Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

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Product Name:	Brexafemme (ibrexafungerp)
Pediatric Labeling Approval Dates:	June 1, 2021 and November 30, 2022
Application Type/Number:	NDA 214900
Applicant:	Scynexis
TTT Record ID:	2024-12207

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Brexafemme (ibrexafungerp) in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with ibrexafungerp in pediatric patients.

Brexafemme (ibrexafungerp) is a triterpenoid antifungal drug and was initially approved in the U.S. on June 1, 2021. Ibrexafungerp is currently indicated for the treatment of vulvovaginal candidiasis (VVC), and the reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC) in adult and post-menarchal pediatric females.

This pediatric postmarketing safety review was prompted by pediatric labeling approved on June 1, 2021 (new drug indicated for the treatment of VVC in post-menarchal pediatric females) and November 30, 2022 (new indication added for the reduction in the incidence of RVVC in post-menarchal pediatric female).

DPV has not previously performed a pediatric postmarketing pharmacovigilance review for ibrexafungerp for the Pediatric Advisory Committee.

DPV searched FAERS for all U.S. serious reports with ibrexafungerp in pediatric patients less than 17 years of age from June 1, 2021 through January 20, 2025, and did not identify any reports.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with ibrexafungerp in pediatric patients less than 17 years of age.

DPV did not identify any new pediatric safety concerns for ibrexafungerp at this time and will continue routine pharmacovigilance monitoring for ibrexafungerp.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Brexafemme (ibrexafungerp) in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with ibrexafungerp in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Brexafemme (ibrexafungerp) is a a triterpenoid antifungal drug and was initially approved in the U.S. on June 1, 2021. Ibrexafungerp is currently indicated for the treatment of vulvovaginal candidiasis (VVC), and the reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC) in adult and post-menarchal pediatric females.

This pediatric postmarketing safety review was prompted by pediatric labeling approved on June 1, 2021 and November 30, 2022. The initial pediatric approval on June 1, 2021[1] was based on two randomized, placebo-controlled trials (VANISH-303 and VANISH-306) enrolling non-pregnant post-menarchal females with acute VVC[2, 3]. The safety and effectiveness of oral ibrexafungerp for treatment of VVC in postmenarchal adolescents have been established based on data from adequate and well-controlled studies in adults and from summary safety data from a pharmacokinetic and safety study in adolescents[4]. While only one adolescent was enrolled in the clinical trials (placebo arm), it was noted that the similarity in disease pathophysiology in postmenarchal adolescents and adult women allowed extrapolation of efficacy for VVC treatment. Furthermore, the safety profile of ibrexafungerp in adolescents was not expected to differ from that of adults, thereby, including postmenarchal pediatric patients in the indication.

On November 30, 2022 a new indication was added for the reduction in the incidence of RVVC in post-menarchal pediatric female. This added indication was based on a single well-designed phase 3 trial (Study SCY-078-304 or Study-304) that supported the efficacy and safety of ibrexafungerp for reduction in the incidence of RVVC[5]. It was noted that the safety and effectiveness of ibrexafungerp for reduction in the incidence of recurrent VVC in adolescents has been extrapolated from the adult RVVC trial given the similarity in disease pathogenesis and pharmacokinetics (PK) between adolescents and adults.

DPV has not previously presented ibrexafungerp to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The ibrexafungerp labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection[6]. For additional ibrexafungerp labeling information, please refer to the full prescribing information.

WARNING: RISK OF EMBRYO-FETAL TOXICITY

See full prescribing information for the complete boxed warning.

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

----------CONTRAINDICATIONS----------

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

----------ADVERSE REACTIONS----------

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

8.4 Pediatric Use

The safety and effectiveness of BREXAFEMME for treatment of VVC have been established in post-menarchal pediatric females. BREXAFEMME is also indicated for the reduction in the incidence of RVVC [see Indications and Usage (1.1)]. 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.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of search	January 21, 2025
Time period of search	June 1, 2021† - January 20, 2025
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product Active Ingredient: ibrexafungerp, ibrexafungerp citrate, ibrexafungerp phosphate
MedDRA search terms (Version 27.1)	All Preferred Terms
Other search terms‡	Case Seriousness: Serious Country Derived: USA

* See Appendix A for a description of the FAERS database.
† U.S. approval date
‡ For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities

3 RESULTS

3.1 FAERS

3.1.1 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved no serious U.S. pediatric reports for patients less than 17 years of age from June 1, 2021 through January 20, 2025 with ibrexafungerp.

3.1.2 Summary of U.S. Fatal Pediatric Cases (N=0)

There are no fatal U.S. pediatric adverse event cases for discussion.

3.1.3 Summary of U.S. Serious Non-Fatal Pediatric Cases (N=0)

There are no non-fatal U.S. pediatric adverse event cases for discussion.

4 DISCUSSION

DPV searched FAERS for all U.S. serious reports with ibrexafungerp in pediatric patients less than 17 years of age from June 1, 2021 through January 20, 2025, and did not identify any reports.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with ibrexafungerp in pediatric patients less than 17 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for ibrexafungerp at this time and will continue routine pharmacovigilance monitoring for ibrexafungerp.

6 REFERENCES

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7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.