Ibrexafungerp: A Novel Oral Triterpenoid Antifungal

Deepa Francis, Shwetha V. Rajiv, Mamatha George

Department of Dermatology, Malabar Medical College Hospital and Research Centre, Kozhikode, Kerala, India

Introduction

Vulvovaginal candidiasis (VVC) is one of the common causes of vaginitis.[1] It is mainly caused by *Candida albicans* (85–90%) and the rest by non-albicans Candida species. The incidence of VVC is very high with up to 70–75% of women experiencing at least an episode of VVC in their lifetime. Recurrent vulvovaginal candidiasis (RVVC) is defined as three or more episodes per year and is seen in up to 8–10% of women.[2] Limitations with currently available oral azoles for treatment include safety and emergence of multidrug resistance.[3] Ibrexafungerp is the first and only FDA-approved non-azole antifungal for the treatment of VVC and reduction in the incidence of RVVC.[4,5]

Structure

Ibrexafungerp (formerly SCY-078 and MK-3118) belongs to triterpenoid class of antifungals.[2] It is chemically designated as C44H67N5O4 • C6H8O7 with a molecular weight of 922.18 grams per mole.[6] The chemical structure is shown in Figure 1.

Mechanism of action

Ibrexafungerp is the first compound of the enfumafungin-derived triterpenoid class of antifungals and the first oral ß-(1,3)-D-glucan synthase inhibitor (GSIs).[6] It acts by inhibiting ß-(1,3)-D-glucan synthase, a key enzyme in the biosynthesis of ß-(1,3)-D-glucan, a major component of the fungal cell wall. The mechanism of action is similar to echinocandins, but it interacts differently with the same target enzyme.[2]

Antimicrobial spectrum

Ibrexafungerp has broad-spectrum fungicidal activity with a safety profile better than other antifungal agents. They are effective against all known species of candida including *C.albicans, C.glabrata, C.parapsilosis, C.krusei, and C.tropicalis*. It is superior to azoles and echinocandins due to its low minimum inhibitory concentration (MIC) in acidic pH.[2]

Resistance

Ibrexafungerp and echinocandins are different in structure and interact differently with the same target enzyme, resulting in a lower rate of resistance to ibrexafungerp.[7] In a recent study, ibrexafungerp demonstrated high activity against both wild-type and echinocandin-resistant candida strains with FKS mutations.[8]

Pharmacokinetics

The oral bioavailability of ibrexafungerp is approximately 50% in animal studies.[2] The maximum plasma concentration (Cmax) is achieved in 4 to 6 hours after single and multiple dosing. The Cmax and area under the curve (AUC) of ibrexafungerp increased 32% and 38%, respectively, with a high-fat meal. It is highly protein bound (>99%). Animal studies showed a nine-fold higher concentration of ibrexafungerp in vaginal tissue than in blood. The drug is eliminated mainly via hepatic metabolism and biliary excretion. The elimination half-life is approximately 20 hours. Ibrexafungerp undergoes hydroxylation by hepatic CYP3A4, followed by glucuronidation and sulfation. Following oral administration of radio-labeled ibrexafungerp, a mean of 90% of the radioactive dose (51% as unchanged ibrexafungerp) was recovered in feces and 1% in the urine of healthy volunteers.[5]

Indications

Ibrexafungerp received FDA approval for the treatment of vulvovaginal candidiasis (VVC) in adult and post-menarchal pediatric females in

How to cite this article: Francis D, Rajiv SV, George M. Ibrexafungerp: A novel oral triterpenoid antifungal. Indian Dermatol Online J 2024;15:169-71.

Received: 21-Apr-2023. **Revised:** 02-Jul-2023. **Accepted:** 13-Jul-2023. **Published:** 24-Nov-2023.

Address for correspondence:
Dr. Shwetha V. Rajiv, Department of Dermatology, Malabar Medical College Hospital and Research Centre, Ulliyeri, Kozhikode - 673 315, Kerala, India.
E-mail: shwethavrajiv@gmail.com

Access this article online

Website: https://journals.lww.com/idoj

DOI: 10.4103/idoj.idoj_310_23

Quick Response Code:

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

June 2021 and prevention of recurrent vulvovaginal candidiasis (RVVC) in December 2022.[4,5]

Efficacy

Two multicenter, randomized, double-blind, placebo-controlled phase 3 studies, VANISH 303 and VANISH 306 evaluated the efficacy and safety of oral ibrexafungerp compared to placebo in female subjects 12 years and older with acute VVC. These clinical trials demonstrated ibrexafungerp to have statistically superior clinical response over placebo. Adverse event rates were low and mostly mild. FDA-approved oral ibrexafungerp after these two study results were reported.[9]

Composition and storage

Ibrexafungerp is available under the brand name Brexafemme. Tablets are purple, oval, and biconvex shaped and each tablet contains 150 mg ibrexafungerp, equivalent to 189.5 mg of ibrexafungerp citrate. The tablets are advised to be stored at 20-25 degree Celsius.[5]

Dosage and administration

Please see Table 1 for dosage and administration. Ibrexafungerp is currently not available in India and the approximate cost in the USA is $500 for four tablets of 150 mg each.[10]

Adverse effects and safety profile

The most common adverse effects of ibrexafungerp include diarrhea, nausea, abdominal pain, dizziness, vomiting, headache, urinary tract infection, and fatigue.[4]

Drug interactions

Ibrexafungerp is a substrate and an inhibitor of CYP3A4 and P-glycoprotein. Drugs that induce or inhibit CYP3A can alter the plasma levels and effect the efficacy and safety of ibrexafungerp.[5] Details of drug interactions are given in Table 2.

Table 1: Dosage and administration of oral ibrexafungerp in vulvovaginal candidiasis[5]

Indication	Dosage in adults and post-menarchal females
Treatment of vulvovaginal candidiasis	300 mg (two tablets of 150 mg) administered approximately 12 h apart for one day, with a total dosage of 600 mg (four 150 mg tablets)
Reduction in the incidence of recurrent vulvovaginal candidiasis	300 mg (two tablets of 150 mg) administered approximately 12 h apart for one day, for a total dosage of 600 mg (four 150 mg tablets)

Contraindications

Hypersensitivity to ibrexafungerp is an absolute contraindication. It is contraindicated in pregnancy as it may cause fetal harm based on findings from animal reproductive studies. Females of the reproductive age group are advised to use effective contraception throughout the treatment period for RVVC and 4 days after the last dose.[5] Reassessing pregnancy status prior to each dose is recommended. There are no data on the presence of ibrexafungerp in the breast milk of lactating mothers. The safety and effectiveness of ibrexafungerp have not been established in pre-menarchal pediatric females.[5]

Conclusion

Unlike echinocandins, ibrexafungerp has the advantage of oral administration and is generally safe and well tolerated with few gastrointestinal adverse effects. Several studies have shown equal or superior *in vitro* activity of ibrexafungerp compared to echinocandin antifungal drugs, against both wildtype and echinocandin-resistant C.glabrata. *In vitro* activity has also shown to be efficacious in low pH environments, which suggests its effectiveness in treating vulvovaginitis. Further clinical and preclinical studies are required to confirm the efficacy and safety of ibrexafungerp in treating other causes of invasive fungal diseases.

Financial support and sponsorship

Nil.

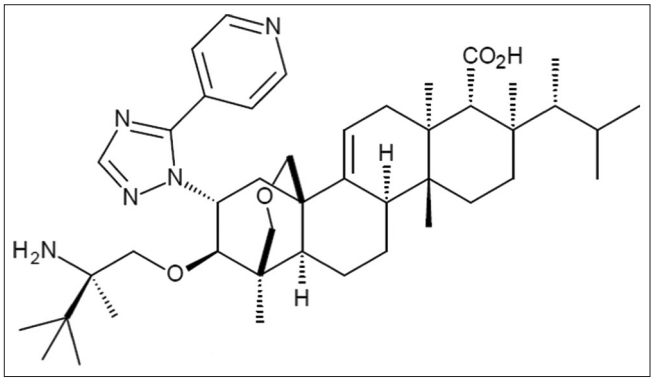

Figure 1: Chemical structure of ibrexafungerp

Table 2: Drug interactions of ibrexafungerp[5]

Interacting drug	Effect on ibrexafungerp levels	Recommendation
Strong CYP3A inhibitors: Ketoconazole, Itraconazole	Significantly increased	Reduce ibrexafungerp dosage to 150 mg twice daily for 1 day
Strong and moderate CYP3A inducers: Rifampin, carbamazepine, phenytoin, St. John's wort, long acting barbiturates, bosentan, efavirenz	May result in significant reduction (not studied *in vivo* or *in vitro*)	Avoid concomitant administration

Conflicts of interest

There are no conflicts of interest.

References

1. Leclair C, Stenson A. Common causes of vaginitis. JAMA 2022;327:2238-9.
2. Azie N, Angulo D, Dehn B, Sobel JD. Oral ibrexafungerp: An investigational agent for the treatment of vulvovaginal candidiasis. Expert Opin Investig Drugs 2020;29:893-900.
3. Arendrup MC, Patterson TF. Multidrug-resistant Candida: Epidemiology, molecular mechanisms, and treatment. J Infect Dis 2017;216(suppl_3):S445-51.
4. Barnes KN, Yancey AM, Forinash AB. Ibrexafungerp in the treatment of vulvovaginal candidiasis. Ann Pharmacother 2023;57:99-106.
5. BREXAFEMME® (ibrexafungerp tablets), for oral use. U.S. Food and Drug Administration. 6/2021. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214900s000lbl.pdf. [Last accessed on 2023 Apr 2].
6. Ghannoum M, Arendrup MC, Chaturvedi VP, Lockhart SR, McCormick TS, Chaturvedi S, *et al*. Ibrexafungerp: A novel oral triterpenoid antifungal in development for the treatment of *Candida auris* infections. Antibiotics (Basel) 2020;9:539.
7. Jiménez-Ortigosa C, Perez WB, Angulo D, Borroto-Esoda K, Perlin DS. *De Novo* acquisition of resistance to SCY-078 in Candida glabrata involves FKS mutations that both overlap and are distinct from those conferring echinocandin resistance. Antimicrob Agents Chemother 2017;61:e00833-17.
8. Pfaller MA, Messer SA, Rhomberg PR, Borroto-Esoda K, Castanheira M. Differential activity of the oral glucan synthase inhibitor SCY-078 against wild-type and echinocandin-resistant strains of Candida species. Antimicrob Agents Chemother 2017;61:e00161-17.
9. McCarthy MW. Pharmacokinetics and pharmacodynamics of ibrexafungerp. Drugs R D 2022;22:9-13.
10. Grant LM, Orenstein R. Treatment of recurrent vulvovaginal candidiasis with ibrexafungerp. J Investig Med High Impact Case Rep 2022;10:23247096221123144.