

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214900Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214900
PDUFA Goal Date	June 1, 2021
OSE RCM #	2020-2075 and 2077
Reviewer Name	Mei-Yean Chen, Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Division Deputy Director	Doris Auth, Pharm.D.
Review Completion Date	May 20, 2021
Subject	Evaluation of Need for a REMS
Established Name	Ibrexafungerp
Trade Name	Brexafemme
Name of Applicant	Scynexis
Therapeutic Class	A triterpenoid antifungal
Formulation(s)	150 mg oral tablet
Dosing Regimen	300 mg twice a day orally for one day, for a total of 600 mg

Table of Contents

EXECUTIVE SUMMARY 3

1 Introduction 3

2 Background 3

 2.1 Product Information 3

 2.2 Regulatory History..... 4

3 Therapeutic Context and Treatment Options 4

 3.1 Description of the Medical Condition 4

 3.2 Description of Current Treatment Options 5

4 Benefit Assessment 5

5 Risk Assessment & Safe-Use Conditions 7

6 Expected Postmarket Use..... 8

7 Risk Management Activities Proposed by the Applicant..... 8

8 Discussion of Need for a REMS..... 8

9 Conclusion & Recommendations..... 9

10 Appendices 9

 10.1 References..... 9

EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Brexafemme (ibrexafungerp) is necessary to ensure the benefits outweigh its risks. Scynexis, Inc. submitted a New Drug Application (NDA) 214900 for ibrexafungerp with the proposed indication for the treatment of adult and post-menarchal pediatric females with vulvovaginal candidiasis (VVC). The dose is 300 mg (two 150mg tablets) twice a day for one day, for a total treatment dosage of 600 mg. Fetal toxicity was seen in nonclinical studies in one species. In animal reproduction studies, oral ibrexafungerp administered to pregnant rabbits during organogenesis was associated with fetal malformations, including absent forelimbs, absent hindpaw, absent ear pinna, and thoracogastroschisis at dose exposures greater or equal to about five times the human exposure at the recommended human dose. The applicant did not submit a proposed REMS or risk management plan with this application.

The Division of Risk Management (DRM) and the Division of Anti-Infectives (DAI) agree that a REMS is not needed to ensure the benefits of ibrexafungerp outweigh its risks. Seventy-five percent of females will experience more than one episode of VVC and 40-45% will experience multiple VVC episodes. Oral ibrexafungerp has a distinct mechanism of action from other approved VVC treatments and demonstrated the efficacy to treat VVC in the clinical trials. If it is approved, the prescribing information will adequately describe the risk of fetal toxicity in Section 5 Warnings and Precautions, as well as pregnancy as a contraindication in section 4. Healthcare providers will be also advised in section 2.3 Dosage and Administration, section 5 Warnings and Precautions, and section 8.3 Females/Males of reproductive potential to obtain a negative pregnancy test in females of reproductive potential before initiation of ibrexafungerp and use effective contraception during and for four days after the last dose. Section 17 Patient counseling information will advise healthcare providers again to educate patients that Ibrexafungerp is contraindicated in pregnancy since it may cause fetal harm based on nonclinical studies.

1. Introduction

This review evaluates whether a REMS for the new molecular entity (NME)^a ibrexafungerp is necessary to ensure the benefits outweigh its risks. Scynexis, Inc. submitted a New Drug Application (NDA) 214900 for ibrexafungerp with the proposed indication for the treatment of adult and post-menarchal pediatric females with vulvovaginal candidiasis (VVC). This application is under review in the Division of Anti-Infectives (DAI). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Brexafemme (ibrexafungerp), an NME, is a triterpenoid antifungal agent proposed for the treatment of post-menarchal females with VVC. Ibrexafungerp inhibits glucan synthase, an enzyme involved in the

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

formation of 1,3-β-D-glucan, an essential component of the fungal cell wall. Ibrexafungerp has concentration-dependent fungicidal activity against *Candida* species. Ibrexafungerp is proposed as 150 mg tablet and recommended dose is 300 mg orally twice a day for one day^b. Ibrexafungerp is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 214900 relevant to this review:

- 01/24/2014: Qualified Infectious Disease Product (QIDP) designation granted
- 12/18/2014: Fast track designation granted
- 10/01/2020: NDA 214900 submission received
- 01/26/2021: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for ibrexafungerp.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

VVC is characterized by vulvovaginal inflammation in the presence of yeast. The symptoms include itching, burning, irritation, edema, redness, and excoriation. Seventy-five percent of females will experience more than one episode of VVC, 40-45% will experience multiple VVC episodes^c, and 10-20% will experience complicated VVC.¹ VVC is mostly commonly caused by *Candida albicans* (*C. albicans*). Complicated VVC is characterized by severe symptoms, isolation of yeast other than *C. albicans*, recurrent episodes, or occurrence in patients with diabetes or immunocompromising conditions^d.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The current treatments of uncomplicated VVC include oral and intravaginal antifungal drugs, available by prescription or over-the-counter (OTC). Fluconazole, an azole antifungal agent administered as a single 150 mg dose, is the only approved oral VVC treatment. The prescribing information of fluconazole² describes warnings of hepatic injury, anaphylaxis, dermatologic reaction, and potential for fetal harm. This drug is not approved with a box warning or REMS for any of these adverse events. The intravaginal drugs currently available for VVC therapy in the United States (US) are also azole antifungals and have similar efficacies to the oral fluconazole regimen. Butoconazole nitrate vaginal cream and

^b Section 505-1 (a) of the FD&C Act: FDAAA factor (D): *The expected or actual duration of treatment with the drug.*

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

terconazole vaginal cream or suppositories are available in the US as prescription drugs. Miconazole vaginal cream or suppositories, clotrimazole vaginal cream, and tioconazole vaginal ointment are available in the US as OTC drugs.

While most VVC infections respond to oral or intravaginal azole therapy (70-80% clinical cure), VVC caused by non-albicans yeast, such as *C. glabrata*, are less likely to be successfully treated with azole therapy. For complicated VVC, treatment guidelines of the Infectious Disease Society of America (IDSA) recommends longer courses of intravaginal drugs (5-7 days) or oral fluconazole (150 mg every 72 hours for three doses; not an approved dose for the VVC treatment indication).³

4 Benefit Assessment

Trial 1 (NCT 03734991) and Trial 2 (NCT 03987620) are two randomized placebo-controlled trials to evaluate the efficacy of a single day of ibrexafungerp 600 mg for the treatment of VVC.⁴ These two trials are the same design to include non-pregnant post-menarchal females with a diagnosis of VVC. A diagnosis of VVC was defined as:

- Minimum composite vulvovaginal signs and symptoms (VSS) score of ≥ 4 with at least two signs or symptoms having a score of 2 (moderate) or greater.
- Positive microscopic examination with 10% potassium hydroxide (KOH) in a vaginal sample revealing yeast forms (hyphae/pseudohyphae) or budding yeasts.
- Normal vaginal pH (≤ 4.5).

The total composite VSS score was based on 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 one dose of study medication.

The MITT population in Trial 1, which was conducted in US, consisted of 190 patients treated with ibrexafungerp 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 were White and 40% were Black or African-American, 26% were Hispanic or Latino ethnicity. The average body mass index (BMI) was 30 and 9% had a history of diabetes. At baseline, the median VSS score was 9 (range 4-18). The majority (92%) of the subjects tested positive for *C. albicans*.

The MITT population in Trial 2, which was conducted in US (39%) and Bulgaria (61%), consisted of 189 patients treated with ibrexafungerp 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 were White and 19% were Black or African-American, 10% were Hispanic or Latino ethnicity. The average BMI was 26 and 5% had a history of diabetes. At baseline, the median VSS score was 10 (range 4-18). The majority (89%) of the subjects tested positive for *C. albicans*.

Efficacy was assessed at the TOC visit by clinical outcome. A complete clinical response was defined as the complete resolution of signs and symptoms (VSS score of 0). Additional endpoints include a negative culture for *Candida* spp. at the TOC visit and clinical outcome at the follow-up visit.

Statistically significantly greater percentage of patients experienced a complete clinical response at TOC^e, negative culture at TOC, and complete clinical response at follow-up with treatment with ibrexafungerp compared to placebo (Table 1).

Table 1 Clinical and mycological response, MITT population

	Trial 1 Ibrexafungerp N=190	Trial 1 Placebo N=100	Trial 2 Ibrexafungerp N=189	Trial 2 Placebo N=89
Complete clinical response at TOC	95 (50%)	28 (28%)	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%)	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	113 (59.5%)	44 (44%)	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		(b) (4)	

^e Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

5 Risk Assessment & Safe-Use Conditions

5.1 FETAL TOXICITY

Based on findings from animal studies, ibrexafungerp use is contraindicated in pregnancy because it may cause fetal harm. In animal reproduction studies, oral ibrexafungerp administered to pregnant rabbits during organogenesis was associated with fetal malformations, including absent forelimbs, absent hindpaw, absent ear pinna, and thoracogastroschisis at dose exposures greater or equal to about five times the human exposure at the recommended human dose. Oral ibrexafungerp administered to pregnant rats during organogenesis was not associated with fetal toxicity or increased fetal malformations at a dose exposure approximately five times the human exposure at the recommended human dose.

Division of Pediatric and Maternal Health (DPMH) was consulted by DAI for embryo-fetal development toxicology study reports and proposed labeling for ibrexafungerp. The review of DPMH on 03/29/2021⁵ reported, in the phase 2 and 3 trials of VVC treatment, three subjects and one subject became pregnant within 10 days and five weeks of receiving ibrexafungerp, respectively. One of the pregnancies that occurred within ten days of therapy was electively terminated with no known reason; the other three pregnancies resulted in live births with no known birth defects. The review also compared prescribing information within the drug class (anti-fungal), dosage administration, drugs contraindicated for pregnancy, or drugs with a boxed warning for pregnancy. Most prescribing information for these products conveys the concern derived from animal studies through section 5. Warnings and Precautions. In the review, DPMH recommends issuing a post market requirement (PMR) for a single-arm pregnancy safety study to capture pregnancy outcomes and infant outcome following any incidental ibrexafungerp exposure during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant.

If ibrexafungerp is approved, healthcare providers will be advised to obtain a negative pregnancy test in females of reproductive potential prior to initiating therapy. Females of reproductive potential will be instructed to use effective contraception during ibrexafungerp therapy and for four days after last dose⁴.

Section 2.3 Dosage and Administration and Section 8.3 Females/Males of reproductive potential will also include the advice to obtain a negative pregnancy test prior to initiating ibrexafungerp.

The safety database included patients treated with ibrexafungerp in two clinical trials (Trial 1 and Trial 2) of females with VVC. The women were administered with ibrexafungerp 300 mg twice a day, 12 hours apart, for one day. In the two trials, there were no serious adverse reactions and 0.4% of patients

discontinued therapy due to vomiting and dizziness^f. Gastrointestinal adverse reactions, such as diarrhea, nausea, and abdominal pain, were common, 16.7% in the ibrexafungerp arm versus 3.3% in the placebo arm, respectively. The following adverse reactions occurred in less than 2% of patients receiving ibrexafungerp: dysmenorrhea, flatulence, back pain, elevated transaminases, vaginal bleeding, and rash/hypersensitivity reaction. These adverse reactions will be communicated in Section 6 Adverse Reactions.

6 Expected Postmarket Use

If ibrexafungerp is approved, it is expected that primary care providers, such as family physicians, internists, gynecologists, and nurse practitioners will be the likely the health care providers to prescribe ibrexafungerp in the outpatient setting.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for ibrexafungerp beyond routine pharmacovigilance and labeling.

After DAI requested post marketing requirements (PMRs) and post marketing commitment (PMC) on 04/30/2021 and modified 05/10/2021, the applicant proposed PMRs on 05/14/2021 as below⁶:

PMRs:

Conduct a worldwide single-arm descriptive study that collects prospective and retrospective data in women exposed to ibrexafungerp during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life.

Perform a milk-only lactation study in lactating women receiving therapeutic doses of ibrexafungerp to assess the concentrations of ibrexafungerp in breast milk using a validated assay.

PMC: Submit the final clinical study report for the oral ibrexafungerp pharmacokinetics and safety study in adolescent female subjects. Study completed and will submit a final study report on 12/2021.

^f Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of ibrexafungerp on the basis of the efficacy and safety information currently available⁷. Seventy-five percent of women will experience more than one episode of VVC and 40-45% will experience multiple VVC episodes. Fluconazole, an azole antifungal drug, is the only approved oral VVC therapy. The prescribing information of fluconazole² describes warnings of hepatic injury, anaphylaxis, dermatologic reaction, and potential for fetal harm. This drug is not approved with a box warning or REMS for any of these adverse events.

Oral ibrexafungerp has a distinct mechanism of action from other approved VVC treatments and demonstrated the efficacy to treat VVC in the clinical trials. The risk associated with ibrexafungerp is fetal toxicity based on animal studies. This reviewer recommends that a REMS is not necessary to ensure its benefits outweigh its risks. If it is approved, the prescribing information will adequately describe the risk of fetal toxicity in Section 5 Warnings and Precautions, as well as pregnancy as a contraindication in section 4. HCPs will be also advised in section 2.3 Dosage and Administration, section 5 Warnings and Precautions, and section 8.3 Females/Males of reproductive potential to obtain a negative pregnancy test in females of reproductive potential before initiation of ibrexafungerp and use effective contraception during and for four days after the last dose. Section 17 Patient counseling information will advise HCPs again to educate patients that Ibrexafungerp is contraindicated in pregnancy since it may cause fetal harm.

9 Conclusion & Recommendations

Based on the clinical review, DRM and DAI agree that the benefit-risk profile is favorable therefore, a REMS is not necessary for ibrexafungerp to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling were ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 REFERENCES

¹ Sobel, JD., Mitchell, C., Candida vulvovaginitis: clinical manifestations and diagnosis, www.uptodate.com accessed 02/26/2021

² Fluconazole prescribing information, accessed Drugs@FDA 03/03/2021

³ Pappas, PG., et al (2015). "Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America." Clinical Infectious Diseases 62 (4): e1-e50.

⁴ Ibrexafungerp NDA 214900 Draft prescribing information accessed 05/18/2021

⁵ Guity, N. clinical analyst, Division of Pediatric and Maternal Health, review of ibrexafungerp NDA 214900, DARRS 03/29/2021, ID#4769878

⁶ Ibrexafungerp NDA 214900, docuBridge submission on 05/14/2021, sequence number 0024

⁷ Unireview of ibrexafungerp NDA 214900, accessed 3/18/20210

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/s/

MEI-YEAN T CHEN
05/20/2021 02:03:45 PM

NAOMI S BOSTON
05/20/2021 02:07:01 PM

DORIS A AUTH
05/20/2021 02:14:13 PM