CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

214900Orig1s001

Trade Name:	BREXAFEMME®
Generic or Proper Name:	ibrexafungerp
Sponsor:	Scynexis, Inc.
Approval Date:	June 15, 2022
Indication:	BREXAFEMME is a triterpenoid antifungal indicated for the treatment of adult and post-menarchal pediatric females with vulvovaginal candidiasis (VVC).

CENTER FOR DRUG EVALUATION AND RESEARCH

214900Orig1s001

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	**X**
Product Quality Review(s)	
Non-Clinical Review(s)	
Statistical Review(s)	
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	**X**
Other Reviews	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214900Orig1s001

APPROVAL LETTER

NDA 214900/S-001

SUPPLEMENT APPROVAL/FULFILLMENT OF POSTMARKET COMMITMENT

SCYNEXIS, Inc.
Attention: Glen D. Park, PharmD, MSJ
Vice President, Regulatory Affairs and Quality Assurance
1 Evertrust Plaza, 13th Floor
Jersey City, NJ 07302

Dear Dr. Park:

Please refer to your supplemental new drug application (sNDA) dated and received December 15, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Brexafemme (ibrexafungerp tablets), 150 mg.

This Prior Approval sNDA updates the Prescribing Information (PI) to include information related to the pharmacokinetics of ibrexafungerp in post-menarchal females and to add information related to the pharmacokinetics of ibrexafungerp in patients with hepatic impairment in subsection **8.4 Pediatric Use**, subsection **8.6 Hepatic Impairment**, and subsection **12.3 Pharmacokinetics**/Specific Populations, along with minor editorial updates throughout the PI.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

FULFILLMENT OF POSTMARKETING COMMITMENT

We have received your submission dated December 15, 2021, containing the final report for the following postmarketing commitment listed in the June 01, 2021, approval letter.

4069-3 Submit the final clinical study report for the oral ibrexafungerp pharmacokinetics and safety study in adolescent female subjects (SCY-078-120).

We have reviewed your submission and conclude that the above commitment was fulfilled.

We remind you that there are postmarketing requirements listed in the June 01, 2021, approval letter that are still open.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jacquelyn Rosenberger, PharmD, RAC, Senior Regulatory Project Manager, at (301) 796-9179.

Sincerely,

{See appended electronic signature page}

Dmitri Iarikov, MD, PhD
Deputy Director
Division of Anti-Infectives
Office of Infectious Diseases
Center for Drug Evaluation and Research

ENCLOSURE:

- Content of Labeling
  - Prescribing Information

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DMITRI IARIKOV
06/15/2022 02:45:09 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214900Orig1s001

LABELING

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 US Approval: 2021

----------INDICATIONS AND USAGE----------
BREXAFEMME is a triterpenoid antifungal indicated for the treatment of adult and post-menarchal pediatric females with vulvovaginal candidiasis (VVC). (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended dosage of BREXAFEMME in adult and post-menarchal pediatric females is 300 mg (two tablets of 150 mg) twice a day for one day, for a total treatment dosage of 600 mg. (2.1)
- BREXAFEMME may be taken with or without food. (2.1)
- Prior to initiating treatment, verify pregnancy status in females of reproductive potential. (2.3)

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

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

----------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.

----------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

FULL PRESCRIBING INFORMATION: CONTENTS

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Vulvovaginal Candidiasis

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

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

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

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

2.3 Pregnancy Evaluation Prior to Initiating Treatment

Verify the pregnancy status in females of reproductive potential prior to initiating treatment with BREXAFEMME *[see Contraindications (4), Warning and Precautions (5.1) and 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)*, and *Use in Specific Populations (8.1, 8.3)]*
- Patients with hypersensitivity to ibrexafungerp

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Fetal Toxicity

Based on findings from animal studies, BREXAFEMME use 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 hindpaw, absent ear pinna, and thoracogastroschisis at dose exposures greater or equal to approximately 5 times the human exposure at the recommended human dose (RHD).

Prior to initiating treatment with BREXAFEMME, verify the pregnancy status in females of reproductive potential. Advise females of reproductive potential to use effective contraception during treatment 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

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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.

A total of 545 patients were exposed to BREXAFEMME in two clinical trials of women with VVC (Trial 1 and Trial 2). The women were treated with BREXAFEMME 300 mg (two 150 mg tablets) twice a day, 12 hours apart, for one day. The women were 18 to 76 years of age (mean 34 years); 69% were White and 28% were Black or African American; 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 Rates ≥2% in BREXAFEMME-Treated Patients

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[1]	62 (11.4%)	14 (5.1%)
Dizziness[2]	18 (3.3%)	7 (2.5%)
Vomiting	11 (2.0%)	2 (0.7%)

[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:

Concomitant Drugs	Effect on Ibrexafungerp Concentration	Recommendation
Strong CYP3A inhibitors: (e.g., ketoconazole, itraconazole)	Significantly increased	Reduce the BREXAFEMME dosage *[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-gp and OATP1B3 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, 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 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 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, thoracogastroschisis, 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, 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

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 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

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

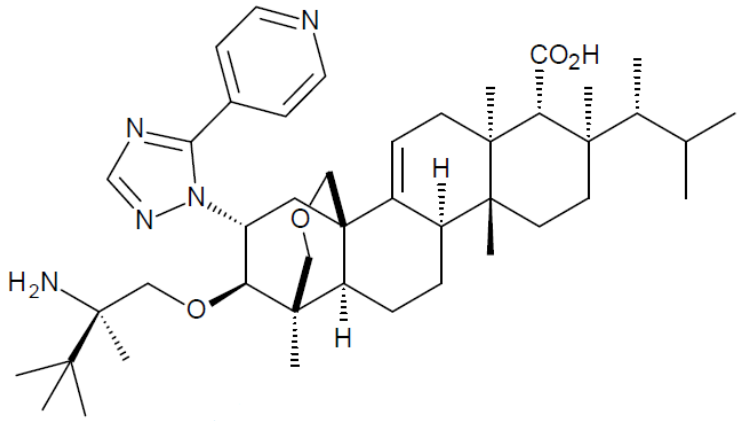
There is no experience with overdosage of BREXAFEMME.

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)-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:



• $C_6H_8O_7$

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 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•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 (800-1000 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: 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 1250 to 1500 mg (2.1 to 2.5 times the approved recommended daily dose) for two days followed by 750 mg (1.25 times the approved recommended daily dose) once daily for 3-7 days.

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.

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.

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 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 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 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 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

	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[1]	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[2]	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	

[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).

17 PATIENT COUNSELING INFORMATION

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

Risk of Fetal Toxicity

BREXAFEMME is contraindicated in pregnancy since it may cause fetal harm. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.1) and 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 SCYNEXIS, Inc. at 1-888-982-7299 *[see Use in Specific Populations (8.1)]*.

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)]*.

Important Administration Instructions

Inform the patient that each BREXAFEMME dose consists of two tablets. A total treatment course is two doses taken approximately 12 hours apart and consists of a total of four tablets.

If the first two tablets are taken in the morning, the second two tablets should be taken that same day in the evening. If the first two tablets are taken in the afternoon or evening, the second two 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)]*.

Manufactured for:
SCYNEXIS, Inc.
Jersey City, NJ

Patent: www.scynexis.com/product/patent

BREXAFEMME® is a registered trademark of SCYNEXIS, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214900Orig1s001

CLINICAL REVIEW(S)

Memorandum: Clinical Review of Safety Data Associated with Labeling Supplement

NDA: 214900/S-001

Sponsor: Scynexis

Drug Product: Ibrexafungerp

Reviewer: Shrimant Mishra MD, MPH

Date: June 14th, 2022

Studies Reviewed:

SCY-078-120: A PHASE 1, OPEN-LABEL STUDY TO EVALUATE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF ORAL IBREXAFUNGERP (SCY-078) IN ADOLESCENT FEMALE SUBJECTS

SCY-078-112: A PHASE 1, OPEN-LABEL STUDY TO EVALUATE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF IBREXAFUNGERP (SCY-078) IN SUBJECTS WITH HEPATIC IMPAIRMENT

Background:

Ibrexafungerp is an antifungal agent that is an orally active, semi-synthetic triterpenoid derivative of the natural product enfumafungin. It was approved by the Agency in 2021 for the treatment of adult and post-menarchal pediatric females with vulvovaginal candidiasis (VVC). The Sponsor has recently conducted two pharmacokinetic and safety studies, one in subjects with hepatic impairment and another in adolescent females with VVC, and has now submitted a labeling supplement based on the study results. Though the Sponsor's proposed labeling is focused on language related to Clinical Pharmacology, safety data was also submitted and is the subject of this review.

Study SCY-078-120

This was a Phase 1, open-label, parallel-group study consisting of 2 cohorts of adolescent female subjects who were enrolled based on their age and presentation with symptoms of vaginitis, which in the opinion of the investigator, were caused by a *Candida spp.* infection and would benefit from antifungal treatment. Within 1 week prior to dosing, subjects underwent a screening visit that included assessment of medical history, physical examination, determination of vital signs, clinical laboratory testing, and an electrocardiogram (ECG). Eligible subjects had symptoms of vaginitis (e.g., vaginal discharge, itching, burning, irritation), when feasible and appropriate for subject's age a vaginal swab sample may have been obtained for confirmation of *Candida spp.* infection via microscopic observation with 10% potassium hydroxide (KOH). Obtaining a vaginal sample for 10% KOH analysis was not mandatory and the diagnosis of suspected *Candida spp.* vaginitis was enough for enrollment into the study if in the opinion of the investigator, the vaginitis would benefit from receiving antifungal therapy. Subjects enrolled in the study received one day of BID (twice daily) oral 300 mg ibrexafungerp citrate salt tablets (2 x 150-mg tablets). The subjects were enrolled in two cohorts by age; subjects from 12 to 14 years of age (Cohort A) and subjects from 15 to 17 years of age (Cohort B) at the screening visit.

Cohorts A and B were enrolled and dosed in parallel, and both received one day of BID oral doses of ibrexafungerp 300-mg citrate tablets given within 30 minutes of consuming food.

Subjects were admitted to the clinical unit on Day -1. Subjects had blood samples taken predose and up to 46 hours post first dose for determination of ibrexafungerp concentrations.

Safety was monitored throughout the study by clinical and laboratory evaluations. If clinical improvement of the vaginitis symptoms was not observed by Day 5, the investigator was to treat with standard of care medicine and recorded medication on the appropriate case report form. A follow-up poststudy visit occurred approximately 10 ±3 days after the last dose of study drug. Adverse events were collected up to 30 days post dose by phone call and a visit was to be scheduled only for those experiencing an adverse event.

Efficacy based on resolution of vaginitis signs and symptoms were collected on Day 10 ±3 [test of cure (TOC)] using a standardized scales. Tablet acceptability was also collected by questioning participants as to size and taste.

Ten subjects enrolled in the study. Cohort A enrolled 4 subjects, all of which completed treatment. Cohort B enrolled 6 subjects, all of which also completed treatment.

There were no deaths or serious adverse events (SAEs) reported in the study. Three TEAEs were reported in two subjects all of which were mild and resolved without sequelae. Two of the AEs were due to vomiting (in two subjects roughly 90 minutes after morning dose) and one was due to abdominal pain. All three AEs were considered possibly related to the study drug.

No significant laboratory changes (hematology, chemistry, coagulation parameters, urinalysis), changes in vital signs (systolic blood pressure, diastolic blood pressure, respiratory rate, heart rate, temperature, or ECG changes (including QT interval) were noted.

Study SCY-078-112

This was a Phase 1, open-label, parallel-group, multicenter study consisting of 3 cohorts of subjects who were enrolled based on their hepatic function assessed by the Child-Pugh classification. Within 4 weeks prior to dosing, subjects underwent a screening visit that included assessment of Child-Pugh score, medical history, physical examination, determination of vital signs, clinical laboratory testing, and an ECG.

Subjects enrolled in the study received single-dose administration of oral 500-mg ibrexafungerp citrate salt tablets (2 x 250-mg tablets) in the fasted state to investigate the PK, safety, and tolerability of ibrexafungerp in subjects with mild (Cohort B) and moderate hepatic impairment (Cohort C), as compared to that of healthy matched control subjects (Cohort A).

Subjects were admitted to the clinical site on the evening of Day -1 and fasted for 10 hours prior to dosing on Day 1. Subjects had blood samples taken pre-dose and up to 120-hours post dose for determination of ibrexafungerp concentrations.

Safety was monitored throughout the study by clinical and laboratory evaluations. A follow-up poststudy visit occurred approximately 14 days after the last dose of study drug.

A total of 32 subjects enrolled in the study. Sixteen subjects were enrolled in Cohort A and 8 subjects each were enrolled in Cohorts B and C, respectively. All subjects completed dosing.

There were no deaths or SAEs reported. Fifteen subjects reported TEAEs, including 10 subjects with mild, 4 subjects with moderate, and 1 subject with a severe TEAE. Diarrhea was reported in 10 subjects, headache in four subjects, and urinary tract infections in two subjects. Other reported TEAEs were abdominal pain, flatulence, nausea, pharyngitis, sinusitis, polyuria and urticaria.

A severe TEAE of nausea occurred in a healthy subject and resolved the same day without sequelae with the use of ©Emetrol (dextrose, levulose, phosphoric acid). Four subjects had moderate TEAEs including diarrhea, flatulence, and headache.

All gastrointestinal TEAEs, including diarrhea (except in one subject), flatulence, abdominal pain and nausea were considered related to study drug. One TEAE of headache and polyuria (both in the same subject) were also considered related to study drug.

No significant laboratory changes (hematology, chemistry, coagulation parameters, urinalysis), changes in vital signs (systolic blood pressure, diastolic blood pressure, respiratory rate, heart rate, temperature, or ECG changes (including QT interval) were noted.

Conclusion:

The safety findings in the above studies did not suggest any new safety signals. The gastrointestinal AEs noted in both studies are already documented in the current labeling. Headache is not included in the labeling because it occurred at similar frequencies in ibrexafungerp-treated and placebo-treated subjects in the phase 3 VVC randomized controlled trials (moreover in the above studies, only one of four headache events was considered treatment-related). No new safety labeling changes are recommended.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHRIMANT MISHRA
06/15/2022 01:56:20 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214900Orig1s001

CLINICAL PHARMACOLOGY REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY MEMO

NDA	214900/S-001
Submission Date	12/15/2021
Drug	Ibrexafungerp (BREXAFEMME)
OCP Reviewer	Abhay Joshi, PhD
OCP Team Leader	Zhixia (Grace) Yan Danielsen, PhD
OCP Division	DIDP
OND Division	DAI
Applicant	Scynexis Inc.
Submission Type	Labeling supplement
Formulation	Oral tablets: 150 mg of ibrexafungerp
Indication	Treatment of adult and post-menarchal pediatric females with vulvovaginal candidiasis
Dosage and Administration	300 mg (two tablets of 150 mg) twice a day for one day, for a total treatment dosage of 600 mg

Summary:

The Applicant submitted a labeling supplement and proposed revisions to the Ibrexafungerp prescribing information. The submission also contained a report for Study SCY-078-120 to address the following postmarketing commitment (PMC) under NDA 214900:

> **4069-3:** Submit the final clinical study report for the oral ibrexafungerp pharmacokinetics and safety study in adolescent female subjects (SCY-078-120)

See clinical pharmacology review by Dr. Miglis in DARRTS dated 06/15/2022 for the assessment of Study SCY-078-120 and labeling recommendations that were communicated to the Applicant.

Recommendations: PMC 4069-3 is fulfilled from a clinical pharmacology perspective.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ABHAY JOSHI
06/29/2022 04:01:16 PM

ZHIXIA YAN
06/29/2022 04:05:01 PM

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	214900/S-001
Submission Date	12/15/2021
Drug	Ibrexafungerp (BREXAFEMME)
OCP Reviewer	Cristina Miglis, PharmD, MS, BCPS
OCP Team Leader	Abhay Joshi, PhD
OCP Division	DIDP
OND Division	DAI
Applicant	Scynexis Inc.
Submission Type	Labeling supplement
Formulation	Oral tablets: 150 mg of ibrexafungerp
Indication	Treatment of adult and post-menarchal pediatric females with vulvovaginal candidiasis
Dosage and Administration	300 mg (two tablets of 150 mg) twice a day for one day, for a total treatment dosage of 600 mg

1. Overview

The Applicant has submitted a labeling supplement and proposes revisions to the Ibrexafungerp prescribing information. Specifically, the Applicant proposes to include information on the pharmacokinetics of ibrexafungerp in post-menarchal females and adult subjects with hepatic impairment in the Specific Population subsection of Section 12.3. The submission includes two clinical studies (Study SCY-078-120 and Study SCY-078-112) that evaluated PK in adolescent females and subjects with hepatic impairment.

Study SCY-078-120 is conducted to address a postmarketing commitment under NDA 214900 for the treatment of vulvovaginal candidiasis (VVC). During the original approval, the ibrexafungerp treatment was not evaluated in adolescent females. Instead, the similarity of the disease pathophysiology in postmenarchal adolescents and adult women allowed the extrapolation of efficacy for VVC treatment.

Study SCY-078-112 was recommended as ibrexafungerp is eliminated mainly via metabolism and biliary excretion. Specifically, 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. The study was initiated prior to the approval of original NDA submission, however, subject enrolment to this study was suspended due to the COVID-19 pandemic. The Agency agreed that study completion was not essential for NDA approval as the ibrexafungerp treatment of VVC is a single day treatment. (b) (4)

Recommendations: Clinical pharmacology related labeling revisions proposed by the Applicant were reviewed and the review team's recommendations discussed in Section 3 of this review were communicated to the Applicant. The Applicant did not agree with the review team's recommendations and proposed further revisions, which were found to be reasonable. See Section 3 of this review for complete details. The Office of Clinical Pharmacology recommends the approval of this labeling supplement.

2. Clinical Pharmacology Summary Findings

Study SCY-078-120: Adolescent PK Study

This was a Phase 1, open-label study to evaluate the PK, safety, and tolerability of oral ibrexafungerp in adolescent female subjects. The study enrolled female adolescent subjects with VVC in one of the following two cohorts by age:

- Cohort A: 4 adolescent female subjects ages 12 to 14 years (Weight range: 41 – 70 kg)
- Cohort B: 6 adolescent female subjects ages 15 to 17 years (Weight range: 43 – 80 kg)

All subjects received oral ibrexafungerp 300 mg (2 X 150-mg citrate salt tablets) twice daily, administered 12 hours apart. This is the approved dosing regimen for treatment of VVC in adults and post-menarchal pediatric females. Ibrexafungerp was administered within 30 minutes of consuming a meal (see Table 1 for meal composition).

Table 1. Composition of Meal Used in Study SCY-078-120

Meal Type	Total Kcal	Fat		
		Kcal	Grams	Percent
Standard	~500 - 700	~125 – 400	~15 - 45	~26 - 40

Source: Study SCY-078-120

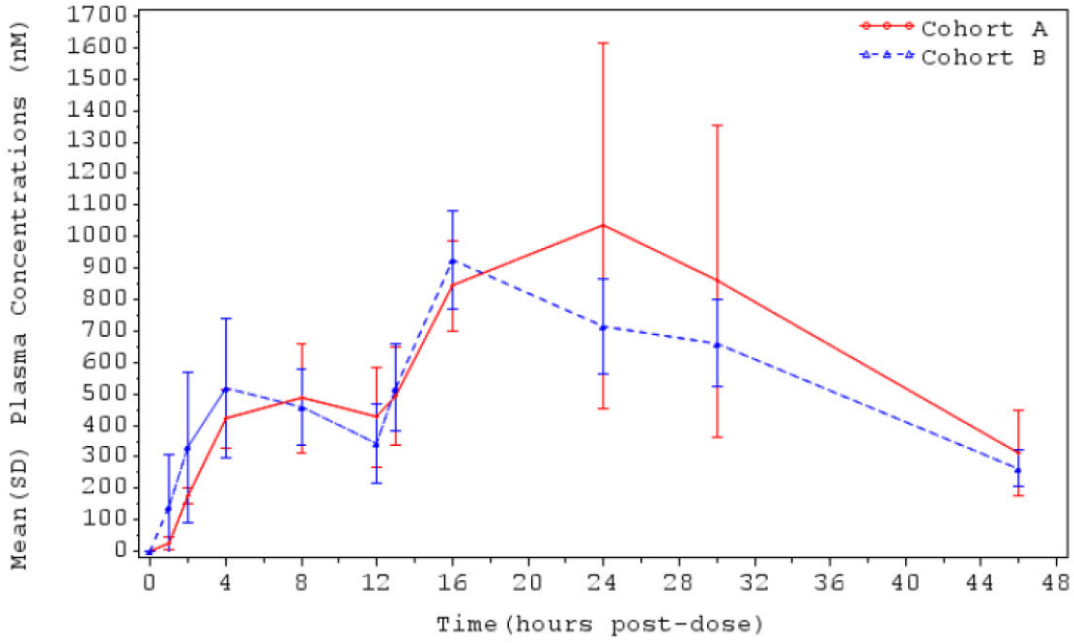
Reviewer's Comments: Ibrexafungerp is labeled to be taken with or without food. Following administration of ibrexafungerp to healthy volunteers, the ibrexafungerp C_{max} increased 32% and the AUC increased 38% with a high fat meal (800-1000 calories; 50% calories from fat), compared to fasted conditions. This exposure change is not considered clinically significant (NDA 214900; BREXAFEMME label).

Blood samples were collected pre-dose and at 1, 2, 4, 8, 12 (prior to the second dose), 13, 16, 24, 30, and 46 hours post first dose for determination of ibrexafungerp plasma concentrations using a validated LC-MS/MS method.

A previously developed population PK model in healthy adult subjects and patients with VVC was updated with the adolescent PK data from Study SCY-078-120. For a more comprehensive review of this model, see NDA 214900; BREXAFEMME; Multidisciplinary Review, Section 16.4.3 Pharmacometrics Review; Version Date 10/12/2018).

Plasma ibrexafungerp concentration-time plots by cohort are presented in Figure 1. Plasma-concentration time profiles were generally similar for Cohort A (adolescent females 12 to 14 years) and Cohort B (adolescent females 15 to 17 years) for the first dose and were slightly higher in Cohort A following administration of the second dose. Plasma ibrexafungerp pharmacokinetic parameters for each Cohort are summarized in Table 3.

Figure 1. Mean (±SD) Plasma Ibrexafungerp Concentration-Time Profiles by Cohort (Linear Plot) – PK Population



Source: Study SCY-078-120

Reviewer's Comment: Higher concentrations were not associated with more adverse events in Cohort A compared to Cohort B. In general, Ibrexafungerp was well tolerated, and all treatment-related AEs were mild in intensity (Table 2).

Table 2. Incidence of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Safety Population

MedDRA System Organ Class Preferred Term	**Number (Percent) of Subjects**		
	Cohort A (N=4)	**Cohort B (N=6)**	**All Subjects (N=10)**
Total Number of TEAEs	0	3	3
Total Number of Subjects with TEAEs	0	2 (33.33)	2 (20.0)
Gastrointestinal Disorders	**0**	**2 (33.3)**	**2 (20.0)**
Vomiting	0	2 (33.3)	2 (20.0)
Abdominal Pain	0	1 (16.7)	1 (10.0)

Source: Study SCY-078-120
Cohort A: Adolescent female subjects ages 12 to 14 years; Cohort B: Adolecent female subjects ages 15 to 17 years.

Table 3. Plasma Ibrexafungerp Pharmacokinetic Parameters Summarized by Cohort Following Oral Administration

Parameter (unit)	Statistic	Cohort A (N=4)	Cohort B (N=4)	All Subjects (N=10)
AUC0-12 (h•nM)	N	4	6	10
	Mean (SD)	4357 (1276)	4720 (1333)	4574 (1251)
	CV%	29.28	28.25	27.35
	Median	4348	4936	4576
	Min, Max	2907, 5823	2623, 6135	2623, 6135
AUC12-24 (h•nM)	N	4	6	10
	Mean (SD)	9982 (2996)	9160 (1702)	9489 (2187)
	CV%	30.02	18.58	23.05
	Median	9397	9598	9598
	Min, Max	7197, 13936	6384, 10915	6384, 13936
AUC12-∞ (h•nM)	N	3	3	6
	Mean (SD)	34532 (15423)	27444 (979)	30988 (10517)
	CV%	44.66	3.57	33.94
	Median	29957	27029	27796
	Min, Max	21914, 51724	26740, 28562	21914, 51724
Cmax (nM) (First Dose)	N	4	6	10
	Mean (SD)	493.6 (164)	589.6 (178)	551.2 (170)
	CV%	33.13	30.19	30.88
	Median	489.1	635.7	583.65
	Min, Max	313.7, 682.3	339.8, 819.3	313.7, 819.3
Tmax (h) (First Dose)	N	4	6	10
	Median	8.00	4.00	6.00
	Min, Max	4.00, 8.00	2.00, 8.00	2.00, 8.00
	Mean (SD)	7.00 (2.00)	5.00 (2.45)	5.80 (2.39)
	CV%	28.57	48.99	41.28
Cmax (nM) (Second Dose)	N	4	6	10
	Mean (SD)	1123.4 (510)	924.5 (155)	1004.1 (333)
	CV%	45.39	16.77	33.12
	Median	965.9	957.0	957.0
	Min, Max	698.7, 1863	680.9, 1089	680.9, 1863
Tmax (h) (Second Dose)	N	4	6	10
	Median	12.00	4.00	4.00
	Min, Max	4.00, 12.00	4.00, 4.00	4.00, 12.00
	Mean (SD)	10.00 (4.00)	4.00 (0.00)	6.40 (3.86)
	CV%	40.00	0.00	60.38
t½ (h)	N	4	6	10
	Mean (SD)	15.22 (3.41)	16.33 (2.62)	15.89 (2.83)
	CV%	22.39	16.03	17.81
	Median	13.73	16.47	15.25
	Min, Max	13.11, 20.31	12.70, 20.39	12.70, 20.39

Source: Study SCY-078-120
Cohort A: Adolescent female subjects ages 12 to 14 years; Cohort B: Adolecent female subjects ages 15 to 17 years.

Post-hoc estimates from the final population PK model were used to predict PK profiles for the adult VVC patients (N=46) and adolescent VVC patients (N=10) who were included in the final population PK model receiving one day dosing of ibrexafungerp citrate tablets of 300 mg BID taken with food (snack, standard meal, or high-fat meal). Ibrexafungerp exposures estimates

(Cmax and AUC_{0-24}) derived from post-hoc estimates from adult and adolescent VVC patients are summarized in Table 4. The range of exposures in adolescents was similar to those in adults.

Table 4. Summary of Predicted exposures (Cmax, AUC_{0-24}) of VVC patients (Adult and Adolescent) Receiving 1 Day Ibrexafungerp Dosing of 300 mg BID With food (snack, standard meal, or high-fat meal)

Population	Age (year)	AUC_{0-24} (ng.h/mL)				C_{max} (ng/mL)			
		5th	Mean	Median	95th	5th	Mean	Median	95th
Adolescents	13-17	7261	10459	11185	13526	455	661	702	872
Adults	19-63	6216	9968	9983	13438	408	634	639	841

Source: Study SCY-078-120

Reviewer's Comment: The predicted adult exposures from this analysis are similar to the predicted adult exposures in patients with VVC in the current ibrexafungerp label, i.e., Mean (CV%) AUC_{0-24} of 9867 (15%) ng•h/mL and C_{max} of 629 (15%) ng/mL following 300 mg twice a day for 2 doses under fed conditions.

Study SCY-078-112: Hepatic Impairment PK Study

This was a Phase 1, open-label study to evaluate the PK, safety, and tolerability of ibrexafungerp in subjects with hepatic impairment. The study enrolled 8 subjects with mild hepatic impairment (Child-Pugh group A) and 8 subjects with moderate hepatic impairment (Child-Pugh group B). These 16 subjects were individually matched by enrolling 16 healthy subjects based on age (18 to 70 years), sex (male or female), race (white, black or African American) and body mass index (18 to 45 kg/m^2). All subjects received a single oral dose of 500 mg ibrexafungerp citrate salt formulation (2 X 250-mg tablets) in the fasted state.

Reviewer's Comment: Two strengths of the ibrexafungerp citrate salt tablet were used in clinical development. The 150 mg strength citrate salt tablet was used to support clinical studies in VVC, (b) (4) *Both tablets have identical quantitative composition (%w/w) and similar in vitro dissolution profiles.*

Blood samples for the determination of ibrexafungerp concentrations were taken pre-dose and up to 120-hours post-dose. A previously conducted clinical ADME study showed that Ibrexafungerp has no major circulating metabolites and therefore, metabolite assessment was not included in this study.

PK parameters' Geometric Least Square Means (GLSM) and GLSM ratios of hepatic impairment subjects with their matched healthy subjects are shown in Table 5. Compared to the healthy control/matched subjects, while AUC values are similar, the mean Cmax values in subjects with hepatic impairment are lower, i.e., approximately 30% and 50% lower in subjects mild and moderate hepatic impairment, respectively. This difference is not expected to be clinically significant since the AUC estimate is the PK/PD driver associated with ibrexafungerp's activity.

Table 5. Comparison of Ibrexafungerp Plasma Pharmacokinetic Parameters for Mild and Moderate Hepatic Impairment Subjects versus Healthy Matched Subjects: Geometric Least Square Means and Ratios

Analyte	Comparison	PK Parameter	N[a]	Healthy Matched (reference) GLSM		Impaired (test) GLSM	GLSM Ratio (test/ reference)	90% Confidence Interval for GLSM Ratio	Intrasubject CV%
SCY-078	Mild versus Mild Matched	$AUC_{0\text{-last}}$	8	10900		10400	0.960	(0.738,1.25)	28.2
		$AUC_{0\text{-}\infty}$	8	11600		12700	1.09	(0.842,1.41)	27.9
		C_{max}	8	424		313	0.740	(0.504,1.09)	42.3
	Moderate versus Moderate Matched	$AUC_{0\text{-last}}$	8	9550		7350	0.770	(0.506,1.17)	50.4
		$AUC_{0\text{-}\infty}$	8	10200		9080	0.892	(0.581,1.37)	51.7
		C_{max}	8	397		219	0.552	(0.383,0.796)	43.5

Source: Study SCY-078-112

3. Summary of Labeling Edits

Overall, we agree with the Applicant's conclusions for Study SCY-078-120 and Study SCY-078-112. Based on the review of aforementioned two studies, we recommended edits to the Applicant's proposed labeling revisions (Table 6). The Applicant submitted a response to these proposed edits on May 17, 2022 and accepted the majority of the Division's recommendations with a few exceptions as discussed below.

One exception was the review team's recommendation to indicate that ibrexafungerp should be avoided in patients with severe hepatic impairment. The Applicant did not agree and proposed (b) (4) The review team did not agree with the proposal as the (b) (4). In addition, (b) (4), it should be underscored that the current language is based on the VVC indication where ibrexafungerp is given as a once daily dosing regimen. Therefore, given the unknown safety profile of the drug in severe hepatic impairment, the review team proposed to revise this language to indicate that the drug has not been studied in this population and conveyed to the Applicant that this language may need further revisions if additional indications are pursued that require multiple daily doses of ibrexafungerp. The Applicant agreed.

An additional exception was the review team's recommendation to add a statement in Section 12.3 highlighting the unknown effect of hepatic impairment on ibrexafungerp's plasma protein binding. This statement was recommended due to 1) unbound plasma ibrexafungerp concentrations not being measured in Study SCY-078-112 and 2) Ibrexafungerp being highly protein bound (greater than 99%). The Applicant disagreed with the review team's proposal and cited the 2003 *Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function* that recommends unbound plasma concentrations be determined for drugs that are: highly extracted by the liver (extraction ratio > 0.7) and that are extensively bound to plasma

proteins (fraction unbound < 10 percent). The Applicant concluded that protein binding evaluation in subjects with hepatic impairment is not needed based on the following:

1) Ibrexafungerp has a low liver extraction ratio of 0.17
2) Subjects with mild and moderate hepatic impairment are expected to have little change in plasma protein concentrations as supported by similar plasma albumin concentrations observed in Study SCY-078-112 (i.e., mild hepatic impairment, moderate hepatic impairment, and healthy controls median values of 4.5 mg/dL, 3.75 mg/dL, and 4.2 mg/dL, respectively).

The review team acknowledges the language in the 2003 guidance but disagrees that protein binding should not be considered due to ibrexafungerp's low extraction ratio. Given the inverse relationship between clearance and protein binding reported in literature[1], there is a potential scenario where the systemic clearance increases for a low extraction ratio drug. In such a scenario, collection of unbound plasma drug concentrations would allow for an evaluation of whether considerations based on total or free drug concentrations are more appropriate. However, the review team agreed that the statement could be removed for the current approved indication of VVC and conveyed to the Applicant that any changes to the approved indication and/or dosage beyond a single daily dose may require further deliberation with respect to the need for revised language.

A complete list of the recommended edits to the Applicant's proposed labeling revisions are summarized below. The Applicant proposed revisions are in red and the review team's recommendations are in blue.

Table 6. Summary of Labeling Edits

	Recommended Edits	Final Agreed Upon Labeling
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, n~~N~~o clinically meaningful differences in the pharmacokinetics of ibrexafungerp were observed in geriatric patients compared to younger adults [see Clinical Pharmacology (12.3)].	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 ~~in geriatric patients~~ compared to younger adults *[see Clinical Pharmacology (12.3)].*
Rationale	*The review team proposed revisions to note that geriatric PK information is from a clinical PK study.*	*The Applicant proposed removal of the second mention of "in geriatric patients" as it was redundant to the first part of the sentence.*
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). There is insufficient	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). There is insufficient information to determine the safety

1 Khateeb E, et al. Review article: time to revisit Child-Pugh score as the basis for predicting drug clearance in hepatic impairment. Aliment Pharmacol Ther. 2021;00:1–14.

	Recommended Edits	Final Agreed Upon Labeling
	information to determine the safety of BREXAFEMME in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, BREXAFEMME is not recommended for use in patients with severe hepatic impairment [see Clinical Pharmacology (12.3)].	of BREXAFEMME in patients with severe hepatic impairment (Child-Pugh Class C). ~~Therefore, BREXAFEMME is not recommended for use in patients with severe hepatic impairment.~~ (b) (4) –Administration of BREXAFEMME in patients with severe hepatic impairment (Child-Pugh Class C) has not been studied. *[see Clinical Pharmacology (12.3)].*
Rationale	*The review team recommended inclusion of Section 8.6 Hepatic Impairment based on the results of the hepatic impairment PK study (Study SCY-078-112).*	*The Applicant proposed to indicate ibrexafungerp should* (b) (4) *rather than not recommended in this population as proposed by the review team. In response, the review team recommended removing any specific recommendation and adding that ibrexafungerp has not been studied in severe hepatic impairment. The Applicant agreed.*
12.3 Pharmacokinetics	Specific Populations ~~Geriatric Patients~~ *Post-Menarchal Pediatric Females and Geriatric Patients* ~~A comparison of elderly healthy males and females (range of 65 to 76 years) with young healthy males (range of 20 to 45 years) showed that the geometric means ratio (GMR) of pooled elderly males and females / young males for the AUC0-inf (90% CI) was 1.39 (1.19, 1.62). Dose adjustment for age is not required.~~ 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). ~~Dose adjustment for age is not required.~~ *Patients with Hepatic Impairment* The pharmacokinetics of ibrexafungerp were (b) (4) not altered in (b) (4) subjects with mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) hepatic impairment (b) (4) when the total AUC estimates were (b) (4)	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 effect of hepatic impairment on ibrexafungerp's plasma protein binding is unknown.~~ The impact of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of ibrexafungerp is unknown.

	Recommended Edits	Final Agreed Upon Labeling
	compared to healthy subjects. The effect of hepatic impairment on ibrexafungerp's plasma protein binding is unknown. (b) (4) [redacted] he impact of (b) (4) severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of ibrexafungerp is unknown.	
Rationale	*As per Clinical Pharmacology Section of Labeling (final guidance) available at https://www.fda.gov/media/74346/download, inclusion of subheading "Post-Menarchal Pediatric Females and Geriatric Patients" was proposed to identify the referenced subpopulations.* *Dosage adjustment related language was removed as per the aforementioned Clinical Pharmacology guidance.* *Exposure parameter AUC was specified.* *Inclusion of a statement on the lack of information related to the effect of hepatic impairment on ibrexafungerp's plasma protein binding was recommended.*	*The Applicant proposed deletion of the sentence "The effect of hepatic impairment on ibrexafungerp's plasma protein binding is unknown" on the basis that ibrexafungerp does not have a high liver extraction ratio. The review team agreed but underscored that any changes to the recommended indication and/or dosage in the future may require further deliberation with respect to the need for revised language.*

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CRISTINA M MIGLIS
06/15/2022 11:08:01 AM

ABHAY JOSHI
06/15/2022 11:21:30 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214900Orig1s001

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

From:	Glen Park
To:	Rosenberger, Jacquelyn
Subject:	[EXTERNAL] RE: NDA 214900 [ibrexafungerp] Labeling Supplement - Division Comments
Date:	Tuesday, June 7, 2022 8:53:18 AM
Attachments:	image007.png image008.png

Received. Thank you.

Glen D. Park, PharmD, MSJ
Vice President, Regulatory Affairs & Quality Assurance

SCYNEXIS
| Work: +1.201.884.5495 |Mobile: +1.212.945.8512
| glen.park@scynexis.com | www.scynexis.com |

From: Rosenberger, Jacquelyn <Jacquelyn.Rosenberger@fda.hhs.gov>
Sent: Tuesday, June 7, 2022 8:49 AM
To: Glen Park <glen.park@scynexis.com>
Subject: NDA 214900 [ibrexafungerp] Labeling Supplement - Division Comments

Good morning Glen,

The Division has reviewed the revised labeling for NDA 214900, Supplement 001. Please see the attached for our comments. After Scynexis' review, please send back the label to me no later than **COB Thursday, June 9, 2022.** If you have any questions, please do not hesitate to reach out to me.

Please confirm receipt of this email.

Best regards,
Jackie

Jacquelyn Rosenberger, PharmD, RAC
Senior Regulatory Project Manager, Anti-Infectives Group 2

Division of Regulatory Operations for Infectious Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9179
Jacquelyn.rosenberger@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

APPEARS THIS WAY IN ORIGINAL

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JACQUELYN C ROSENBERGER
06/07/2022 09:01:30 AM

From:	Glen Park
To:	Rosenberger, Jacquelyn
Subject:	[EXTERNAL] RE: NDA 214900 S-001 [Brexafemme] Labeling Comments
Date:	Thursday, May 5, 2022 9:39:30 AM
Attachments:	image007.png image008.png

Received. Thank you.

Glen D. Park, PharmD, MSJ
Vice President, Regulatory Affairs & Quality Assurance

SCYNEXIS

| Work: +1.201.884.5495 |Mobile: +1.212.945.8512
| glen.park@scynexis.com | www.scynexis.com |

From: Rosenberger, Jacquelyn <Jacquelyn.Rosenberger@fda.hhs.gov>
Sent: Thursday, May 5, 2022 9:23 AM
To: Glen Park <glen.park@scynexis.com>
Subject: NDA 214900 S-001 [Brexafemme] Labeling Comments

Good morning Glen,

The Division has reviewed the proposed revised labeling for NDA 214900, supplement 1. Please see the attached for the label with our comments. After your review of the label, please send your revised labeling to the NDA by **COB May 18th.** If you have any questions, please do not hesitate to reach out to me.

Please confirm receipt of this email.

Best regards,
Jackie

Jacquelyn Rosenberger, PharmD, RAC
Senior Regulatory Project Manager, Anti-Infectives Group 2

Division of Regulatory Operations for Infectious Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9179
Jacquelyn.rosenberger@fda.hhs.gov

APPEARS THIS WAY IN ORIGINAL

15 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JACQUELYN C ROSENBERGER
05/05/2022 09:46:35 AM

From: Glen Park
To: Rosenberger, Jacquelyn
Subject: [EXTERNAL] RE: NDA 214900 [Brexafemme] Labeling Supplement Information Request
Date: Friday, January 7, 2022 9:12:05 AM
Attachments: image007.png
image008.png

Hi Jackie – received.

Glen D. Park, PharmD, MSJ
Vice President, Regulatory Affairs & Quality Assurance

SCYNEXIS

| Work: +1.201.884.5495 |Mobile: +1.212.945.8512
| glen.park@scynexis.com | www.scynexis.com |

From: Rosenberger, Jacquelyn <Jacquelyn.Rosenberger@fda.hhs.gov>
Sent: Friday, January 7, 2022 9:02 AM
To: Glen Park <glen.park@scynexis.com>
Subject: NDA 214900 [Brexafemme] Labeling Supplement Information Request

Good morning Glen,

The team is in process of review of the labeling supplement for NDA 214900 and has the following request for information:

Clinical Pharmacology Information Request
Regarding the submission dated December 15, 2021, under NDA 214900 (Serial 31), provide the bioanalytical method validation and performance reports for Studies SCY-078-120 and SCY-078-112. To facilitate efficient review of the bioanalytical method performance, please also complete the provided method validation template for each study.

In addition, we recommend you submit data on the effect of hepatic impairment on unbound plasma ibrexafungerp concentrations given the drug is extensively bound to plasma proteins. For more information see Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function (https://www.fda.gov/media/71311/download).

Please respond within two weeks from the receipt of this request.

Please confirm receipt of this email.

Best regards,
Jackie

Jacquelyn Rosenberger, PharmD, RAC
Regulatory Project Manager, Anti-Infectives Group 2

Division of Regulatory Operations for Infectious Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9179
Jacquelyn.rosenberger@fda.hhs.gov

BioAnalytical method validation summary

Regarding NDA 214900/S-001, please complete the bioanalytical method performance summary table below for the bioanalytical assay and its performance in Study SCY-078-120 and SCY-078-112. Do not delete any rows from the tables. Include any other additional bioanalytical information in a separate table that might be relevant for review in your NDA submission. We recommend you submit these tables in eCTD Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods as pdf and docx formats.

Table 1. Summary method performance of a bioanalytical method to measure [analyte] in [matrix]

Bioanalytical method validation report name, amendments, and hyperlinks			
Method description			
Materials used for calibration curve & concentration			
Validated assay range			
Material used for QCs & concentration			
Minimum required dilutions (MRDs)			
Source & lot of reagents (LBA)			
Regression model & weighting			
Validation parameters	**Method validation summary**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	x	Eg. Table 1 of report # 123
	Cumulative accuracy (%bias) from LLOQ to ULOQ Product A Product B and/or C [Applicable for bioanalytical method in 351(k). Delete for other applications]	 x to y% x to y%	Table y of 2 report #123
	Cumulative precision (%CV) from LLOQ to ULOQ Product A Product B and/or C [Applicable for bioanalytical method in 351(k). Delete for other applications]	 ≤ x% ≤ x%	Table 4 of report #123
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 5 QCs** QCs: Product A Product B and/or C	 x to y% x to y%	Table 5 of report #123
	Inter-batch %CV QCs: Product A Product B and/or C	 ≤ x% ≤ x%	Table 6 of report #123
	Total Error (TE) QCs: Product A Product B and/or C	 ≤ x% ≤ x%	Table 7 of report #123

Selectivity & matrix effect	Number of total lots tested. Range of observed bias. State any issue	
Interference & specificity	Number of total lots tested. Range of observed bias. State any issue	
Hemolysis effect	Number of total lots tested. Range of observed bias. State any issue	
Lipemic effect	Number of total lots tested. Range of observed bias. State any issue	
Dilution linearity & hook effect	Highest concentration tested and number of dilution factors. Range of observed bias	
Bench-top/process stability	Describe summary data here Product A Product B/C	
Freeze-Thaw stability	Describe summary data here Product A Product B/C	
Long-term storage	Describe summary data here Product A Product B/C	
Parallelism	Describe summary data here.	
Carry over	Describe summary data here	
Method performance in study number (In addition to the report name, also provide hyperlink to the report)		
Assay passing rate	(including incurred sample reanalysis (ISR))	
Standard curve performance	• Cumulative bias range: x to y% • Cumulative precision: ≤ x% CV	
QC performance	• Cumulative bias range: x to y% • Cumulative precision: ≤ x% CV • TE: ≤ x% (LBA only)	
Method reproducibility	Incurred sample reanalysis was performed in x% of study samples and x % of samples met the pre-specified criteria	
Study sample analysis/ stability	Describe the length of storage stability for standard/QCs and study samples and the coverage	

If the method above was modified, describe the modification(s) and cross-validation results, with any additional information in Table 2 below.

Table 2. Summary of method [x] modification(s) and cross-validation results

Bioanalytical method validation report name and hyperlink		
Changes in method		
New validated assay range if any		
Validation parameters	**Cross-validation performance**	**Source location (hyperlinked)**

Standard calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	x to y%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ x%	
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	x to y%	
	Inter-batch %CV	≤ x%	
	Percent total error (TE)	≤ x%	
Cross-validation	Numbers of spiked or incurred samples analyzed and result		
List other parameters			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JACQUELYN C ROSENBERGER
01/07/2022 09:30:45 AM

NDA 214900/S-001

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

SCYNEXIS, Inc.
Attention: Glen D. Park, PharmD, MSJ
Vice President, Regulatory Affairs and Quality Assurance
1 Evertrust Plaza, 13th Floor
Jersey City, NJ 07302

Dear Dr. Park:

We have received your supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 214900

SUPPLEMENT NUMBER: 001

PRODUCT NAME: Brexafemme (ibrexafungerp) tablet, 150 mg

DATE OF SUBMISSION: December 15, 2021

DATE OF RECEIPT: December 15, 2021

This supplemental application proposes to update the Prescribing Information (PI) to include information related to the pharmacokinetics of ibrexafungerp in post-menarchal females and to add information related to the pharmacokinetics of ibrexafungerp in hepatic impairment in subsection **12.3 Pharmacokinetics**/Special Populations and minor editorial updates throughout the PI.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 13, 2022, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be June 15, 2022.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[1] Failure to submit the content of labeling in SPL format may result in a refusal-to-file action.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

If you have questions, call Jacquelyn Rosenberger, PharmD, RAC, Regulatory Project Manager, at (301) 796-9179.

Sincerely,

{See appended electronic signature page}

Gregory F. DiBernardo
Chief, Regulatory Project Management Staff
Anti-Infectives Group 2
Division of Regulatory Operations
for Infectious Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GREGORY F DIBERNARDO
01/04/2022 02:50:36 PM