Health Technology Briefing
May 2024

Diclofenac-clotrimazole for treating recurrent vulvovaginal candidiasis

Company/Developer	ProFem GmbH

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 31250	NICE ID: Not available	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase II/III clinical development.

Summary

Diclofenac-clotrimazole is in clinical development for the treatment of recurrent vulvovaginal candidiasis (RVVC). Vulvovaginal candidiasis (genital thrush) is an inflammation of the vagina and/or vulva caused by a superficial fungal infection (usually yeast). Symptoms of RVVC include vulval or vaginal itch and irritation, a non-offensive vaginal discharge, painful intercourse, and painful urination. Recurrent RVVC refers to four or more episodes within a year. Affected patients frequently suffer from long-lasting pain and impairment, such as avoidance of sexual activity and depression, which results in significantly impaired quality of life. RVVC is chronic and difficult to treat with limited therapeutic options available, thereby highlighting the need for new therapies for this indication.

Diclofenac-clotrimazole is a fixed dose combination of diclofenac and clotrimazole. Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) which acts by blocking the effects of the two enzymes (types of protein), known as COX-1 and COX-2, resulting in a reduced production of substances called prostaglandins (hormone-like substances). Some prostaglandins are involved in causing pain and inflammation at sites of injury or damage in the body, so a reduced production of prostaglandins reduces pain and inflammation. Clotrimazole is an antifungal medicine that works by preventing the formation of ergosterol, which is an important part of fungal cell walls. Without ergosterol, the fungus is killed or prevented from spreading. Diclofenac-clotrimazole is administered by vulvar/ intravaginal application of the cream. If approved, diclofenac-clotrimazole will provide a novel treatment option for RVVC.

Proposed Indication

Treatment of patients with recurrent vulvovaginal candidiasis (RVVC).[1]

Technology

Description

Diclofenac-clotrimazole (ProF-001, Candiplus) is a fixed dose combination of diclofenac and clotrimazole. Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that has analgesic, anti-inflammatory, and antipyretic properties.[2] Diclofenac inhibits cyclooxygenase (COX)-1 and-2 which are the enzymes responsible for producing prostaglandins which contribute to inflammation and pain signalling.[3] Clotrimazole is a broad-spectrum anti-fungal agent, under the imidazole category of azole antifungals, which acts primarily by damaging the permeability barrier in the cell membrane of fungi. Clotrimazole causes inhibition of ergosterol biosynthesis, an essential constituent of fungal cell membranes. If ergosterol synthesis is either completely or partially inhibited, the cell is no longer able to construct an intact and functional cell membrane. Because ergosterol directly promotes the growth of fungal cells in a hormone-like fashion, rapid onset of the above events leads to dose-dependent inhibition of fungal growth.[4] The clinical efficacy of diclofenac-clotrimazole is based on the synergistic effects of the active ingredient components.[5]

Diclofenac-clotrimazole is in clinical development for the treatment of RVVC. In the phase IIb/III clinical trial (NCT04734405), 5g of diclofenac-clotrimazole cream is applied for 6 days (twice daily 2.5g vulvar/ intravaginal application), followed by 4 days of 2.5g of diclofenac-clotrimazole at bedtime in the induction period. In the maintenance period, two doses of 2.5g of diclofenac-clotrimazole is applied per week for 22 weeks.[1]

Key Innovation

There remains unmet need in the treatment of RVVC as around 57% of patients who use current treatment options experience recurrence after 6 months of discontinuation.[6] The poor therapeutic outcome in RVVC leads to impairments to quality of life (QoL) and sexual health in affected women.[7] Diclofenac-clotrimazole is designed as a local treatment for frequently recurring vaginal fungal infections. The onset of action of diclofenac-clotrimazole is thought to be rapid and effective, while at the same time frequent relapses and chronicity are prevented.[5]

Chronic inflammatory processes and the accompanying expression of cellular adhesion molecules play a central role both in the transition of harmless (saprophytic) candida spores to the disease-causing candida hyphae and in the formation of biofilms. In addition, specific resistance mechanisms develop in biofilms, which lead to the failure of conventional therapeutic approaches and subsequently to the clinical pattern of recurrent disease episodes. Conventional drugs that attack fungal growth temporarily inhibit the disease by suppressing fungal growth, but usually do not lead to complete regression of the microorganism to its initial saprophytic (peaceful) state. However, with diclofenac-clotrimazole, adhesion and invasion are specifically blocked, resistance mechanisms in the biofilm are overcome and the interaction between microorganism and host is normalised.[5]

If licensed, diclofenac-clotrimazole will offer an additional treatment option for patients with RVVC who currently have few effective therapies available.

Regulatory & Development Status

Diclofenac-clotrimazole does not currently have Marketing Authorisation in the EU/UK for any indication.

Diclofenac-clotrimazole is not currently in clinical development for any other indication.

Patient Group

Disease Area and Clinical Need

Vulvovaginal candidiasis (genital thrush) is a symptomatic inflammation of the vagina and/or vulva caused by a superficial fungal infection, usually with Candida albicans.[8] It typically causes symptoms of vulval or vaginal itch and irritation, a non-offensive vaginal discharge, superficial dyspareunia (painful intercourse), and dysuria (painful urination). Recurrent infection describes four or more symptomatic episodes in one year. Risk factors for developing infection are uncertain; there may be no obvious predisposing or underlying conditions, but the following may be associated with occurrence of RVVC: recent antibiotic use, local irritants, uncontrolled diabetes or other causes of immunosuppression, and increases in endogenous and exogenous oestrogen such as pregnancy and use of the combined oral contraceptive pill. Possible complications include recurrent infection, reduced quality of life and psychosexual difficulties.[8]

RVVC has an annual global prevalence of 3,871 per 100,000 women.[9] Data from a survey suggests the probability of developing RVVC after an initial infection was 10% by the age of 25 years and 25% by the age of 50 years.[9] Approximately 9% of women aged 25-34 globally suffer from RVVC.[10] In England, 2022-23, there were 546 finished consultant episodes (FCE) and 481 admissions for candidiasis of vulva and vagina (ICD-10 code B37.3) which resulted in 710 FCE bed days and 28 day cases.[11]

Recommended Treatment Options

NICE recommends the following treatment options for RVVC:[12]

- Induction regimen: three doses of oral fluconazole 150 mg (to be taken every 72 hours) first line.
- Maintenance treatment: oral fluconazole 150 mg once a week for six months first-line.
- Alternative treatment regimens if first-line oral azole therapy is contraindicated or not tolerated for recurrent infection:
    - Induction therapy: Topical imidazole therapy (such as clotrimazole 500 mg intravaginal pessary) can be increased to 7–14 days, depending on symptom response.
    - Maintenance therapy: Clotrimazole 500 mg pessary inserted intravaginally once a week for six months, or oral itraconazole 50–100 mg daily for six months.
- After completing an induction and maintenance regimen, for recurrent symptoms between maintenance treatment doses:
    - Oral fluconazole 150 mg twice-weekly instead of once a week, or
    - Cetirizine 10 mg once daily for six months, particularly if there is a history of allergy (off-label indication).

Clinical Trial Information

Trial	NCT04734405; Phase IIb/III Parallel-arm, Random., Active-controlled, Double-blind, Double-dummy, Multicenter, Non-inferiority Study in Patients With RVVC to Compare Efficacy, Safety and Tolerability of Topically Administered ProF-001 to Oral Fluconazole **Phase IIb/III –** Active, not recruiting **Location(s):** 3 EU countries **Study completion date:** December 2022

Trial Design	Randomised, parallel assignment, double-blind, double-dummy, active-controlled, quadruple masked
Population	N=432 (estimated); female subjects suffering from an acute episode of RVVC; aged 18 years and older
Intervention(s)	• 5g of diclofenac-clotrimazole for 6 days (twice daily 2.5 g vulvar/ intravaginal application of cream), followed by 4 days of 2.5g of diclofenac-clotrimazole at bedtime and one placebo capsule on days 1,4 and 7 (induction period) • 2 doses of 2.5g diclofenac-clotrimazole per week for 22 weeks and one placebo capsule per week for 44 weeks (maintenance period)
Comparator(s)	• One fluconazole 150 mg capsule on days 1, 4, and 7 and a daily dose of 5g of placebo cream for 6 days (twice daily 2.5 g vulvar/ intravaginal application of cream), followed by 4 days of 2.5g of placebo cream at bedtime (induction period) • One capsule of fluconazole 150 mg per week for 24 weeks and two doses of 2.5 g of placebo cream per week for 22 weeks (maintenance period)
Outcome(s)	Primary outcome measure: Percentage of patients with at least one episode of clinical relapse of VVC during the 12 months study period. [Time Frame: after 12 months] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of diclofenac-clotrimazole is not yet known.

Relevant Guidance

NICE Guidance

No NICE guidance identified.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- British Association for Sexual Health and HIV (BASHH). British Association for Sexual Health and HIV national guideline for the management of vulvovaginal candidiasis. 2019.[13]
- van der Meijden, W.I., Boffa, M.J., ter Harmsel, W.A., et al. 2016 European guideline for the management of vulval conditions. 2017.[14]

Additional Information

ProFem GmbH did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

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