Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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dequalinium chloride 10mg vaginal tablets (Fluomizin®) SMC No. (1194/16)

Kora Healthcare

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

dequalinium chloride (Fluomizin®) is accepted for restricted use within NHS Scotland.

Indication under review: Treatment of bacterial vaginosis.

SMC restriction: In patients for whom the initial treatment is not effective or well tolerated.

Non-inferiority of dequalinium vaginal tablets to an antibiotic vaginal cream was demonstrated in a study that included treatment-naive and treatment-experienced patients.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

For the treatment of bacterial vaginosis. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Dosing Information

One 10mg vaginal tablet daily for six days.

Product availability date

April 2016

Summary of evidence on comparative efficacy

Bacterial vaginosis (BV) causes an imbalance of the normal vaginal flora with a reduction in the predominant *Lactobacillus* species and a large increase in anaerobic bacteria.[1] Dequalinium chloride (subsequently referred to as dequalinium) is a bactericidal quaternary ammonium anti-infective agent with a broad spectrum of action against gram-positive and gram-negative bacteria, yeasts and protozoa.[2,3] The aim of treatment is to alleviate symptoms and restore balance in vaginal flora.[3] The submitting company requested that SMC considers dequalinium when positioned for use in patients with BV where the initial treatment is not effective or well tolerated.

Evidence of efficacy comes from a phase III, single-blind, randomised, non-inferiority study that recruited women aged 18 to 55 years who were premenopausal and had a diagnosis of BV, defined as fulfilling all four Amsel criteria: (1) characteristic grey, homogeneous, malodorous discharge, (2) vaginal pH >4.5, (3) positive potassium hydroxide test for amines and (4) ≥20% of the epithelial cells of the wet mount are clue cells. Patients were randomised equally to treatment with dequalinium chloride 10mg vaginal tablet daily for six days or clindamycin 2% vaginal cream for seven days. Efficacy was assessed by a physician blinded to study treatment, and safety and tolerability were assessed in an unblinded manner.[1]

The primary outcome was clinical cure seven days after treatment completion and was defined as absence of clue cells and a negative result for at least two other Amsel criteria. The primary analysis was conducted in the per protocol (PP) population which excluded patients with major protocol deviations. Criteria for non-inferiority were that the lower limit of the 95% confidence interval (CI) was greater than -15% and (because there had been an interim analysis) the product of the p values for the interim and post-interim analyses was below a critical value of 0.0038. In the PP population the primary outcome was achieved in 81% (110/135) of patients in the dequalinium group and in 78% (91/116) of patients in the clindamycin group; 95% CI for treatment difference (–6.9% to 13%); product of p values=0.00004. Therefore non-inferiority was demonstrated.[1]

Analyses were also conducted in the intention to treat (ITT) population for the primary and secondary outcomes and the results were presented in the published report. The published report did not define the ITT population which, in fact, excluded six randomised patients due to study withdrawal or no treatment received.[1]

Table 1: Results of primary and key secondary outcomes[1]

Outcome	Dequalinium vaginal tablets	Clindamycin vaginal cream	95% CI
Clinical cure at 7 days PP population	81% (110/135)	78% (91/116)	(-6.9% to 13%)
Clinical cure at 7 days ITT population	77% (126/163)	73% (111/152)	-
Clinical cure at 25 days PP population	78% (105/135)	78% (90/116)	-
Clinical cure at 25 days ITT population	71% (116/163)	70% (107/152)	-
Rate of treatment failure at 25 days ITT population	24% (39/163)	24% (37/152)	-

CI=confidence interval; PP=per protocol; ITT=intention to treat; treatment failure is defined as patients with recurrence plus non-responders

There were no significant differences between treatment groups in other secondary outcomes: incidence of clinical vulvovaginal candidiasis; lactobacillary grade classification of flora; total symptom score (calculated as the sum of the individual scores [0 to 3] for discharge, pruritus and burning) and global assessment of efficacy. Quality of life was not assessed.[1]

Summary of evidence on comparative safety

The overall safety profile was acceptable and comparable between treatment groups. Adverse events were reported in 40% (66/163) of patients in the dequalinium group and in 48% (73/153) of patients in the clindamycin group. These were considered to be treatment-related in 18% (29/163) and 20% (31/153) of patients, respectively. The most common treatment-related adverse events were vaginal discharge (9.2% versus 4.6%) and vulvovaginal pruritus (4.9% versus 8.5%) of patients, respectively. There were no serious adverse events.[1]

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

BV is a common cause of vaginal infection in women of reproductive age**.** The alteration in microbial flora causes an increase in pH and loss of the protective acidic environment. Patients with BV are more susceptible to sexually transmitted infections, including HIV, and pelvic inflammatory disease. Pregnant women with BV have an increased risk of spontaneous miscarriage and of giving birth prematurely.[1,4] BV has a very high recurrence rate – this occurs in more than two-thirds of patients within three months of treatment. The reasons are unclear, but are not thought to include antibiotic resistance. The normal healthy microbial balance does not seem to be completely regained. Current treatment options for BV are oral or vaginal metronidazole, oral or vaginal clindamycin and oral tinidazole.[5] In NHS Scotland the predominant initial therapy is oral metronidazole.[6-10] There is no consensus about treatment of recurrent infections. The submitting company requested that SMC considers dequalinium when positioned for use in patients with BV where the initial treatment is not effective or well tolerated.

The non-inferiority of dequalinium vaginal tablets to clindamycin vaginal cream was demonstrated in women with BV. A total of 70% of study patients had had at least one prior episode of BV.[1] No evidence was presented versus other relevant comparators.

The study had a number of limitations. It did not specifically recruit women who had failed or not tolerated initial treatment, which is the proposed positioning. It excluded pregnant women. It had a short follow-up duration and as there is a high recurrence rate for BV, longer follow-up would have been appropriate. The study was not double-blind so there was a risk that patients could have inadvertently communicated their treatment allocation to the blinded physician. The 15% non-inferiority margin is relatively wide and no justification was provided for this. The ITT population was not formally defined and excluded six randomised patients due to study withdrawal or no treatment received. The primary analysis was conducted in a PP population.

The availability of dequalinium vaginal tablets would provide an additional treatment option for BV. The treatment course is one day shorter for dequalinium than for clindamycin vaginal cream. Furthermore, in contrast to clindamycin vaginal cream, dequalinium does not weaken latex condoms.[2,11]

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis (CMA) which compared dequalinium vaginal tablets against clindamycin vaginal (2%) cream in premenopausal women with BV. The company requested that dequalinium was considered as a second line treatment option where the initial treatment is not effective or well tolerated.

A decision analytic model was developed in order to evaluate the cost-effectiveness of dequalinium versus clindamycin. In terms of model structure, women aged 18 to 55 years old with BV entered the model and were treated with either dequalinium or clindamycin. Patients who were initiated to dequalinium received treatment for 6 days and patients initiated to clindamycin received treatment for 7 days. After 25 days, response to treatment was measured through assessing complete clearance or no clearance of BV. The time horizon for the analysis was 25 days.

The company stated that the economic analysis was based on clinical data available in the pivotal study which reported clearance and non-clearance rates for dequalinium and clindamycin. In addition, the pivotal study supported the non-inferiority of dequalinium to clindamycin. The company also referenced a separate published study which compared oral metronidazole, metronidazole vaginal gel, and clindamycin cream in order to further support the equivalence of the medicines included in the economic analysis.

The analysis included the medicine cost for each comparator as well as the cost of a GP visit at £44.

The base case result indicated that the cost of dequalinium was £51 and clindamycin was £55. Therefore, the base case analysis reported that dequalinium was cost-minimising and generated a saving of £4.

The company provided a sensitivity analysis which extended the time horizon to 1 year; this included recurrence and vulvo-vaginal candidosis in the analysis. The extended model used data from the pivotal study and published literature in order to model the additional efficacy parameters. The results reported that the cost of dequalinium was £189 and clindamycin was £193; therefore, dequalinium generated a saving of £4.

Additional sensitivity analyses which explored changes to the extended economic model discussed above were also provided by the company. In most scenarios, dequalinium remained cost-minimising versus clindamycin. However, when the lower bound of the clearance rate 95% confidence interval for dequalinium (clearance: 71.2%), and the upper bound of the interval for clindamycin (clearance:

89.8%) were used in the analysis, dequalinium was not cost-minimising. The results reported that the cost of dequalinium was £192.57 and clindamycin was £191.18; therefore, dequalinium cost £1.39 more.

The main weaknesses were

- The economic analysis compared dequalinium against clindamycin cream; however, other treatment options are available such as vaginal metronidazole, oral clindamycin and oral tinidazole. It is also worth noting that vaginal metronidazole and oral tinidazole may be less expensive than dequalinium. However, following discussions at New Drugs Committee (NDC), clindamycin cream was identified as the most appropriate comparator for the economic analysis.
- Initial SMC expert responses suggested that patients may switch treatment because of treatment failure or recurrence, and BV is reported to have a very high recurrence rate. Sensitivity analyses were provided by the company which modelled switching treatment due to treatment failure or recurrence but the analyses were limited. This was mainly because they only included switching to dequalinium or clindamycin cream after treatment failure or BV recurrence, and other medicines were not included in the scenarios. The company did not provide a requested analysis allowing patients to switch to medicines other than dequalinium and clindamycin in the economic model when they discontinued treatment. However, the SMC clinical experts did note that subsequent therapies would not differ significantly for patients initiated to dequalinium or clindamycin. As a result, the costs associated with subsequent therapy may cancel out across treatment arms.
- The clinical data may not reflect the proposed positioning for dequalinium. Following discussions at the NDC, the clinical data were considered generalisable to the second line positioning of the medicine.
- The base case analysis used numerical differences in clearance rates between dequalinium and clindamycin, which is not appropriate for a CMA. Revised analyses were provided by the company which removed numerical differences in clearance rates and dequalinium remained cost-minimising.

Despite the above uncertainties the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Group submission was not made.

Additional information: guidelines and protocols

The British Association for Sexual Health and HIV (BASHH) published guidelines for the management of BV in 2013.'[5] The guidelines recommend treatment of symptomatic BV (and asymptomatic BV if offered) as follows:

- Metronidazole 400mg to 500mg taken orally twice daily for five to seven days or
- Metronidazole 2g single dose taken orally or
- Metronidazole gel (0.75%) administered vaginally once daily for five days or
- Clindamycin cream (2%) administered vaginally once daily for seven days or
- Tinidazole 2g single dose taken orally or
- Clindamycin 300mg taken orally twice daily for seven days

There is no consensus on treatment of recurrent infections.[5]

The guideline was published before the licensing of dequalinium vaginal tablets.

Additional information: comparators

The main comparator in the restricted population is vaginal clindamycin. Alternative treatments are oral or vaginal metronidazole, oral tinidazole or oral clindamycin.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Dequalinium chloride	**10mg vaginal tablet daily for six days**	**7**
Clindamycin*	300mg orally twice daily for seven days	17
Clindamycin	2% vaginal cream once daily for seven days**	11
Metronidazole	0.75% vaginal gel once daily for five days	4
Tinidazole*	2g orally as a single dose	3
Metronidazole	400mg orally twice daily for five to seven days	1
Metronidazole	2g orally as a single dose	0.39

Doses are for general comparison and do not imply therapeutic equivalence. *Bacterial vaginosis not listed as a licensed indication. **In patients in whom a shorter treatment course is desirable, a three day regimen has been shown to be effective.[11] Doses from UK guidance: Sexually Transmitted Infections in Primary Care 2013 and from the summary of product characteristics for clindamycin cream.[5,11] Costs from eVadis July 2016 and dequalinium chloride from eMC Dictionary of Medicines and Devices site.

Additional information: budget impact

The submitting company estimated there would be 12,105 patients eligible for treatment with dequalinium in all years, to which confidential estimates of treatment uptake were applied.

The gross impact on the medicines budget was estimated to be £21k in year 1, rising to £67k in year 5. As medicines were assumed to be displaced, the net medicines budget impact was estimated to be a saving of £12k in year 1 and a saving of £38k in year 5.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Weissenbacher ER, Donders G, Unzeitig V et al. A comparison of dequalinium chloride vaginal tablets (Fluomizin®) and clindamycin vaginal cream in the treatment of bacterial vaginosis: a single-blind, randomized clinical trial of efficacy and safety. Gynecologic and Obstetric Investigation (2012); 73: 8-15.

2. Dequalinium chloride 10mg vaginal tablets (Fluomizin®) Summary of product characteristics. Kora Healthcare. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 16 February 2016.

3. Mendling W, Weissenbacher ER, Gerber S et al. Use of locally delivered dequalinium chloride in the treatment of vaginal infections: a review. Arch Gynecol Obstet 2016 293:469-84

4. Donders GG, Zodzika J, Rezeberga D. Treatment of bacterial vaginosis: what we have and what we miss. Expert Opinion on Pharmacotherapy February 2014

5. Sexually Transmitted Infections in Primary Care 2013 (RCGP/BASHH) by Lazaro N. available at www.rcgp.org and www.bashh.org/guidelines

6. NHS Lothian Joint Formulary
http://www.ljf.scot.nhs.uk/Search/Results.aspx?k=bacterial%20vaginosis

7. GP Adult Empirical Treatment of Infection Guidance
http://www.medednhsl.com/sites/sitestore/PRESCRIBING09122011/MPRGPANTI64906L-974494-29-08-2014.pdf

8. NHS Tayside Guide to Antimicrobial Use
http://www.nhstaysideadtc.scot.nhs.uk/Antibiotic%20site/gtibvag.htm

9. NHS Highland Formulary
http://www.nhshighland.scot.nhs.uk/publications/documents/guidelines/formulary/highland%20formulary.pdf

10. West of Scotland Sexual Health Managed Clinical Network
http://www.wossexualhealthmcn.org.uk/west-of-scotland-managed-clinical-network/resources/guidelines.htm

11. Pfizer Limited. Dalacin cream 2% summary of product characteristics. www.medicines.org.uk Last updated September 2014.

This assessment is based on data submitted by the applicant company up to and including 16 September 2016.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.