PDL DRUG REVIEW

Proprietary Name: Brexafemme®
Common Name: ibrexafungerp
PDL Category: Antifungals- Assorted

Comparable Products	Preferred Drug List Status
Terconazole Vaginal Cream	Preferred

Summary

Pharmacology/Usage: Ibrexafungerp citrate, the active ingredient of Brexafemme®, is a triterpenoid antifungal agent. It 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 and it retains in vitro antifungal activity when tested at pH 4.5 (the normal vaginal pH).

Indication: For the treatment of adult and post-menarchal pediatric females with vulvovaginal candidiasis (VVC). 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.

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings from animal studies, Brexafemme® use is contraindicated in pregnancy as it may cause fetal harm. Available data on use in pregnant women are not sufficient 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 1-888-982-7299. Verify the pregnancy status in females of reproductive potential prior to starting treatment with Brexafemme®. Advise females of reproductive potential to use effective contraception during treatment with Brexafemme® and for 4 days after the last dose. The safety and efficacy of use have not been established in pre-menarchal pediatric females.

Dosage Form: Tablets: 150mg

Recommended Dosage: Prior to starting treatment, verify the pregnancy status in females of reproductive potential.

In adults and post-menarchal pediatric females, take 300mg (two 150mg tablets) about 12 hours apart (e.g. in the morning and in the evening) for one day, for a total daily dosage of 600mg. It can be taken with or without food.

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®.

Concomitant use of strong CYP3A inhibitors (e.g. ketoconazole, itraconazole) can significantly increase ibrexafungerp concentration. Thus, it is recommended to reduce the dose of Brexafemme® to 150mg about 12 hours apart for one day.

Avoid the concomitant use of Brexafemme® with strong and moderate CYP3A inducers (e.g. rifampin, carbamazepine, phenytoin, St. John's wort, long-acting barbiturates, bosentan, efavirenz, or etravirine).

Ibrexafungerp is an inhibitor of CYP3A4, P-gp, and OATP1B3 transporter. However, given the short treatment duration for VVC, the effect of Brexafemme® on the pharmacokinetics of substrates of CYP3A4, P-gp, and OATP1B3 transporters is not considered to be clinically significant.

Box Warning: There is no box warning associated with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Brexafemme®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than the placebo.* The most frequently reported adverse events included diarrhea (13.4%), nausea (7.9%), abdominal pain (6.3%), dizziness (0.8%), and vomiting (1.3%).

Contraindications: In:

- Pregnancy
- Patients with hypersensitivity to ibrexafungerp

Manufacturer: Scynexis, Inc.

Analysis: The safety and efficacy of Brexafemme® were assessed in two randomized, placebo-controlled trials with a similar design that included non-pregnant, post-menarchal females with a diagnosis of VVC. A diagnosis of VVC was defined as a minimum composite vulvovaginal signs and symptoms (VSS) score of ≥4 with at least 2 signs or symptoms having a score of 2 (moderate) or greater, as well as a positive microscopic examination with 10% KOH in a vaginal sample revealing yeast forms or budding yeasts and a 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 1 was conducted in the US and patients (N=290) were treated with either Brexafemme® or placebo. The average age of included patient was 34 years (range 17-67), with 91% less than 50 years. In addition, 54% were white, the average BMI was 30, 9% had a history of diabetes, the median VSS score at baseline was 9, and most were culture-positive with *C. albicans* (92%).

Study 2 was conducted in the US and Bulgaria and patients (N=278) were treated with either Brexafemme® or placebo. The average age of included patients was 34 years (range 18-65), with 92% less than 50 years. In addition, 81% were white, the average BMI was 26, 5% had a history of diabetes, the median VSS score at baseline was 10, and most subjects were culture-positive with *C. albicans* (89%).

Efficacy was assessed by clinical outcome at the test of cure (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. Results suggested that 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 Brexafemme® treatment as compared with placebo. Results can be seen in the table below, which was adapted from the prescribing information.

	Study 1		Study 2	
	Brexafemme® (N=190)	Placebo (N=100)	Brexafemme® (N=189)	Placebo (N=89)
Complete Clinical Response at TOC[1]	95 (50%)	28 (28%)	120 (63.5%)	40 (44.9%)
Difference; p-value (*NNT calculated by CHC*)	22%, p=0.001 (NNT 5)		18.6%, p=0.009 (NNT 6)	
Negative Culture at TOC	94 (49.5%)	19 (19%)	111 (58.7%)	26 (29.2%)
Difference, p-value (*NNT calculated by CHC*)	30.5%, p<0.001 (NNT 4)		29.5%, p<0.001 (NNT 4)	
Complete Clinical Response at follow-up[2]	113 (59.5%)	44 (44%)	137 (72.5%)	44 (49.4%)
Difference, p-value (*NNT calculated by CHC*)	15.5%, p=0.007 (NNT 7)		23.1%, p=0.006 (NNT 5)	

[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 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

Place in Therapy: Brexafemme® is a first-in-class oral triterpenoid antifungal agent that is indicated for the treatment of adult and post-menarchal pediatric females with vulvovaginal candidiasis. 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. Pregnancy status should be verified before starting treatment in females of reproductive potential. In two placebo-controlled studies, statistically significantly greater percentages of patients experienced a complete clinical response at test of cure visit (TOC; primary endpoint), negative culture at TOC visit, and complete clinical response at follow-up visit in those treated with Brexafemme® as compared with placebo. Head-to-head studies with active comparators were not currently found.

There is no evidence at this time to support that Brexafemme® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Brexafemme® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Brexafemme [package insert]. Jersey City, NJ: Scynexis, Inc; 2021.