lactating women.

**Hypersensitivity:** VIVJOA is contraindicated in patients with known hypersensitivity to oteseconazole.

## CONCLUSION

Affecting up to 9% of women worldwide, RVVC is a recurrent type of yeast infection that poses a substantial clinical and economic burden.<sup>1,11</sup> Management of RVVC is challenging due to limited treatment options.<sup>1</sup>

VIVJOA is a novel, oral azole antifungal that is indicated to reduce the incidence of RVVC in females with a history of RVVC who are not of reproductive potential. In clinical trials, VIVJOA was generally well-tolerated and demonstrated significant reductions in rates of acute VVC episodes versus comparators. VIVJOA is notably contraindicated in females of reproductive potential, and in pregnant and lactating women.<sup>3</sup> As the first FDA-approved medication option to reduce the incidence of RVVC, VIVJOA represents an advancement in RVVC management among postmenopausal women or those in a state of permanent infertility due to surgical and non-surgical reasons.

When evaluating VIVJOA for inclusion in a formulary, P&T committees must consider the product's safety and efficacy, costs, and place in therapy within the treatment landscape to identify patient populations for whom this product may be beneficial and develop appropriate utilization management criteria. •

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## IMPORTANT SAFETY INFORMATION (CON'T)

### 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.

### ADVERSE REACTIONS

The most frequently reported adverse reactions among VIVJOA-treated patients in clinical studies included headache (7.4%) and nausea (3.6%).

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## IMPORTANT SAFETY INFORMATION (CON'T)

### CONTRAINDICATIONS

**Females of Reproductive Potential:** VIVJOA is contraindicated in females of reproductive potential. Females who are NOT of reproductive potential are defined as: persons who are biological females who are postmenopausal or have another reason for permanent infertility (e.g., tubal ligation, hysterectomy, salpingo-oophorectomy).

**Pregnant and Lactating Women:** VIVJOA is contraindicated in pregnant and lactating women.

**Hypersensitivity:** VIVJOA is contraindicated in patients with known hypersensitivity to oteseconazole.

## 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](http://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

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# FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

### 1.1 Vulvovaginal Candidiasis

VIVJOA is indicated to reduce the incidence of recurrent vulvovaginal candidiasis (RVVC) in females with a history of RVVC who are NOT of reproductive potential [see *Warnings and Precautions (5.1)*, *Use in Specific Populations (8.3)*, and *Clinical Studies (14)*].

### 1.2 Usage

If specimens for fungal culture are obtained prior to therapy, antifungal therapy may be instituted before the results of the cultures are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Dosage Overview and Important Administration Instructions

There are two recommended VIVJOA dosage regimens: a VIVJOA-only regimen and a Fluconazole/VIVJOA regimen. Use one of the following two dosage regimens:

- VIVJOA-only dosage regimen [see *Dosage and Administration (2.2)*]
- Fluconazole/VIVJOA dosage regimen [see *Dosage and Administration (2.3)*].

Administer VIVJOA orally with food [see *Clinical Pharmacology (12.3)*]. Swallow the capsules whole. Do not chew, crush, dissolve, or open the capsules.

### 2.2 VIVJOA-only Dosage Regimen

For the VIVJOA-only dosage regimen:

- **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).

### 2.3 Fluconazole/VIVJOA Dosage Regimen

For the Fluconazole/VIVJOA dosage regimen, prescribe fluconazole and:

- **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).

## 3 DOSAGE FORMS AND STRENGTHS

VIVJOA Capsules: 150 mg of oteseconazole in lavender hard gelatin capsules imprinted with OTE 150 in black ink.

Fluconazole is not supplied in the carton.

## 4 CONTRAINDICATIONS

VIVJOA is contraindicated in:

- Females of reproductive potential [see *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.3)*]

- Pregnant and lactating women [see *Warnings and Precautions (5.1), and Use in Specific Populations (8.1, 8.2)*]
- Patients with known hypersensitivity to oteseconazole.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Embryo-Fetal Toxicity

VIVJOA is 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 were observed in the offspring of pregnant rats dosed at 7.5-mg/kg/day during organogenesis through lactation in pre and postnatal developmental studies. The observed ocular abnormalities included cataracts, opacities, exophthalmos/buphthalmos, optic nerve/retinal atrophy, lens degeneration and hemorrhage. 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 [see *Use in Specific Populations (8.1, 8.2, 8.3)*].

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of one drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 580 patients were treated with VIVJOA in three clinical trials (Trial 1, Trial 2, and Trial 3) [see *Clinical Studies (14)*]. Patients in the clinical trials were women with RVVC who received VIVJOA treatment for 12 weeks. The mean age of the patient population was 34 years (range:16-78 years), with 84% of patients aged 18-44 years and 16% of patients aged 45 years and older. Although females of reproductive potential were included in the clinical safety data, VIVJOA is contraindicated in females of reproductive potential due to the risk of embryo-fetal toxicity [see *Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.1, 8.3, 8.4)*].

The clinical trials population was 75% (435/580) White, 17% (96/580) Black or African American, 6% (36/580) Asian, and 2% (13/580) Other women. Fifteen percent (86/580) of all women were Hispanic/Latino. Patients enrolled in the induction and maintenance phases of the clinical trials were treated with different VIVJOA dosage regimens versus comparators [see *Clinical Studies (14)*].

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%).

## Other Adverse Reactions

The following selected adverse reactions occurred in <2% of patients receiving VIVJOA in Trial 1, Trial 2 and Trial 3:

- *Laboratory investigations*: Increased blood creatine phosphokinase
- *Gastrointestinal disorders*: Dyspepsia
- *Vascular disorders*: Hot flush
- *Renal and urinary disorders*: Dysuria
- *Reproductive system and breast disorders*: Menorrhagia (includes genital hemorrhage, menorrhagia; menometrorrhagia; uterine hemorrhage, vaginal hemorrhage) metrorrhagia; vulvovaginal irritation (includes vulvovaginal burning sensation, vulvovaginal discomfort, and vulvovaginal pain)

## Laboratory Findings

### *Elevations in Creatine Phosphokinase*

Serum creatine phosphokinase (CPK) (an indirect marker of muscle injury/necrosis) elevations greater than or equal to 10 times the upper limit of normal were observed in 11 (1.9%) patients treated with VIVJOA versus 2 (0.7%) patients in the comparator groups during the VIVJOA clinical trials. The elevations were transient.

## **7 DRUG INTERACTIONS**

### **7.1 Effect of VIVJOA on Other Drugs**

#### BCRP (Breast Cancer Resistance Protein) Transporter Substrates

Oteseconazole is a BCRP inhibitor. Concomitant use of VIVJOA with BCRP substrates (e.g., rosuvastatin) may increase the exposure of BCRP substrates (e.g., rosuvastatin), 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 drug and monitor for adverse reactions [see *Clinical Pharmacology (12.3)*].

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

VIVJOA is contraindicated in females of reproductive potential and in pregnant women. Based on animal studies, VIVJOA may cause fetal harm when administered to pregnant women. In addition, 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 [see *Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)*].

Ocular abnormalities were observed in a pre and postnatal animal study in the offspring of rats administered oteseconazole from Gestation Day 6 through Lactation Day 20 at doses about 3.5 times the recommended human dose based on AUC comparisons (see *Data*). The observed ocular abnormalities included cataracts, opacities, exophthalmos/buphthalmos, optic nerve/retinal atrophy, lens degeneration and hemorrhage.

There are limited human data in pregnant women who were exposed to VIVJOA during the clinical trials; these data are insufficient to exclude a potential risk of cataracts or other eye abnormalities in human infants.

## Data

### *Animal Data*

Rat and rabbit embryofetal development was assessed after oral administration of oteseconazole. There was no embryofetal toxicity or malformations at 40 mg/kg/day following administration of oteseconazole during organogenesis in pregnant rats at doses about 10 times the maximum human exposure for RVVC based on AUC comparisons. Abortions occurred in rabbits in the presence of maternal toxicity (reduced bodyweight gain with reduced food consumption) but there were no malformations at 15 mg/kg/day following administration of oteseconazole during organogenesis in pregnant rabbits about 6 times the maximum human exposure for RVVC based on AUC comparisons.

Ocular abnormalities including cataracts, opacities, exophthalmos/buphthalmos, optic nerve/retinal atrophy, lens degeneration and hemorrhage were observed in the offspring of rats administered oteseconazole from Gestation Day 6 through Lactation Day 20 at 7.5 mg/kg day (about 3.5 times the recommended human dose based on AUC comparisons). There were no effects on pregnancy or parturition in these pre and postnatal studies at any dose.

## **8.2 Lactation**

### Risk Summary

VIVJOA is contraindicated in lactating women and females of reproductive potential. There are no data on the presence of oteseconazole in human or animal milk or data on the effects of oteseconazole on milk production. There were no reported adverse effects in breastfed infants following maternal exposure to oteseconazole during lactation; however, given the limited duration of follow-up of the oteseconazole-exposed infants during the post-natal period, no conclusions can be drawn from these data [see *Warnings and Precautions (5.1)*].

Ocular abnormalities were observed in a pre and postnatal study in the offspring of rats administered oteseconazole from Gestation Day 6 through Lactation Day 20 at doses approximately 3.5 times the recommended human dose based on AUC comparisons [see *Use in Specific Populations (8.1)*]. The relationship between the observed animal findings and breastfed infants is unknown.

## **8.3 Females of Reproductive Potential**

VIVJOA is contraindicated in females of reproductive potential based on animal findings. 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 [see *Warnings and Precautions (5.1)*, *Use in Specific Populations (8.1)* and *Clinical Pharmacology (12.3)*].

Females who are NOT of reproductive potential are defined as: persons who are biological females who are postmenopausal or have another reason for permanent infertility (e.g., tubal ligation, hysterectomy, salpingo-oophorectomy).

## **8.4 Pediatric Use**

VIVJOA is contraindicated in females of reproductive potential. Based on animal studies, VIVJOA may cause fetal harm when administered to a pregnant woman or potential harm to the breastfed infant. 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 associated with VIVJOA use [see *Contraindications (4)*, *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.1, 8.2, 8.3)* and *Clinical Pharmacology (12.3)*].

The safety and effectiveness of VIVJOA have not been established in pre-menarchal pediatric females.

## 8.5 Geriatric Use

Clinical studies of VIVJOA did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients.

## 8.6 Renal Impairment

No dosage adjustment of VIVJOA is recommended in patients with mild to moderate renal impairment (i.e., estimated glomerular filtration rate (eGFR) by the modification of diet in renal disease (MDRD) equation 30-89 mL/min). Clinical studies of VIVJOA did not include sufficient numbers of patients with severe renal impairment (eGFR 15-29 mL/min) or end-stage renal disease (ESRD), defined as eGFR <15 mL/min, to determine the safety of VIVJOA in this population. Therefore, VIVJOA is not recommended for use in patients with severe renal impairment or ESRD (with or without dialysis) [see *Clinical Pharmacology (12.3)*].

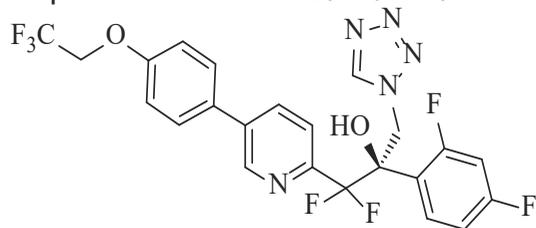
## 8.7 Hepatic Impairment

No dosage adjustment of VIVJOA is recommended in patients with mild hepatic impairment (Child-Pugh A). There is insufficient information to determine the safety of VIVJOA in patients with moderate or severe hepatic impairment (Child-Pugh B-C). Therefore, VIVJOA is not recommended for use in patients with moderate or severe hepatic impairment [see *Clinical Pharmacology (12.3)*].

## 11 DESCRIPTION

VIVJOA (oteseconazole capsules) contains oteseconazole which is an oral azole antifungal agent.

The chemical name of oteseconazole is (*R*)-2-(2,4-difluorophenyl)-1,1-difluoro-3-(1*H*-tetrazol-1-yl)-1-(5-(4-(2,2,2-trifluoroethoxy)phenyl)pyridin-2-yl)propan-2-ol or 2-Pyridineethanol,  $\alpha$ -(2,4-difluorophenyl)- $\beta$   $\beta$ -difluoro-  $\alpha$ -(1*H*-tetrazol-1-ylmethyl)-5-(4-(2,2,2-trifluoroethoxy)phenyl)-, ( $\alpha$ *R*)-. The empirical formula is C<sub>23</sub>H<sub>16</sub>F<sub>7</sub>N<sub>5</sub>O<sub>2</sub>. The molecular weight is 527.39 g/mol. The structural formula is



Oteseconazole is a white to off-white crystalline powder and is practically insoluble in water within a pH range of 1 to 9 but is soluble in a variety of organic solvents.

Each oteseconazole capsule, for oral use, contains 150 mg oteseconazole and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose, magnesium stearate, silicified microcrystalline cellulose, and sodium lauryl sulfate. Capsule shell and print constituents: FD&C Blue #1, FD&C Red #3, gelatin, Opacode SW-9008/SW-9009 and titanium dioxide. Contains no ingredient made from a gluten-containing grain (wheat, barley, or rye).

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Oteseconazole is an antifungal drug [see *Microbiology (12.4)*].

### 12.2 Pharmacodynamics

Oteseconazole exposure-response relationships and the time course of pharmacodynamic response are unknown.

## Cardiac Electrophysiology

At 5 times the maximum exposures for the recommended dose, VIVJOA does not prolong the QT interval to any clinically relevant extent.

## **12.3 Pharmacokinetics**

The AUC of oteseconazole increased approximately dose proportionally while the  $C_{max}$  increased less than dose proportionally over a dose range of 20 mg (0.13 times the lowest recommended dose) to 320 mg (0.53 times the highest recommended dose). The pharmacokinetic parameters of oteseconazole associated with the administration of the recommended dosing regimen of VIVJOA are presented in Table 1.

**Table 1: Pharmacokinetic (PK) Parameters of Oteseconazole**

<b>PK Parameter<sup>a</sup></b>	<b>Mean (<math>\pm</math> SD)</b>
$C_{max}$ ( $\mu\text{g/mL}$ )	2.8 (1.25)
AUC <sub>24h</sub> ( $\text{h}\cdot\mu\text{g/mL}$ )	64.2 (29.4)
$C_{min}$ ( $\mu\text{g/mL}$ )	2.5 (1.19)

<sup>a</sup> Following repeat dose administration of VIVJOA at the approved recommended dosage for RVVC at the end of treatment.

## Absorption

The time to peak plasma concentrations of oteseconazole was approximately 5 to 10 hours.

## *Effect of Food*

Administration of VIVJOA with a high-fat, high-calorie meal (800-1000 Calories; 50% fat) increased  $C_{max}$  and AUC<sub>0-72h</sub> by 45% and 36%, but no significant differences were observed with a low-fat, low-calorie meal.

## Distribution

The central volume of distribution of oteseconazole is approximately 423 L. Oteseconazole is 99.5-99.7% bound to plasma proteins. Animal studies indicated that oteseconazole exposures in vaginal tissue are comparable to plasma exposures.

## Elimination

The median terminal half-life of oteseconazole is approximately 138 days.

## Metabolism

Oteseconazole does not undergo significant metabolism.

## Excretion

Following oral administration of radiolabeled oteseconazole, approximately 56% of the radiolabeled dose was recovered in feces primarily through biliary excretion and 26% was recovered in urine.

## Specific Populations

There were no clinically significant differences in the pharmacokinetics of oteseconazole based on sex, race/ethnicity or mild to moderate renal impairment.

## Drug Interaction Studies

**BCRP substrates:** Oteseconazole increased the  $C_{max}$  and AUC<sub>0-24h</sub> of rosuvastatin, a BCRP substrate, by 118% and 114%, respectively.

**Other Drugs:** No clinically significant differences in the pharmacokinetics of the following drugs were observed when co-administered with oteseconazole: Midazolam (sensitive CYP3A4 substrate), ethinyl estradiol (CYP3A4 substrate), norethindrone (CYP3A4 substrate), or digoxin (P-gp substrate).

## 12.4 Microbiology

### Mechanism of Action:

Oteseconazole is an azole metalloenzyme inhibitor targeting the fungal sterol, 14 $\alpha$  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.

### Resistance:

The potential for increases in minimum inhibitory concentrations (MIC) to oteseconazole has been evaluated *in vitro* including specific mechanisms of resistance. Increases in oteseconazole MIC were associated with upregulation of the efflux pumps CDR1, MDR1, and the azole target, lanosterol 14-alpha-demethylase (CYP51). Against certain *Candida* spp. oteseconazole maintained meaningful *in vitro* activity against clinical isolates that were resistant to fluconazole.

### Antimicrobial Activity:

The following *in vitro* data is available, but their clinical significance is unknown. Oteseconazole has been shown to be active against most isolates of the following microorganisms associated with RVVC [see *Indications and Usage (1.1)*]:

- *Candida albicans*
- *Candida glabrata*
- *Candida krusei*
- *Candida parapsilosis*
- *Candida tropicalis*
- *Candida lusitaniae*
- *Candida dubliniensis*

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Carcinogenesis

There was no increase in the incidence of tumors following daily oral administration of oteseconazole to Tg.rasH2 mice for 6 months at doses of 5 mg/kg/day (males) and 15 mg/kg/day (females), which are up to 3 and 10 times, respectively, the maximum human exposure for RVVC based on AUC comparisons.

In an oral carcinogenicity study, Sprague Dawley rats were administered doses of 0.5, 1.5, or 5 mg/kg/day oteseconazole once daily for up to 90 weeks. The high dose was initially reduced from 5 to 3 mg/kg/day due to excess mortality in males and reduced body weight in females. In males, an increase in the incidence in Leydig cell adenomas of the testes and thyroid follicular cell adenomas/carcinomas (combined) were increased at  $\geq 1.5$  mg/kg/day (similar to the maximum human exposure for RVVC based on AUC comparisons). In females, thyroid follicular cell adenomas and carcinomas (combined) were increased at  $\geq 1.5$  mg/kg/day (similar to the maximum human exposure for RVVC based on AUC comparisons) and thyroid carcinomas were increased at 5 to 3 mg/kg/day

(5 times the maximum human exposure for RVVC based on AUC comparisons). The Leydig and thyroid findings are of uncertain relevance to humans.

### Mutagenesis

Oteseconazole was negative in the bacterial reverse mutation assay, *in vitro* chromosomal aberration assay and micronucleus assay in rats.

### Impairment of Fertility

Male rats were administered daily oral doses of 0, 0.5, 3, or 10 mg/kg/day oteseconazole beginning 42 days prior to pairing with untreated females, through the mating and post-mating period until euthanasia on Day 76 of treatment followed by a 12-week recovery period. There were no effects on reproductive and/or fertility parameters at the time of mating at 10 mg/kg/day (7 times the maximum human exposure for RVVC based on AUC comparisons). Increased incidences of abnormal sperm were observed at 3 mg/kg/day and sperm counts were reduced at 10 mg/kg/day. Although fertility was unaffected, sperm concentration remained reduced at the end of the recovery period.

Female rats were administered daily oral doses of 0, 1.5, 5, or 25 mg/kg/day oteseconazole beginning 28 days prior to cohabitation with untreated males, continuing throughout mating and through gestational day 7. Although there were no effects on estrous cyclicity, effects on reproductive and fertility parameters were observed at 25 mg/kg/day in the presence of maternal toxicity (11 times the maximum human exposure for RVVC based on AUC comparisons).

## **13.2 Animal Toxicology and/or Pharmacology**

In an oral carcinogenicity study, Sprague Dawley rats were administered doses of 0.5, 1.5, or 5 mg/kg/day oteseconazole once daily for up to 90 weeks. The high dose was initially reduced from 5 to 3 mg/kg/day in males due to excess mortality. Incidences of hemorrhage were increased in the adrenals, brain, coagulating gland, ears, epididymides, head, heart, lung, nose, pancreas, pharynx, prostate, seminal vesicles, spinal cord, testes, thymus, and bladder of male CrI:CD<sup>®</sup>(SD) rats (after 77 weeks of dosing at about 5 times the MRHD based on AUC comparisons). There were no increases in the incidence of hemorrhage in rats after 26 weeks at 5 mg/kg. The clinical relevance of these findings after very high doses (5 to 7 times the MRHD) for the lifetime of the rat remains unclear.

## **14 CLINICAL STUDIES**

### Overview of the Clinical Studies

A total of 656 adults and post-menarchal pediatric females with RVVC (defined as  $\geq 3$  episodes of vulvovaginal candidiasis (VVC) in a 12-month period) were randomized in two multicenter, multinational, double-blind, placebo-controlled trials: Trial 1 (NCT#03562156) and Trial 2 (NCT#03561701). A total of 219 adults and post-menarchal pediatric females with RVVC were randomized in a multicenter, double-blind trial [Trial 3 (NCT#03840616)]. Although females of reproductive potential were included in the clinical efficacy data, VIVJOA is contraindicated in females of reproductive potential due to the risk of embryo-fetal toxicity [see *Contraindications (4)*, *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.1, 8.3, 8.4)*].

### Trial 1 and Trial 2

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 an 11-week maintenance phase. Patients received three sequential 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.

In Trial 1, a total of 483 patients were enrolled in the induction phase with 326 patients entering the maintenance phase with 217 patients randomized to VIVJOA and 109 patients randomized to placebo. A total of 182 patients (84%) in the VIVJOA group and 91 patients (83%) in the placebo group completed the trial. The mean age of patients was 34 years old (range 17-78 years old) with 85% of patients aged 18-44 years and 15% of patients aged 45 years and older. Patients were 72% White, 13% Black or African American, 14% Asian, and 8% were of Hispanic or Latino ethnicity.

In Trial 2, a total of 425 patients were enrolled into the induction phase with 330 patients entering the maintenance phase with 220 subjects randomized to VIVJOA and 110 patients randomized to placebo. A total of 191 patients (87%) in the VIVJOA group and 91 patients (83%) in the placebo group completed the trial. The mean age of patients was 34 years old (range 18-73 years old) with 85% of patients aged 18-44 years and 15% of patients aged 45 years and older. Patients were 89% White, 10% Black or African American and 15% were of Hispanic or Latino ethnicity.

For both Trial 1 and Trial 2, efficacy was assessed by the proportion of patients with  $\geq 1$  culture-verified acute VVC episode (positive fungal culture for *Candida* species associated with a clinical signs and symptoms score of  $\geq 3$ ) during the Maintenance Phase through Week 48. Evaluation of clinical signs and symptoms included erythema (redness), edema (swelling), excoriation (skin picking), itching, burning and irritation. Since treatment for acute VVC was allowed to be provided to a patient if it was deemed to be clinically needed when the patient had a signs and symptoms score  $\geq 3$  and a positive KOH test, the proportion of patients with  $\geq 1$  culture-verified acute VVC episode or who took medication known to treat VVC during the Maintenance Phase through Week 48 is also presented.

VIVJOA was superior to placebo with reference to the proportion of patients with  $\geq 1$  culture-verified acute VVC episode through Week 48 (Table 2) or the proportion of patients with  $\geq 1$  culture-verified acute VVC episode or who took medication known to treat VVC during the Maintenance Phase through Week 48. For both Trial 1 and Trial 2, the average percentage of patients was lower in the VIVJOA groups compared with the placebo group (Table 2).

**Table 2: Trial 1 and 2 Efficacy Endpoints: ITT Population**

	Trial 1		Trial 2	
	VIVJOA (N=217)	Placebo (N=109)	VIVJOA (N=218)	Placebo (N=108)
Proportion of Patients with $\geq 1$ Culture-verified Acute VVC Episode (Day 1 through Week 48) <sup>a</sup>	6.7%	42.8%	3.9%	39.4%
Treatment Difference p-value <sup>b</sup>	<0.001		<0.001	
Proportion of Patients with $\geq 1$ Culture-verified Acute VVC Episode or received VVC medication (Day 1 through Week 48) <sup>a</sup>	27.3%	50.8%	21.3%	49.7%
Treatment Difference p-value <sup>b</sup>	<0.001		<0.001	

Abbreviations: ITT=Intent-to-Treat (Population); VVC=vulvovaginal candidiasis.

a. Average %. Missing values were imputed with multiple imputation using the following auxiliary information: region, treatment, Baseline body mass index, Baseline age, ethnicity, and visit.

b. The p-value was obtained using a Chi-square test comparing VIVJOA with placebo.

### Trial 3

Trial 3 was a randomized, double-blind trial evaluating the efficacy and safety of VIVJOA versus fluconazole and placebo in adults and post-menarchal pediatric females with RVVC. The trial consisted of two phases: induction and maintenance.

During the induction phase, patients received 1050 mg of VIVJOA over two days (600 mg [4x150mg] on Day 1 and 450 mg [3x150mg] on Day 2) 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.

A total of 219 patients were randomized (2:1) into the induction phase: 147 to VIVJOA and 72 to fluconazole/placebo. One patient in the VIVJOA group did not receive drug therefore 146 patients received VIVJOA. A total of 112 patients (76%) in the VIVJOA group and 55 patients (76%) in the fluconazole/placebo group completed the trial.

The mean age of patients was 35 years (range 16-78) with 80% of patients aged 18-44 years and 19% of patients aged 45 years and older. Patients were 59% White, 34% Black or African American, 1% Asian and 26% were of Hispanic or Latino ethnicity. The trial was conducted completely in the United States.

Efficacy was assessed by the proportion of patients with  $\geq 1$  culture verified acute VVC episode during the maintenance phase (post-randomization through Week 50) or who failed clearing their infection during the induction phase. A recurring acute VVC episode was defined as a positive culture for *Candida* species and a clinical signs and symptoms score of  $\geq 3$ . Evaluation of clinical signs and symptoms included erythema (redness), edema (swelling), excoriation (skin picking), itching, burning and irritation. Additionally, the proportion of patients with  $\geq 1$  culture verified acute VVC episode or who took medication known to treat VVC during the maintenance phase (post-randomization through Week 50) or who failed clearing their infection during the induction phase is presented.

VIVJOA was superior to fluconazole/placebo in the proportion of patients with  $\geq 1$  culture-verified recurring acute VVC episode during the maintenance phase (post randomization through Week 50) or failed clearing their infection during the induction phase and the proportion of patients with  $\geq 1$  culture-verified recurring acute VVC episode or took VVC medication known to treat VVC during the maintenance phase (post randomization through Week 50) or who failed clearing their infection during the induction phase. The average percentage of patients was lower in the VIVJOA group compared with the fluconazole/placebo group (Table 3).

**Table 3: Trial 3 Efficacy Endpoints ITT population**

	VIVJOA (N=147)	Fluconazole/Placebo (N=72)	Treatment Difference p-value <sup>b</sup>
Proportion of Patients with ≥1 Culture-verified Acute VVC Episode through Week 50 or Unresolved VVC Episode During the Induction Phase <sup>a</sup>	10.3%	42.9%	<0.001
Proportion of Patients with ≥1 Culture-verified Acute VVC Episode or took VVC medication through Week 50 or Unresolved VVC Episode During the Induction Phase <sup>a</sup>	43.5%	59.0%	0.039

Abbreviations: ITT=Intent-to-Treat (Population); VVC=vulvovaginal candidiasis

a. Average %, Missing values were imputed with multiple imputation using the following auxiliary information: treatment, baseline body mass index, baseline age, ethnicity, and visit.

b. The p-value was obtained using a Chi-square test comparing VIVJOA with fluconazole/placebo.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

VIVJOA (oteseconazole capsules) are supplied as lavender hard gelatin capsules. Printed black “OTE 150” on the capsule and contain 150 mg oteseconazole. They are available in an 18-count (NDC 74695-823-18) blister package within a child resistant wallet. There will be one blister pack per wallet and one wallet per outer carton.

The fluconazole/VIVJOA dosage regimen is in an 18-count (NDC 74695-945-18) blister package within a child resistant wallet. There is one blister pack of VIVJOA (oteseconazole capsules) per wallet and one wallet per outer carton. The outer carton and wallet contain the following: “fluconazole/VIVJOA dosage regimen” and “fluconazole is prescribed separately”.

Fluconazole is not supplied in the carton.

### 16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F to 86°F) [See *USP Controlled Room Temperature*]. Protect from light when removed from the outer carton.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

### Embryo-Fetal Toxicity

Advise patients that VIVJOA is contraindicated in females of reproductive potential and in pregnant women because it may cause fetal harm [see *Contraindications (4), Warnings and Precautions (5.1) and Use in Specific Populations (8.1, 8.3)*].

### Lactation

Advise patients that VIVJOA is contraindicated in lactating women because it may cause harm to the breastfed infant [see *Contraindications (4), Warnings and Precautions (5.1) and Use in Specific Populations (8.2)*].

### Important Administration Instructions

Advise patients that VIVJOA must be taken with food, and that capsules must be swallowed whole and not chewed, crushed, dissolved, or opened [see *Dosage and Administration (2.1)*].

Concomitant Administration with BCRP Transporter Substrates

Advise patients to inform their health care provider if they are taking a BCRP substrate (e.g., rosuvastatin). Concomitant use with VIVJOA may increase the exposure of drugs that are BCRP substrates, which may increase the risk of adverse reactions associated with these drugs [see *Drug Interactions (7.1)*].

Manufactured for and distributed by:

**Mycovia Pharmaceuticals, Inc.**

Durham, NC 27703

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