Drug Monograph

Drug Name: **Brexafemme® (ibrexafungerp) tablet**
Drug Class: **Anti-infectives: Vaginal Antifungals**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Brexafemme is available in 150 mg tablets.
Manufacturer:	Distributed by: Scynexis, Inc., Jersey City, NJ 07302.
Summary of Findings:	The safety and efficacy of Brexafemme was established in two multicenter, randomized, double-blind, placebo-controlled Phase 3 trials. The first (VANISH 303, N=290) was conducted in post-menarchal females ≥12 years while acute vulvovaginal candidiasis in the United States, while the other (VANISH 306, N=278) was conducted in the U.S. and Bulgaria. Participants were randomized 2:1 to receive 600 mg of Brexafemme (two 150 mg tablets per dose administered 12 hours apart) or placebo. The modified intent-to-treat (MITT) population included randomized patients with a baseline culture positive for Candida species who took at least one dose of the study medication. Statistically significantly greater percentages of patients experienced a complete clinical response at Test of Cure (TOC) visit (Days 8-14), negative culture at TOC, and complete clinical response at follow-up with treatment with Brexafemme compared to placebo (95% vs 28%, *p*=0.001 in VANISH 303 and 63.5% vs 44.9%, *p*=0.009 in VANISH 306).
Status Recommendation:	☒ Clinical Edit ☐ PA Required ☐ Open Access ☐ PDL
Type of PA Criteria:	☒ Appropriate Indications ☐ Non-Preferred ☐ No PA Required ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Yeast and bacteria normally exist in a balance inside the body in places such as the mouth, throat, gut and vagina. An overgrowth of yeast, particularly the Candida species, in the vagina is termed vulvovaginal candidiasis (VVC). After bacterial vaginosis, VVC is the second most common cause of vaginal inflammation in the United States. It is estimated that 75% of all women will have a vaginal yeast infection at least once in their life and about 40-45% will have two or more episodes of vaginal yeast overgrowth. VVC can be present without any symptoms at all or in any range from mild to severe redness, itching or soreness, swelling, pain during intercourse or urination, abnormal vaginal discharge, and cracks in the wall of the vagina. Women are more likely to have VVC episodes during certain phases of life, such as pregnancy, or changes in the human environment like using hormonal contraceptives, having high blood sugar, and taking steroids, immunosuppressants, or antibiotics. Diagnosis is made by taking a small sample of vaginal discharge and culturing the sample for fungus, although the presence of fungus does not always mean that a case of VVC has been identified.

Dosage Form [3]

Brexafemme is available in 150 mg tablets.

Manufacturer [3]

Distributed by: Scynexis, Inc., Jersey City, NJ 07302.

Indication(s) [3]

Brexafemme is indicated for the treatment of adult and post-menarchal pediatric females with vulvovaginal candidiasis.

Clinical Efficacy [3,4,5] (mechanism of action/pharmacology, comparative efficacy)

Brexafemme is a triterpenoid antifungal drug which inhibits glucan synthase, an enzyme involved in the formation of 1,3-β-D-glucan, an essential component of the fungal cell wall. It has concentration-dependent fungicidal activity against *Candida* species as measured by time-kill studies. The drug also retains in vitro antifungal activity when tested at pH 4.5 (the normal vaginal pH) and against most fluconazole resistant *Candida* species.

Pharmacokinetics:

Absorption	t_{max}=4 to 6 hours
Metabolism	Hydroxylation by CYP3A4, followed by glucuronidation and sulfation
Excretion	Fecal: 90%; Renal: 1%
Half-life	$t_{1/2}$=20 hours

Clinical Trials Experience

	VANISH 303 (NCT03734991)	**VANISH 306 (NCT03987620)**
STUDY DESIGN	Multicenter, randomized, double-blind, placebo-controlled Phase 3 trial conducted in the United States **(N=290)**	Multicenter, randomized, double-blind, placebo-controlled Phase 3 trial conducted in the United States (39% of patients) and Bulgaria (61% of patients) **(N=278)**

INCLUSION CRITERIA	• Post-menarchal females ≥12 years
	• Diagnosis of acute VVC (AVVC), defined as:
	  ○ 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
	  ▪ The total composite VSS score was based on the vulvovaginal signs (erythema, edema, excoriation) and symptoms (itching, burning or irritation), with each scored as 0=absent, 1=mild, 2=moderate, 3=severe.
	  ○ Positive microscopic examination with 10% KOH in a vaginal sample revealing yeast forms (hyphae/pseudohyphae) or budding yeasts AND,
	  ○ Normal vaginal pH (≤4.5)	

EXCLUSION CRITERIA	• Vaginal conditions other than AVVC • Patients who used systemic or topical (vaginal) antifungal treatments during the study and treatment for VVC 28 days prior to treatment • Patients with uncontrolled diabetes • Patients with a history of or active cervical or vaginal cancer	
TREATMENT REGIMEN	Participants were randomized 2:1 to receive 600 mg of Brexafemme (two 150 mg tablets per dose administered 12 hours apart) or placebo. The modified intent-to-treat (MITT) population included randomized patients with a baseline culture positive for Candida species who took at least one dose of the study medication. The primary endpoint was clinical cure (VSS score of 0), measured by percentage of patients with clinical cure at the test of cure (TOC) visit (Days 8-14). Secondary endpoints included mycological eradication (negative culture for growth of yeast), clinical cure and mycological eradication (responder outcome), complete resolution of signs and symptoms at follow-up (Day 25), and number of patients with treatment-related adverse events.	

<table>
<tr><td>RESULTS</td><td>
Brexafemme Clinical and Mycological Response in Modified Intent-to-Treat Population
<table>
<tr><td colspan="3">Trial 1 (VANISH 303)</td></tr>
<tr><td></td><td>Brexafemme (N=190)
n (%)</td><td>Placebo (N=100)
n (%)</td></tr>
<tr><td>Clinical Response at TOC</td><td>95 (50.0)</td><td>28 (28.0)</td></tr>
<tr><td>Difference (95% CI)</td><td colspan="2">22.0 (10.2, 32.8)</td></tr>
<tr><td>P value</td><td colspan="2">0.001</td></tr>
<tr><td>Negative Culture at TOC</td><td>94 (49.5)</td><td>19 (19.0)</td></tr>
<tr><td>Difference (95% CI)</td><td colspan="2">30.5 (19.4, 40.3)</td></tr>
<tr><td>P Value</td><td colspan="2"><0.001</td></tr>
<tr><td>Complete Clinical Response at Follow-up</td><td>113 (59.5)</td><td>44 (44.0)</td></tr>
<tr><td>Difference (95% CI)</td><td colspan="2">(15.5 (3.4, 27.1)</td></tr>
<tr><td>P Value</td><td colspan="2">0.007</td></tr>
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<table>
<tr><td colspan="3">Trial 2 (VANISH 306)</td></tr>
<tr><td></td><td>Brexafemme (N=189)
n (%)</td><td>Placebo (N=89)
n (%)</td></tr>
<tr><td>Clinical Response at TOC</td><td>120 (63.5)</td><td>40 (44.9)</td></tr>
<tr><td>Difference (95% CI)</td><td colspan="2">18.6 (6.0, 30.6)</td></tr>
<tr><td>P value</td><td colspan="2">0.009</td></tr>
<tr><td>Negative Culture at TOC</td><td>111 (58.7)</td><td>26 (29.2)</td></tr>
<tr><td>Difference (95% CI)</td><td colspan="2">29.5 (17.2, 40.6)</td></tr>
<tr><td>P Value</td><td colspan="2"><0.001</td></tr>
<tr><td>Complete Clinical Response at Follow-up</td><td>137 (72.5)</td><td>44 (49.4)</td></tr>
<tr><td>Difference (95% CI)</td><td colspan="2">23.1 (10.8, 35.0)</td></tr>
<tr><td>P Value</td><td colspan="2">0.006</td></tr>
</table>
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.
</td></tr>
<tr><td>SAFETY</td><td>Discussed in the Adverse Effects section below.</td></tr>
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Contraindications [3,4]

- Pregnancy
- Patients with hypersensitivity to Brexafemme

Warnings and Precautions [3,4]

- Risk of fetal toxicity-advise females of reproductive potential to use effective contraception during treatment with Brexafemme and for 4 days after the last dose.

Adverse Effects [3,4]

Most common, ≥ 2%	Brexafemme (N=545) n (%)	Placebo (N=275) n (%)
Diarrhea	91 (16.7)	9 (3.3)
Nausea	65 (11.9)	11 (4.0)
Abdominal pain	62 (11.4)	14 (5.1)
Dizziness	18 (3.3)	7 (2.5)
Vomiting	11 (2.0)	2 (0.7)

Drug Interactions [3,4]

Concomitant Drugs	Effect of Brexafemme Concentration	Recommendation
Strong CYP3A inhibitors: (e.g., ketoconazole, itraconazole)	Significantly increased	Reduce the Brexafemme dosage to 150 mg orally approximately 12 hours apart for one day
Strong and Moderate CYP3A inducers: (e.g., rifampin, carbamazepine, phenytoin, St. John's wort, long-acting barbiturates, bosentan, efavirenz, or etravirine)	Not studied in vivo or in vitro, but likely to result in significant reduction	Avoid concomitant administration

- Brexafemme 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.

Dosage and Administration [3,4]

The recommended dosage of Brexafemme in adult and post-menarchal pediatric females is 300 mg (two 150 mg tablets) orally administered 12 hours apart for one day, for a total daily dosage of 600 mg (four 150 mg tablets). Brexafemme may be taken with or without food.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Dose
Ibrexafungerp	Brexafemme®	Scynexis	300 mg (2 tabs) orally 12 hours apart for one day	$475 for 4 tablets
Fluconazole	Diflucan®	Pfizer, various	150mg orally for 1 dose	$2.80 (generic)

** Wholesale Acquisition Cost

Conclusion

Brexafemme is a triterpenoid antifungal drug which displays concentration-dependent fungicidal activity against *Candida* species. It is active at normal vaginal pH and effective against most fluconazole resistant *Candida* species. In two multicenter, randomized, double-blind, placebo-controlled Phase 3 trials, participants were randomized 2:1 to receive 600 mg of Brexafemme (two 150 mg tablets per dose administered 12 hours apart) or placebo. Statistically significantly greater percentages of patients experienced a complete clinical response at Test of Cure (TOC) visit (Days 8-14), negative culture at TOC, and complete clinical response at follow-up with treatment with Brexafemme compared to placebo. Adverse effects include diarrhea, nausea, abdominal pain, dizziness, and vomiting. Based on the drug's ability to treat yeast overgrowth resistant to typical first-line treatment (fluconazole) and cost, the use of Brexafemme should be reserved for cases of medical necessity.

Recommendation

The MO Healthnet Division recommends adding this drug to the current systemic antifungals clinical edit.

References

1) IPD Analytics. New Drug Review: Brexafemme (ibrexafungerp tablets). June 2021.
2) Vaginal Candidiasis. Centers for Disease Control and Prevention. https://www.cdc.gov/fungal/diseases/candidiasis/genital/index.html. Accessed September 8, 2021.
3) Brexafemme [package insert]. Jersey City, NJ: Scynexis, Inc.; June 2021.
4) Clinical Pharmacology {drug information database]. Available at: https://www.clinicalkey.com/pharmacology/monograph/5338?n=BREXAFEMME. Accessed September 2, 2021.

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Date: September 10, 2021

