

Review of Application of **Clotrimazole** for topical or intravaginal use in vulvovaginal candidiasis

This application has been submitted by UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research with consultation from BMJ Knowledge.

Summary of application: The application states that clotrimazole is a readily available and effective topical and intravaginal antifungal used in vulvovaginal candidiasis; that it is safer (especially in pregnant women) than antifungals currently listed on the WHO Essential Drugs List.

Applications are reviewed on several factors, including the disease burden and sound and adequate data on the efficacy, safety and comparative cost-effectiveness of available treatments. Each of these factors is discussed below.

Disease Burden

The application cites 2 recent reviews of international data that establish the high prevalence of vaginal candidiasis. Roughly, 72% of women will have at least one episode and recurrence is common.

Efficacy

The review of efficacy relies on the strongest study designs (systematic reviews and randomized controlled trials only). In addition, only reviews or trials assessing the outcome of clinical cure were included. Studies measuring only mycological cure were not included.

Clotrimazole vs. placebo. The application presents convincing evidence from 4 RCTs comparing clotrimazole to placebo. In two trials, the 95% confidence interval of the relative risk for symptoms at 27 to 38 days was 0.01 to 0.15.

Clotrimazole vs. other antifungals

Two RCTs and one systematic review cited in the application found no significant differences the persistence of symptoms in patients treated with clotrimazole or other other topical topical azoles or oral ketoconazole.

An additional Cochrane review (1) comparing oral vs. intra-vaginal imidazole and triazole anti-fungal treatments found no differences between clotrimazole and fluconazole or itraconazole for clinical cure at long (2 to 12 weeks) or short term (5-15 days) follow up.

A cursory search of PubMed identified an additional newer trial that has similar findings (2).

Clotrimazole in pregnant women

One RCT provides evidence that clotrimazole is more effective than placebo in reducing persistent candidiasis. Two RCTs found that clotrimazole reduced persistence of candidiasis compared to nystatin. All of these trials measured mycological rather than clinical outcomes in the mother or child.

Clotrimazole for recurrent vulvovaginal candidiasis

Evidence regarding the effect of clotrimazole compared to placebo or itraconazole on recurrence was conflicting or poor in quality.

In summary, clotrimazole (500 mg, 1X / day) is highly effective compared to placebo. There are no significant differences in efficacy when compared to other anti-fungals.

Safety

Clotrimazole is available without prescription in most countries and this regulatory approval status indicates that the drug is generally recognized as safe. Reported adverse effects have been rare and not serious.

Although topical clotrimazole is considered safe to use in pregnancy due to its poor absorption, its distribution in human milk following topical or vaginal application is not known.

Adverse effects were not routinely reported in the RCTs. One RCT compared self-reported adverse events associated with clotrimazole compared to those associated with oral fluconazole and found that clotrimazole had significantly lower incidence rates.

Comparative cost-effectiveness

Data on cost and cost-effectiveness are not presented as average generic world market prices as listed in the International Drug Price Indicator Guide. United Kingdom data from the British Medical Association and Royal Pharmaceutical Society suggest that the medicine is reasonably priced. Due to its non-prescription status in many countries, prices are likely to be variable.

The application does not present data on cost-effectiveness. A Cochrane review (1) notes that none of the included trials assessed the relative cost-effectiveness of clotrimazole compared to any other products. The review also notes that, in the UK, oral anti-fungals are more expensive than intra-vaginal anti-fungals.

Other factors to consider

WHO Reproductive Health Guidelines include clotrimazole as a treatment for candidiasis, but the drug is not currently on the Essential Drug List. Use of clotrimazole is also recommended by Medicines Sans Frontieres and the Centers for Disease Control, USA.

The application does not address possible variations in safety due to health systems and patient factors. The variable regulatory status of the drug in different countries could result in different safety monitoring procedures.

The caution that clotrimazole damages latex condoms and diaphragms should be noted.

Recommendation

Although the data on relative cost-effectiveness are weak, cost issues alone should not prevent registration. The strong evidence on public health significance of the disease, efficacy and safety support the recommendation that clotrimazole for topical or intravaginal use in vulvovaginal candidiasis be added to the list as proposed in the application.

Reference

1. Watson MC, Grimshaw JM, Bond CM, Mollison J, Ludbrook A. Oral versus intravaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush). *The Cochrane Database of Systematic Reviews* 2001, Issue 3. Art. No.: CD002845. Date of most recent substantive amendment: 28 May 2001.
2. Mendling W, Krauss C, Fladung B. A clinical multicenter study comparing efficacy and tolerability of topical combination therapy with clotrimazole (Canestan, two forms) with oral single dose fluconazole (Diflucan) in vulvovaginal mycoses. *Mycoses*. 2004 April; 47(3-4): 136-142.

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