HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BREXAFEMME safely and effectively. See full prescribing information for BREXAFEMME.

BREXAFEMME (ibrexafungerp) tablets, for oral use
Initial U.S. Approval: 2021

WARNING: RISK OF EMBRYO-FETAL TOXICITY
See full prescribing information for the complete boxed warning.
- **BREXAFEMME is contraindicated in pregnancy because it may cause fetal harm based on findings from animal reproductive studies. (4, 5.1)**
- **For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment. Reassessing pregnancy status prior to each dose is recommended when BREXAFEMME is used monthly for 6 months for reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC). (2.3, 5.1)**
- **Advise females of reproductive potential to use effective contraception during treatment of vulvovaginal candidiasis (VVC) and throughout the 6-month treatment period for reduction in the incidence of RVVC with BREXAFEMME and for 4 days after the last dose. (5.1, 8.3)**

---------- INDICATIONS AND USAGE----------
BREXAFEMME is a triterpenoid antifungal indicated in adult and post-menarchal pediatric females for:
- Treatment of vulvovaginal candidiasis (VVC). (1.1)
- Reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC). (1.1)

----------DOSAGE AND ADMINISTRATION----------
- Treatment of VVC: The recommended dosage of BREXAFEMME in adult and post-menarchal pediatric females is 300 mg (two 150 mg tablets) administered orally approximately 12 hours apart (e.g., in the morning and in the evening) for 1 day, for a total daily dosage of 600 mg (four 150 mg tablets). (2.1)
- Reduction in the Incidence of RVVC: The recommended dosage of BREXAFEMME in adult and post-menarchal pediatric females is 300 mg (two 150 mg tablets) administered orally approximately 12 hours apart (e.g., in the morning and in the evening) for 1 day, for a total daily dosage of 600 mg (four 150 mg tablets) monthly for 6 months. (2.1)
- BREXAFEMME may be taken with or without food. (2.1)

---------- DOSAGE FORMS AND STRENGTHS----------
Tablets: 150 mg of ibrexafungerp. (3)

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

---------- ADVERSE REACTIONS ----------
- Treatment of VVC: The most frequent adverse reactions (incidence ≥2%) reported were diarrhea, nausea, abdominal pain, dizziness, and vomiting. (6.1)
- Reduction in the Incidence of RVVC: The most frequent adverse reactions (incidence ≥2%) reported were headache, abdominal pain, diarrhea, nausea, urinary tract infection, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------
- Concomitant use of strong CYP3A inhibitors increases the exposure of ibrexafungerp. Reduce the dose of BREXAFEMME with concomitant use of a strong CYP3A inhibitor to 150 mg twice daily for 1 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 Medication Guide.

Revised: 7/2026

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF EMBRYO-FETAL TOXICITY

- **BREXAFEMME is contraindicated in pregnancy because it may cause fetal harm based on findings from animal reproductive studies *[see Contraindications (4), Warnings and Precautions (5.1)]*.**
- **For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment with BREXAFEMME. Reassessing pregnancy status prior to each dose is recommended when BREXAFEMME is used monthly for 6 months for reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC) *[see Dosage and Administration (2.3)*, *Warnings and Precautions (5.1), Use in Specific Populations (8.3)]*.**
- **Advise females of reproductive potential to use effective contraception during treatment of vulvovaginal candidiasis (VVC) and throughout the 6-month treatment period for reduction in the incidence of RVVC with BREXAFEMME and for 4 days after the last dose *[see Warnings and Precautions (5.1), Use in Specific Populations (8.3)]*.**

1 INDICATIONS AND USAGE

1.1 Vulvovaginal Candidiasis

BREXAFEMME is indicated in adult and post-menarchal pediatric females for:

- Treatment of vulvovaginal candidiasis (VVC).
- Reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC).

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 Recommended Dosage

Treatment of VVC: The recommended dosage of BREXAFEMME in adult and post-menarchal pediatric females is 300 mg (two 150 mg tablets) administered orally approximately 12 hours apart (e.g., in the morning and in the evening) for 1 day, for a total daily dosage of 600 mg (four 150 mg tablets).

Reduction in the Incidence of RVVC: The recommended dosage of BREXAFEMME in adult and post-menarchal pediatric females to prevent recurrences is 300 mg (two 150 mg tablets)

administered orally approximately 12 hours apart (e.g., in the morning and in the evening) for 1 day, for a total daily dosage of 600 mg (four 150 mg tablets) monthly for 6 months.

BREXAFEMME may be taken with or without food.

2.2 Dosage Modifications in Patients due to Concomitant Use of a Strong Inhibitor of Cytochrome P450 Isoenzymes (CYP) 3A

With concomitant use of a strong CYP3A inhibitor, administer BREXAFEMME 150 mg orally approximately 12 hours apart (e.g., in the morning and in the evening) for 1 day. No dosage adjustment is warranted in patients with concomitant use of a weak or moderate CYP3A inhibitor *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.

2.3 Pregnancy Evaluation Prior to Initiating Treatment

For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment with BREXAFEMME. Reassessment of pregnancy status prior to each dose is recommended when BREXAFEMME is used monthly for 6 months for reduction in the incidence of RVVC *[see Contraindications (4), Warnings and Precautions (5.1), Use in Specific Populations (8.1, 8.3)]*.

3 DOSAGE FORMS AND STRENGTHS

BREXAFEMME tablets are purple, oval, biconvex shaped tablets debossed with 150 on one side and SCYX on the other side containing 150 mg of ibrexafungerp.

4 CONTRAINDICATIONS

BREXAFEMME is contraindicated in:

- Pregnancy *[see Warnings and Precautions (5.1)*, *Use in Specific Populations (8.1, 8.3)].*
- Patients with hypersensitivity to ibrexafungerp.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Embryo-Fetal Toxicity

Based on findings from animal studies, use of BREXAFEMME is contraindicated in pregnancy because it may cause fetal harm. In animal reproduction studies, ibrexafungerp administered orally to pregnant rabbits during organogenesis was associated with fetal malformations including absent forelimb(s), absent hind paw, absent ear pinna, and thoracogastroschisis at dose exposures greater or equal to approximately 5 times the human exposure at the recommended human dose (RHD).

For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment with BREXAFEMME. Reassessment of pregnancy status prior to each dose is recommended when BREXAFEMME is used monthly for 6 months for reduction in the

incidence of RVVC. Advise females of reproductive potential to use effective contraception during treatment of VVC and throughout the 6-month treatment period for reduction in the incidence of RVVC with BREXAFEMME and, for 4 days after the last dose *[see Use in Specific Populations (8.1, 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 a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Treatment of VVC

A total of 545 patients were exposed to BREXAFEMME in 2 clinical trials of post-menarchal females with VVC (Trial 1 and Trial 2). The patients were treated with BREXAFEMME 300 mg (two 150 mg tablets) twice a day, 12 hours apart, for 1 day. The patients were 18 to 76 years of age (mean 34 years), 69% were White, 28% were Black or African American, and 18% were of Hispanic or Latina ethnicity.

The most frequently reported adverse reactions are presented in Table 1.

There were no serious adverse reactions and 2 out of 545 (0.4%) patients discontinued treatment with BREXAFEMME due to vomiting (1 patient) and dizziness (1 patient).

Table 1. Adverse Reactions with Incidence Rates ≥2% in Patients with Vulvovaginal Candidiasis Treated with BREXAFEMME in Trials 1 and 2

Adverse Reaction	BREXAFEMME N = 545 n (%)	Placebo N = 275 n (%)
Diarrhea	91 (16.7%)	9 (3.3%)
Nausea	65 (11.9%)	11 (4.0%)
Abdominal pain[a]	62 (11.4%)	14 (5.1%)
Dizziness[b]	18 (3.3%)	7 (2.5%)
Vomiting	11 (2.0%)	2 (0.7%)

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort

[b] 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, and rash/hypersensitivity reaction.

Reduction in the Incidence of RVVC

A total of 130 patients were exposed to BREXAFEMME in a clinical trial of post-menarchal females with RVVC (Trial 3). The patients were treated with BREXAFEMME 300 mg (two 150 mg tablets) twice a day, 12 hours apart, for 1 day, monthly for 6 consecutive months. The patients were 18 to 65 years of age (mean 34 years), of which, 59% of patients were between 18 to 35 years, and 41% between 36 to 65 years. Ninety-two percent (92%) were White, 7% were Black or African American, and 1% were Asian. Nine percent (9%) of patients were of Hispanic or Latina ethnicity.

The most frequently reported adverse reactions are presented in Table 2.

There were no serious adverse reactions and no patients discontinued treatment with BREXAFEMME due to adverse reaction.

Table 2. Adverse Reactions with Incidence Rates ≥2% in Patients with Recurrent Vulvovaginal Candidiasis Treated with BREXAFEMME in Trial 3

Adverse Reaction[a]	BREXAFEMME N = 130 n (%)	Placebo N = 130 n (%)
Headache	23 (17.6)	10 (7.6)
Abdominal pain[b]	13 (10.0)	9 (6.9)
Diarrhea	10 (7.7)	5 (3.8)
Nausea	7 (5.4)	5 (3.8)
Urinary tract infection	5 (3.8)	1 (0.8)
Fatigue	4 (3.1)	0

[a] A single patient may have had multiple instances of adverse reactions. Only 1 episode of adverse reaction is counted per patient.

[b] Includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort.

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 3. Effect of Coadministered Drugs on Ibrexafungerp Pharmacokinetics

Concomitant Drugs	Effect on Ibrexafungerp Concentration	Recommendation
Strong CYP3A inhibitors (e.g., ketoconazole, itraconazole)	Significantly increased	Reduce the dosage of BREXAFEMME *[see Dosage and Administration (2.2)]*
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

Ibrexafungerp is an inhibitor of CYP3A4, P-glycoprotein (P-gp), and organic anion transporter polypeptide (OATP)1B3 transporter *[see Clinical Pharmacology (12.3)]*. 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies, use of BREXAFEMME is contraindicated in pregnancy because it may cause fetal harm. In pregnant rabbits, oral ibrexafungerp administered during organogenesis was associated with fetal malformations including absent forelimb(s), absent hind paw, absent ear pinna, and thoracogastroschisis 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 the use of BREXAFEMME 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 GlaxoSmithKline at 1-888-825-5249.

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 area under the curve [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, thoracogastroschisis, trunk kyphosis, absent forelimbs, absent forepaws, and absent hind paw occurred in a single fetus. Malformations including absent hind paw 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, thoracogastroschisis, 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

A milk-only pharmacokinetic lactation study (n = 5) demonstrated that ibrexafungerp is present in maternal milk and plasma. The estimated average daily infant dose of ibrexafungerp from breast milk was <1% of the maternal weight-adjusted dose *(see Data)*. There are no data on the effects of ibrexafungerp on the breastfed 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.

Data

A milk-only pharmacokinetic lactation study evaluated concentrations of ibrexafungerp in the plasma and breast milk of 5 healthy lactating women, who were between 33 and 346 days postpartum. Two oral doses of 300 mg of BREXAFEMME were administered 12 hours apart for 1 day (600 mg total daily dose). Ibrexafungerp was detected in breast milk at a mean (standard

deviation) average concentration (C_{av}) of 45.39 (13.669) ng/mL. The mean (standard deviation) calculated daily infant dosage was 0.05 (0.06) mg/day which is <1% of the maternal weight-adjusted dose. There are no data on infant exposure after repeated maternal dosing of ibrexafungerp.

8.3 Females and Males 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

For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment with BREXAFEMME. Reassessment of pregnancy status prior to each dose is recommended when BREXAFEMME is used monthly for 6 months for reduction in the incidence of RVVC *[see Dosage and Administration (2.3), Contraindications (4), Use in Specific Populations (8.1)]*.

Contraception

Females: For treatment of VVC, advise females of reproductive potential to use effective contraception during treatment with BREXAFEMME and for 4 days after the last dose.

For reduction in the incidence of RVVC, advise females of reproductive potential to use effective contraception throughout the 6-month treatment period 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. The safety and effectiveness of BREXAFEMME for the reduction in the incidence of RVVC have been established in post-menarchal pediatric females. *[see Indications and Usage (1.1)]*. Use of BREXAFEMME in post-menarchal pediatric females for VVC and RVVC 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), 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 BREXAFEMME did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects. No clinically meaningful differences in the pharmacokinetics of ibrexafungerp were observed in geriatric patients 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)]*.

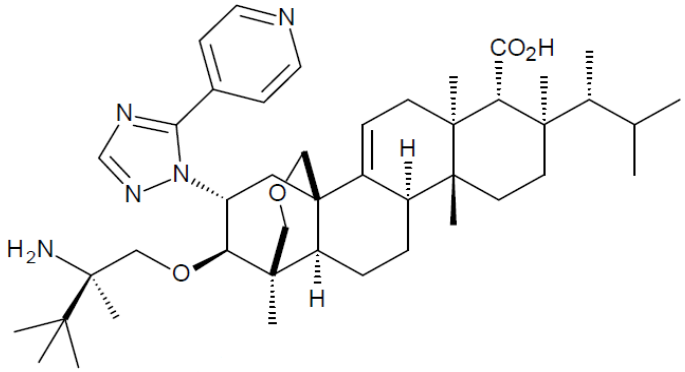
10 OVERDOSAGE

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)-15-[(2R)-2-amino-2,3,3-trimethylbutoxy]-1,6a,8,10a-tetramethyl-8-[(2R)-3-methylbutan-2-yl]-14-[5-(pyridine-4-yl)-1H-1,2,4-triazol-1-yl]-1,6,6a,7,8,9,10,10a,10b,11,12,12a-dodecahydro-2H,4H-1,4a-propanophenanthro[1,2-c]pyran-7-carboxylic acid compound with 2-hydroxypropane-1,2,3-tricarboxylic acid (1:1) with an empirical formula of $C_{44}H_{67}N_5O_4 \bullet C_6H_8O_7$ and a molecular weight of 922.18 grams per mole. The chemical structure is:



$\bullet C_6H_8O_7$

BREXAFEMME tablet for oral administration is a purple, oval, biconvex shaped, film-coated tablet containing 189.5 mg of ibrexafungerp citrate equivalent to 150 mg of ibrexafungerp. In addition to the active ingredient, the tablet formulation contains butylated hydroxyanisole, colloidal silicon dioxide, crospovidone, magnesium stearate, mannitol, and microcrystalline cellulose. The tablet film-coating contains FD&C Blue #2, FD&C Red #40, hydroxypropyl cellulose, hydroxypropylmethyl cellulose 2910, talc and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

Cardiac Electrophysiology

At a concentration of 5 times or greater than that achieved after a single day 300 mg twice daily dose, ibrexafungerp does not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

In healthy subjects, ibrexafungerp AUC and maximal concentration (C_{max}) increased approximately dose-proportionally following single dose administration from 10 to 1,600 mg (0.02 to 2.67 times the approved recommended daily dose) and multiple-dose administration from 300 to 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 6,832 (15%) ng•hr/mL and C_{max} of 435 (15%) ng/mL under fasted conditions and a mean AUC_{0-24} exposure of 9,867 (15%) ng•h/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 to 1,000 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 (V_{ss}) 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 (13 to 17 years of age) or in geriatric patients (65 to 76 years of age).

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: Diltiazem (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 VVC.

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 VVC.

Effect of Ibrexafungerp on the Pharmacokinetics of Coadministered Drugs: The effects of ibrexafungerp on substrates of CYP2C8, CYP3A4, P-gp, and OATP1B3 transporters were evaluated in studies that included loading doses of ibrexafungerp of 1,250 to 1,500 mg (2.1 to 2.5 times the approved recommended daily dose) for 2 days followed by 750 mg (1.25 times the approved recommended daily dose) once daily for 3 to 7 days. The effect of ibrexafungerp on a once daily combined oral contraceptive regimen containing ethinyl estradiol (35 µg) and

norethindrone (1 mg) was assessed in a study that evaluated 300 mg of ibrexafungerp administered twice daily (12 hours apart) for 1 day during a 21-day cycle of contraception.

CYP2C8 substrates: Ibrexafungerp did not increase the $AUC_{0\text{-}inf}$ or C_{max} of rosiglitazone, a moderate sensitive CYP2C8 substrate.

CYP3A4 substrates: Ibrexafungerp resulted in 1.4-fold increase in the $AUC_{0\text{-}inf}$ and no effect on the C_{max} of the sensitive CYP3A4 and P-gp substrate tacrolimus.

P-gp substrates: Ibrexafungerp resulted in a 1.4-fold increase in the $AUC_{0\text{-}48}$ and a 1.25-fold increase in the C_{max} of the P-gp substrate dabigatran.

OATP1B3 transporters: Ibrexafungerp resulted in a 2.8-fold increase in the $AUC_{0\text{-}24}$ and a 3.5-fold increase in the C_{max} of the OATP1B3 transporter substrate pravastatin.

Oral Contraceptives: Coadministration of ibrexafungerp resulted in an approximately 17% decrease in ethinyl estradiol and norethindrone C_{max} and an approximately 9% decrease in ethinyl estradiol $AUC_{0\text{-}24}$ and 1% decrease in norethindrone $AUC_{0\text{-}24}$. These exposure changes are not considered clinically significant at the approved recommended dosage for VVC.

12.4 Microbiology

Mechanism of Action

Ibrexafungerp, a triterpenoid 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. No resistance development was observed after monthly dosing of BREXAFEMME in patients with RVVC.

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

The following in vitro data are available, but their clinical significance is unknown. Ibrexafungerp has in vitro activity against most isolates of the following microorganisms:

Candida auris

Candida dubliniensis

Candida glabrata

Candida guilliermondii

Candida keyfr

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 mating and to female rats for 15 days before mating, during mating, and until 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).

13.2 Animal Toxicity and/or Pharmacology

Daily administration of oral ibrexafungerp for 26 weeks in rats, at the highest dose of 80 mg/kg/day (approximately 10 times the RHD based on AUC comparison), was associated with marked, but reversible, phospholipidosis and foamy histiocytes in alveolar tissue in the lung and labored breathing, marked irritation and metaplasia in gastric mucosa, and peripheral nerve degeneration accompanied by hind-limb paralysis.

14 CLINICAL STUDIES

14.1 Treatment of VVC

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 VVC. Non-pregnant post-menarchal females with a diagnosis of VVC were eligible. 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; (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 U.S. The MITT population consisted of 190 patients treated with BREXAFEMME and 100 patients treated with placebo. The average age was 34 years (range 17 to 67 years), with 91% less than 50 years. Fifty-four percent (54%) were White and 40% were Black or African American, 26% were of Hispanic or Latina ethnicity. The average BMI was 30 and 9% had a history of diabetes. The median VSS score at baseline was 9 (range 4 to 18). The majority (92%) of the subjects were culture-positive with *C. albicans*.

Trial 2 was conducted in the U.S. (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 to 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 Latina ethnicity. The average BMI was 26 and 5% had a history of diabetes. The median VSS score at baseline was 10 (range 4 to 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 4.

Table 4. Clinical and Mycological Response in Post-Menarchal Females with Vulvovaginal Candidiasis in Trials 1 and 2, Modified Intent to Treat Population

	Trial 1		Trial 2	
	BREXAFEMME N = 190 n (%)	**Placebo N = 100 n (%)**	**BREXAFEMME N = 189 n (%)**	**Placebo N = 89 n (%)**
Complete Clinical Response at TOC[a]	95 (50.0)	28 (28.0)	120 (63.5)	40 (44.9)
Difference (95% CI)	22.0 (10.2, 32.8)		18.6 (6.0, 30.6)	
***P*-Value**	0.001		0.009	
Negative Culture at TOC	94 (49.5)	19 (19.0)	111 (58.7)	26 (29.2)
Difference (95% CI)	30.5 (19.4, 40.3)		29.5 (17.2, 40.6)	
***P*-Value**	<0.001		<0.001	
Complete Clinical Response at Follow-Up[b]	113 (59.5)	44 (44.0)	137 (72.5)	44 (49.4)
Difference (95% CI)	15.5 (3.4, 27.1)		23.1 (10.8, 35.0)	
***P*-Value**	0.007		0.006	

[a] 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.

[b] 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.

14.2 Reduction in the Incidence of RVVC

A randomized placebo-controlled clinical trial (Trial 3, NCT04029116) was conducted to evaluate the safety and efficacy of BREXAFEMME 300 mg (two 150 mg tablets) administered approximately 12 hours apart (e.g., in the morning and in the evening) for 1 day, for a total daily dosage of 600 mg (four 150 mg tablets) administered once monthly for 6 months. Trial 3 was conducted in the U.S. (33%), Bulgaria (28%), Poland (12%), and Russia (28%). Non-pregnant post-menarchal females presenting with a symptomatic VVC episode and a history of recurrent VVC (at least 3 episodes of VVC in the previous 12 months) were eligible. The symptomatic episode at screening was treated with 3 doses of fluconazole 150 mg 3 days apart.

To be randomized, patients had to have a culture-confirmed VVC episode at screening and had to achieve significant resolution of their vulvovaginal signs and symptoms (defined as a total composite score ≤2 on the VSS Scale) after fluconazole treatment. Patients were randomized at a 1:1 ratio to receive double-blind BREXAFEMME or placebo administered as a single-day treatment repeated every 4 weeks for a total of 6 single-day treatments. Study visits included the TOC at Week 24 (4 weeks after the last dose) and a follow-up visit at Week 36. The intent to treat (ITT) population was all randomized patients.

The ITT population consisted of 130 patients treated with BREXAFEMME and 130 patients treated with placebo. The average age was 34 years (range 18 to 65 years) with 95% less than 50 years. Ninety percent (90%) of patients were White, 8% were Black or African American, and 2% were Asian and other race. Eight percent (8%) of patients were of Hispanic or Latina ethnicity. The average BMI of the patient population was 25 and 16.5% were obese (BMI >30).

Efficacy was assessed as the percentage of patients with Clinical Success, defined as subjects with No Culture Proven, Presumed or Suspected Recurrence of VVC requiring antifungal therapy up to TOC at Week 24. Clinical Success was also assessed at the Week 36 follow-up visit.

Statistically significantly greater percentages of patients experienced Clinical Success at TOC compared to placebo. The clinical success rate at TOC was lower for patients in the U.S. when compared to patients outside the U.S. (ex-U.S.) for both BREXAFEMME and placebo groups. In both regions, the BREXAFEMME group had a higher clinical success rate compared to placebo (U.S.: 33% vs 23% and ex-U.S.: 81% vs 68% in BREXAFEMME vs. placebo arms, respectively) and the difference between the treatment groups was consistent [U.S.: 10.1% (-9.0, 29.1) and ex-U.S.: 12.9% (0.04, 25.7)]. Clinical Success at Week 36 was also greater for BREXAFEMME compared to placebo. The results for Clinical Success and reasons for clinical failure are presented in Table 5.

Table 5. Clinical and Mycological Response in Post-Menarchal Females with Recurrent Vulvovaginal Candidiasis in Trial 3, Intent to Treat Population

	Trial 3		
	BREXAFEMME N = 130 n (%)	**Placebo N = 130 n (%)**	**Difference (95% CI) *P*-Value**
Clinical Success at TOC (Week 24)	85 (65.4)	69 (53.1)	12.7 (2.2, 23.1) 0.020
Reasons for Clinical Failure at TOC			
Mycologically Proven Recurrence	30 (23.1)	47 (36.2)	
Presumed Recurrence	7 (5.4)	3 (2.3)	
Suspected Recurrence	2 (1.5)	4 (3.1)	
Imputed Recurrence[a]	6 (4.6)	7 (5.4)	
Clinical Success at Week 36 Follow-Up Visit	75 (57.7)	60 (46.2)	11.9 (1.1, 22.6) 0.034
Reasons for Clinical Failure at Week 36 Follow-Up Visit			
Mycologically Proven Recurrence	37 (28.5)	51 (39.2)	
Presumed Recurrence	8 (6.2)	5 (3.8)	
Suspected Recurrence	4 (3.1)	5 (3.8)	
Imputed Recurrence[a]	6 (4.6)	9 (6.9)	

Abbreviations: CI = confidence interval; TOC = test of cure.

[a] Imputed recurrences are subjects whose clinical outcome cannot be determined due to early termination or missing critical efficacy assessment at TOC.

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, 4 tablets per pack (NDC 0173-1000-00).

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).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Risk of Embryo-Fetal Toxicity

- Advise patients that BREXAFEMME is contraindicated in pregnancy since it may cause fetal harm *[see Warnings and Precautions (5.1), Use in Specific Populations (8.1)]*.
- Inform females of reproductive potential that their healthcare provider will verify that they are not pregnant prior to initiating BREXAFEMME treatment *[see Dosage and Administration (2.3)]*.
- Advise females of reproductive potential that reassessing pregnancy status prior to each dose is recommended when BREXAFEMME is used monthly for 6 months for reduction in the incidence of RVVC *[see Dosage and Administration (2.3)]*.
- For treatment of VVC, advise females of reproductive potential to use effective contraception while taking BREXAFEMME and for 4 days after the last dose *[see Use in Specific Populations (8.3)]*.
- For reduction in the incidence of RVVC, advise females of reproductive potential to use effective contraception throughout the 6-month treatment period with BREXAFEMME and for 4 days after the last dose *[see Use in Specific Populations (8.3)]*.
- Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.1), Use in Specific Populations (8.1)]*.
- Advise patients who have inadvertently taken BREXAFEMME during pregnancy that there is a pregnancy safety study that monitors pregnancy outcomes. Encourage these patients to report their pregnancy to GlaxoSmithKline at 1-888-825-5249 *[see Use in Specific Populations (8.1)]*.

Important Administration Instructions

For treatment of VVC, inform the patient that each BREXAFEMME dose consists of 2 tablets. A total treatment course for VVC is 2 doses taken approximately 12 hours apart and consists of a total of 4 tablets.

For reduction in the incidence of RVVC, inform the patients that the total treatment course is for 6 months. Each dose consists of 2 tablets taken approximately 12 hours apart for a total daily dosage of 4 tablets, taken monthly for 6 months.

If the first 2 tablets are taken in the morning, the second 2 tablets should be taken that same day in the evening. If the first 2 tablets are taken in the afternoon or evening, the second 2 tablets should be taken the following morning.

Inform the patient that BREXAFEMME can be taken with or without food *[see Dosage and Administration (2.1)]*.

Concomitant Medications

Advise the patient to inform their health care provider if they are taking any other medications as certain medications can increase or decrease blood concentrations of BREXAFEMME or BREXAFEMME may increase or decrease blood concentrations of certain medications *[see Dosage and Administration (2.2)]*.

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Manufactured for:



GlaxoSmithKline
Durham, NC 27701

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BRX:2PI

PHARMACIST—DETACH HERE AND GIVE LEAFLET TO PATIENT

MEDICATION GUIDE

BREXAFEMME (BREX a fem)

(ibrexafungerp) tablets, for oral use

What is the most important information I should know about BREXAFEMME?

BREXAFEMME may cause serious side effects, including:

- **Harm to your unborn baby.** Treatment with BREXAFEMME during pregnancy may cause harm to your unborn baby.

  Women who can become pregnant may be asked by their healthcare provider to take a pregnancy test before each treatment with BREXAFEMME. Women who can become pregnant should use effective birth control throughout the duration of treatment with BREXAFEMME and for 4 days after the last dose of BREXAFEMME. Talk to your healthcare provider about birth control methods that may be right for you.
- See **"Do not take BREXAFEMME if you:"**

What is BREXAFEMME?

- BREXAFEMME is a prescription medicine used to treat vaginal yeast infection and reduce the number of recurrent vaginal yeast infections in adults and adolescent females who have started their menstruation.
- It is not known if BREXAFEMME is safe and effective in pre-adolescent females who have not started their menstruation.

Do not take BREXAFEMME if you:

- are pregnant or plan to become pregnant. BREXAFEMME may harm your unborn baby. Tell your healthcare provider if you are pregnant, think you might be pregnant, or plan to become pregnant.
- are allergic to ibrexafungerp.

Before you take BREXAFEMME, tell your healthcare provider about all of your medical conditions, including if you:

- are breastfeeding or plan to breastfeed. BREXAFEMME passes into your breast milk. You and your healthcare provider should decide the best way to feed your baby while taking BREXAFEMME.

BREXAFEMME may affect the way other medicines work, and other medicines may affect how BREXAFEMME works.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I take BREXAFEMME?

- Take BREXAFEMME exactly as your healthcare provider tells you to take it.
- Take BREXAFEMME tablets by mouth with or without food.

What are the possible side effects of BREXAFEMME?

- See **"What is the most important information I should know about BREXAFEMME?"**

The most common side effects of BREXAFEMME when used to treat vaginal yeast infection include:

- loose stools
- nausea
- stomach pain
- dizziness
- vomiting

The most common side effects of BREXAFEMME when used to reduce the number of recurrent vaginal yeast infections include:

- headache
- stomach pain
- loose stools
- nausea
- urinary tract infection
- tiredness (fatigue)

These are not all the possible side effects of BREXAFEMME.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store BREXAFEMME?

- Store BREXAFEMME at room temperature between 68°F to 77°F (20°C to 25°C).
- BREXAFEMME is supplied in child resistant packaging.

Keep BREXAFEMME and all medicines out of reach of children.

General information about the safe and effective use of BREXAFEMME.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BREXAFEMME for a condition for which it was not prescribed. Do not give BREXAFEMME to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about BREXAFEMME that is written for health professionals.

What are the ingredients in BREXAFEMME?

Active ingredient: ibrexafungerp

Inactive ingredients: Tablet core: butylated hydroxyanisole, colloidal silicon dioxide, crospovidone, magnesium stearate, mannitol, and microcrystalline cellulose. **Tablet film coating:** FD&C Blue #2, FD&C Red #40, hydroxypropyl cellulose, hydroxypropylmethyl cellulose 2910, talc and titanium dioxide.

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Manufactured for:

GSK

GlaxoSmithKline, Durham, NC 27701

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For more information about BREXAFEMME, call 1-888-825-5249 or visit our website at www.brexafemme.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: July/2026