BREXAFEMME® (ibrexafungerp tablets), for oral use

**INDICATIONS AND USAGE**

BREXAFEMME® is indicated for the treatment of adult and post-menarchal pediatric females with vulvovaginal candidiasis (VVC). (1)

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**CONTRAINDICATIONS**

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

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**WARNINGS AND PRECAUTIONS**

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

**ADVERSE REACTIONS**

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

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

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**DRUG INTERACTIONS**

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

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling. Revised: 6/2022
Ibrexafungerp (BREXAFEMME) is a fungal antifungal agent.

**Pharmacology**

Ibrexafungerp is a substrate of CYP3A4. Drugs that inhibit or induce CYP3A may alter the plasma concentrations of ibrexafungerp and affect the safety and efficacy of BREXAFEMME.

**Adverse Reactions**

**Table 2. Adverse Reactions Rates ≥2% in BREXAFEMME-Treated Patients**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>BREXAFEMME</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 545</td>
<td>N = 275</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>91 (16.4%)</td>
<td>9 (3.3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>65 (11.9%)</td>
<td>11 (4.0%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>62 (11.4%)</td>
<td>14 (5.1%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18 (3.3%)</td>
<td>7 (2.5%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (2.0%)</td>
<td>2 (0.7%)</td>
</tr>
</tbody>
</table>

1 Includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort
2 Includes dizziness and postural dizziness

**Other Adverse Reactions**

The following adverse reactions occurred in < 2% of patients receiving BREXAFEMME in Trial 1 and Trial 2: dysmenorrhea, flatulence, back pain, elevated transaminases, vaginal bleeding, rash/hypersensitivity reaction.

**7 DRUG INTERACTIONS**

Ibrexafungerp is a substrate of CYP3A4. Drugs that inhibit or induce CYP3A may alter the plasma concentrations of ibrexafungerp and affect the safety and efficacy of BREXAFEMME (see Clinical Pharmacology (12.3)).

**Table 2. Effect of Coadministered Drugs on Ibrexafungerp Pharmacokinetics:**

<table>
<thead>
<tr>
<th>Concomitant Drugs</th>
<th>Effect on Ibrexafungerp Concentration</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP3A inhibitors: (e.g., ketoconazole, itraconazole)</td>
<td>Significantly increased</td>
<td>Reduce the BREXAFEMME dosage (see Dosage and Administration (2.2))</td>
</tr>
<tr>
<td>Strong and Moderate CYP3A inducers: (e.g., rifampin, carbamazepine, phenytoin, St. John’s wort, long acting barbiturates, bosentan, efavirenz, or etravirine)</td>
<td>Not studied in vivo or in vitro, but likely to result in significant reduction</td>
<td>Avoid concomitant administration</td>
</tr>
</tbody>
</table>

**USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

**Risk Summary**

Based on findings from animal studies, BREXAFEMME use is contraindicated in pregnancy because it may cause fetal harm. In pregnant rabbits, oral ibrexafungerp administered during organogenesis was associated with rare malformations including absent forelimb(s), absent hindpaw, absent ear pinna, and thoracogastrochisis at dose exposures greater or equal to approximately 5 times the human exposure at the RHD. Oral ibrexafungerp administered to pregnant rats during organogenesis was not associated with fetal toxicity or increased fetal malformations at a dose exposure approximately 5 times the human exposure at the RHD (see Data). Available data on BREXAFEMME use in pregnant women are insufficient to draw conclusions about any drug-associated risks of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

There is a pregnancy safety study for BREXAFEMME. If BREXAFEMME is inadvertently administered during pregnancy or if pregnancy is detected within 4 days after a patient receives BREXAFEMME, pregnant women exposed to BREXAFEMME and healthcare providers should report pregnancies to SCYNEXIS, Inc. at 1-888-982-SCYX (7299).

**Data**

**Animal Data**

In a rat embryo-fetal study, ibrexafungerp was administered to pregnant rats by oral gavage from gestation days (GDs) 6 through 17 at doses of 10, 20, 35, and 50 mg/kg/day. No fetal malformations or changes in embryo-fetal survival or fetal body weights occurred with any of the doses of ibrexafungerp up to the high-dose of 50 mg/kg/day (approximately 5 times the RHD based on plasma AUC comparison).

In an embryo-fetal study in rabbits, ibrexafungerp was administered by oral gavage at doses of 10, 25, and 50 mg/kg/day from GD 7 through GD 19. In the mid-dose group administered 25 mg/kg/day (approximately 5 times the RHD based on AUC comparison), fetal malformations, including absent ear pinna, craniorachischisis, thoracogastrochisis, trunk kyphosis, absent forelimbs, absent forepaws, and absent hindpaw occurred in a single fetus. Malformations including absent hindpaw and anencephaly occurred with an increased litter incidence in the high-dose group of 50 mg/kg/day (approximately 13 times the RHD based on AUC comparison), and other malformations occurred in single fetuses and litters including absent ear pinna, thoracogastrochisis, absent forelimb, and absent thyroid gland. No changes in embryo-fetal survival or fetal body weights were observed with any of the ibrexafungerp doses, and fetal malformations were not observed with the 10 mg/kg/day dose of ibrexafungerp (approximately 2 times the RHD based on AUC comparison).

In a pre-postnatal study in rats, ibrexafungerp was administered by oral gavage from GD 6 through the lactation period until lactation day 20 in maternal doses of 10, 20, 35, and 50 mg/kg/day. No maternal toxicity or adverse effects on the survival, growth, behavior, or reproduction of first-generation offspring occurred with any of the ibrexafungerp doses up to the high dose of 50 mg/kg/day (approximately 5 times the RHD based on AUC comparison).

**8.2 Lactation**

**Risk Summary**

There are no data on the presence of ibrexafungerp in either human or animal milk, the effects on the breast-fed infant, or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for BREXAFEMME and any potential adverse effects on the breastfed child from BREXAFEMME or from the underlying maternal condition.

**8.3 Males and Females of Reproductive Potential**

Based on animal data, BREXAFEMME may cause fetal harm when administered to a pregnant female (see Use in Specific Populations (8.1)).

**Pregnancy Testing**

Verify the pregnancy status in females of reproductive potential prior to initiating treatment with BREXAFEMME (see Dosage and Administration (2.3), Contraindications (4) and Use in Specific Populations (8.1)).

**Contraception**

Females

Advise females of reproductive potential to use effective contraception during treatment with BREXAFEMME and for 4 days after the last dose.

**8.4 Pediatric Use**

The safety and effectiveness of BREXAFEMME for treatment of VVC have been established in post-menarchal pediatric females. Use of BREXAFEMME in post-menarchal pediatric patients is supported by evidence from adequate and well-controlled studies of BREXAFEMME in adult non-pregnant women with additional pharmacokinetic and safety data from post-menarchal pediatric females (see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1)).

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

**8.5 Geriatric Use**

Clinical studies with ibrexafungerp did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In a pharmacokinetic study in geriatric patients, no clinically meaningful differences in the pharmacokinetics of ibrexafungerp were observed compared to younger adults (see Clinical Pharmacology (12.3)).

**8.6 Hepatic Impairment**

No dosage adjustment of BREXAFEMME is recommended in patients with mild hepatic impairment (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B). Administration of BREXAFEMME in patients with severe hepatic impairment (Child-Pugh Class C) has not been studied (see Clinical Pharmacology (12.3)).

**10 OVERDOSAGE**

There is no experience with overdosage of BREXAFEMME.

There is no specific antidote for ibrexafungerp. Treatment should be supportive with appropriate monitoring.

**11 DESCRIPTION**

BREXAFEMME, available as an oral tablet, contains ibrexafungerp citrate, a triterpenoid antifungal agent.

Ibrexafungerp is designated chemically as (1S,4aR,6aS,7R,8R,10aR,10bR,12aR,14R,15R)-11-desoxy-15-[[2R]-2-amino-2,3,3-trimethylbutyloxy]-1,6a,8,10a-tetramethyl-8-[[2R]-3-methylbutan-2-yl]-14-[[5-(pyridin-4-yl)-1H-1,2,4-triazole-1-yl]-1-6,6a,7,8,9,10a,10b,11,12,12a-dodecahydro-2H-4H-1,4a-propano[anthenol][1,2]pyran-7-carboxylic acid compound with 2-hydroxypropane-1,2,3-tricarboxylic acid (1:1) with an empirical formula of C_{44}H_{67}N_{5}O_{4} • C_{6}H_{8}O_{7} and a molecular weight of 922.18 grams per mole. The chemical structure is:
**12 CLINICAL PHARMACOLOGY**

**12.1 Mechanism of Action**

Ibrexafungerp is a tripterpenoid antifungal drug [see Microbiology (12.4)].

**12.2 Pharmacodynamics**

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

**12.3 Pharmacokinetics**

In healthy subjects, ibrexafungerp area under the curve (AUC) and maximal concentration (C_{max}) increased approximately dose-proportionally following single dose administration from 10 to 1600 mg (0.02 to 2.67 times the approved recommended daily dose) and multiple-dose administration from 300–800 mg (0.50 to 1.33 times the approved recommended daily dose).

Based on a population pharmacokinetic analysis in patients with VVC, the model predicts that 300 mg twice a day for 2 doses achieves a mean (%CV) AUC_{0-24} exposure of 6832 (15%) ng•hr/mL and C_{max} of 435 (15%) ng/mL under fasted conditions and a mean AUC_{0-24} exposure of 9867 (15%) ng•hr/mL and C_{max} of 629 (15%) ng/mL under fed conditions.

**Absorption**

After oral administration of BREXAFEMME in healthy volunteers, ibrexafungerp generally reaches maximum plasma concentrations 4 to 6 hours after single and multiple dosing.

**Effect of Food**

Following administration of BREXAFEMME to healthy volunteers, the ibrexafungerp C_{max} increased 32% and the AUC increased 38% with a high fat meal (800-1000 calories; 50% fat), compared to fasted conditions. This exposure change is not considered clinically significant [see Dosage and Administration (2.1)].

**Distribution**

The mean steady state volume of distribution (Vss) of ibrexafungerp is approximately 600 L. Ibrexafungerp is highly protein bound (greater than 99%), predominantly to albumin. Animal studies demonstrate a 9-fold higher exposure in vaginal tissue than in blood.

**Elimination**

Ibrexafungerp is eliminated mainly via metabolism and biliary excretion. The elimination half-life is approximately 20 hours.

**Metabolism**

In vitro studies show that ibrexafungerp undergoes hydroxylation by CYP3A4, followed by glucuronidation and sulfation of a hydroxylated inactive metabolite.

**Excretion**

Following oral administration of radio-labeled ibrexafungerp to healthy volunteers, a mean of 90% of the radioactive dose (51% as unchanged ibrexafungerp) was recovered in feces and 1% was recovered in urine.

**Specific Populations**

**Post-Menarchal Pediatric Females and Geriatric Patients**

The pharmacokinetics of ibrexafungerp were not altered in post-menarchal pediatric females (ages 13 to 17 years) or in geriatric patients (ages 65 to 76 years).

**Patients with Hepatic Impairment**

The pharmacokinetics of ibrexafungerp were not altered in subjects with mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) hepatic impairment when the total AUC estimates were compared to healthy subjects.

The impact of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of ibrexafungerp is unknown.

**Drug Interaction Studies**

Ibrexafungerp is a substrate of CYP3A4 and P-gp. In vitro, ibrexafungerp is an inhibitor of CYP2C8, CYP3A4, P-gp transporter, and OATP1B3 transporter. Ibrexafungerp is not an inducer of CYP3A4.

The effect of coadministration of drugs on the pharmacokinetics of ibrexafungerp and the effect of ibrexafungerp on the pharmacokinetics of coadministered drugs were studied in healthy subjects.

**Effect of Coadministered Drugs on Ibrexafungerp Pharmacokinetics**

- **Strong CYP3A4 Inhibitor: Ketoconazole** (400 mg once daily for 15 days), a strong CYP3A4 and P-gp inhibitor, increased the ibrexafungerp AUC by 5.8-fold and C_{max} by 2.5-fold (see Drug Interactions (7)).

- **Moderate CYP3A4 Inhibitor: Dilatazem** (240 mg once daily for 15 days) increased the ibrexafungerp AUC by 2.5-fold and C_{max} by 2.2-fold. This exposure change is not considered clinically significant at the approved recommended dosage for VFC.

- **Proton Pump Inhibitor: Pantoprazole** (40 mg once daily for 5 days) decreased ibrexafungerp AUC by approximately 25% and C_{max} by 22%. This exposure change is not considered clinically significant at the approved recommended dosage for VFC.

**12.4 Microbiology**

**Mechanism of Action**

Ibrexafungerp, a tripterpenoid antifungal agent, inhibits glucan synthase, an enzyme involved in the formation of 1,3-β-D-glucan, an essential component of the fungal cell wall.

Ibrexafungerp has concentration-dependent fungicidal activity against Candida species as measured by time kill studies. Ibrexafungerp retains in vitro antifungal activity when tested at pH 4.5 (the normal vaginal pH).

**Resistance**

The potential for resistance to ibrexafungerp has been evaluated in vitro and is associated with mutations of the fks-2 gene; the clinical relevance of these findings is unknown. Ibrexafungerp retains activity against most fluconazole resistant Candida spp.

**Interaction with Other Antifungals**

In vitro studies have not demonstrated antagonism between ibrexafungerp and azoles or echinocandins.

**Antimicrobial Activity**

Ibrexafungerp has been shown to be active against most isolates of the following microorganism both in vitro and in clinical infections [see Indications and Usage (1)]:

- **Candida albicans**
- **Candida glabrata**
- **Candida guilliermondii**
- **Candida kefyr**
- **Candida krusei**
- **Candida lusitaniae**
- **Candida parapsilosis**
- **Candida tropicalis**

**13 NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

**Carcinogenesis**

Two-year carcinogenicity studies of ibrexafungerp have not been performed.

**Mutagenesis**

No mutagenic or clastogenic effects were detected in an in vitro bacterial reverse mutation assay, an in vitro chromosomal aberration assay, and an in vivo bone marrow micronucleus assay in rats.

**Impairment of Fertility**

In a male and female fertility study in rats, ibrexafungerp was administered to male rats by oral gavage in doses of 10, 20, 40, and 80 mg/kg/day for 28 days before mating and throughout maturation and to female rats for 15 days before mating, during mating, and until gestation day (GD) 6. Ibrexafungerp did not impair fertility in either sex at any dose up to the highest dose of 80 mg/kg/day (approximately 10 times the RHD based on AUC comparison).

**14 CLINICAL STUDIES**

Two randomized placebo-controlled clinical trials (Trial 1, NCT03734991 and Trial 2, NCT03987620) with a similar design were conducted to evaluate the safety and efficacy of a single day of BREXAFEMME 600 mg (two 150 mg tablets per dose, administered 12 hours apart) for the treatment of VFC. Non-pregnant post-menarchal females with a diagnosis of VFC were eligible. A diagnosis of VFC was defined as (a) minimum composite vulvovaginal signs and symptoms (VSS) score of ≥4 with at least two signs or symptoms having a score of 2 (moderate) or greater; (b) positive microscopic examination with 10% KOH in a vaginal sample revealing yeast forms (hyphae/pseudohyphae) or budding yeasts, and (c) normal vaginal pH (≤4.5). The total composite VSS score was based on the vulvovaginal signs (erythema, edema, excoriation) and vulvovaginal symptoms (itching, burning, or irritation) where each was scored as 0= absent, 1= mild, 2= moderate, or 3= severe. Study visits included the test of cure (TOC; Day 8 to 14) visit and a follow-up (Day 21 to 29) visit. The modified intent to treat (MITT) population included randomized subjects with a baseline culture positive for Candida species who took at least 1 dose of study medication.

Trial 1 was conducted in the United States. The MITT population consisted of 190 patients treated with BREXAFEMME and 100 patients treated with placebo. The average age was 34 years (range 17-67 years), with 91% less than 50 years. Fifty-four percent (54%) were White women.
and 40% were Black or African American, 26% were of Hispanic or Latino ethnicity. The average BMI was 30 and 9% had a history of diabetes. The median VSS score at baseline was 9 (range 4-18). The majority (92%) of the subjects were culture-positive with C. albicans.

Trial 2 was conducted in the United States (39%) and Bulgaria (61%). The MITT population consisted of 189 patients treated with BREXAFEMME and 89 patients treated with placebo. The average age was 34 years (range 18-65 years), with 92% less than 50 years. Eighty-one percent (81%) were White and 19% were Black or African American, 10% were of Hispanic or Latino ethnicity. The average BMI was 26 and 5% had a history of diabetes. The median VSS score at baseline was 10 (range 4-18). The majority (89%) of the subjects were culture-positive with C. albicans.

Efficacy was assessed by clinical outcome at the TOC visit. A complete clinical response was defined as the complete resolution of signs and symptoms (VSS score of 0). Additional endpoints included a negative culture for Candida spp. at the TOC visit, and clinical outcome at the follow-up visit. Statistically significantly greater percentages of patients experienced a complete clinical response at TOC, negative culture at TOC, and complete clinical response at follow-up with treatment with BREXAFEMME compared to placebo. The results for the clinical and mycological responses are presented in Table 3.

Table 3. Clinical and Mycological Response, MITT Population

<table>
<thead>
<tr>
<th></th>
<th>Trial 1</th>
<th>Trial 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 190</td>
<td>N = 189</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Complete Clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response at TOC1</td>
<td>95 (50.0)</td>
<td>120 (63.5)</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>22.0 (10.2, 32.8)</td>
<td>18.6 (6.0, 30.6)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.001</td>
<td>0.009</td>
</tr>
<tr>
<td>Negative Culture at</td>
<td>94 (49.5)</td>
<td>111 (58.7)</td>
</tr>
<tr>
<td>TOC</td>
<td>19 (19.0)</td>
<td>26 (29.2)</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>30.5 (19.4, 40.3)</td>
<td>29.5 (17.2, 40.6)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Complete Clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response at follow-up2</td>
<td>113 (59.5)</td>
<td>137 (72.5)</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>15.5 (3.4, 27.1)</td>
<td>23.1 (10.8, 35.0)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.007</td>
<td>0.006</td>
</tr>
</tbody>
</table>

1 Absence of signs and symptoms (VSS Score of 0) without need for additional antifungal therapy or topical drug therapy for the treatment of vulvovaginal symptoms at test of cure (TOC) visit.

2 Absence of signs and symptoms (VSS Score of 0) without need for further antifungal treatment or topical drug therapy for the treatment of vulvovaginal symptoms prior to follow-up visit.

16 HOW SUPPLIED / STORAGE AND HANDLING

16.1 How Supplied
BREXAFEMME (ibrexafungerp tablets) are purple, oval, biconvex shaped tablets debossed with 150 on one side and SCYX on the other side. Each tablet contains 150 mg ibrexafungerp (equivalent to 189.5 mg of ibrexafungerp citrate). Tablets are packaged in polyvinyl/polyvinylidene chloride child-resistant blister packs, four (4) tablets per pack. (NDC number 75788-115-04)

16.2 Storage and Handling
Store BREXAFEMME tablets at 20°C to 25°C (68°F to 77°F). Brief exposure to 15°C to 30°C (59°F to 86°F) permitted (see USP Controlled Room Temperature).