Scottish Medicines Consortium

Re-Submission

eflornithine 11.5% cream (Vaniqa®) No. (159/05)
Shire Pharmaceutical Contracts Ltd

5th August 2005

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 resubmission

Eflornithine 11.5% cream (Vaniqa®) is accepted for restricted use within NHS Scotland for the treatment of facial hirsutism in women.

It is restricted to use in women for whom alternative drug therapy is ineffective, contra-indicated or considered inappropriate. Eflornithine 11.5% cream, as a topical treatment, may offer advantages over existing therapy for some women as it avoids the risks associated with systemic therapies.

Overleaf is the detailed advice on this product.

Vice Chairman,
Scottish Medicines Consortium

Eflornithine 11.5% cream (Vaniqa®)

Licensed indication under review

Treatment of facial hirsutism in women

Dosing information under review

The cream should be applied to affected areas of the face and chin twice daily at least eight hours apart.

UK launch date

July 2004

Comparator medications

Co-cyprindiol (combined cyproterone acetate and ethinylestradiol) Dianette®

Cost per treatment period and relevant comparators

The only other product licensed in the UK for the treatment of hirsutism in women is co-cyprindiol.

Medication	Monthly dose	Annual costs (£)*
Eflornithine 11.5% cream	**15 - 30g**	**156 - 312**
Co-cyprindiol	1 tablet daily for 21 days	48

* costs from eVadis drug dictionary accessed in June 2005

Summary of evidence on comparative efficacy

Eflornithine irreversibly inhibits ornithine decarboxylase, an enzyme involved in the production of the hair shaft by the hair follicle.

Two double-blind, phase III trials recruited 596 women with a diagnosis of facial hirsutism, chin and upper lip terminal hair density of at least five hairs per square centimetre, as assessed by video image analysis, and a routine of facial hair removal twice weekly or more. Patients were randomised to treatment with eflornithine 11.5% cream or vehicle cream alone applied twice daily to affected facial areas for 24 weeks, with a treatment-free follow-up period of eight weeks.

The primary efficacy variable in both studies was the Physician's Global Assessment (PGA) of the improvement or worsening of the patient's facial hirsutism from baseline, performed 48 hours after supervised shaving, using a four-point scale: clear/almost clear, marked improvement, improved or no improvement/worse. In the statistical analysis data were dichotomised into treatment success (clear/almost clear and marked improvement) or failure (improved and no improvement/worse). All randomised subjects who received study medication were included in the efficacy evaluation. Subjects who withdrew from the trials had their last observation carried forward. In one study, the success rate in the efficacy population at the end of the 24-week treatment period was significantly greater in the eflornithine group, 24% (95% CI=18–32), than the vehicle group, 4.3% (95% CI=1.2–11)

p≤0.001. The corresponding 24-week success rate in the other study was also significantly greater in the eflornithine group, 44% (95% CI=37–51), than the vehicle group, 13% (95% CI=7.0–21) p≤0.001. The treatment effects were reversed during the eight-week follow-up period after treatment cessation. Evaluation of the primary efficacy variable showed that the rate of treatment success was higher in patients treated with eflornithine compared with vehicle reaching statistical significance from Week 4 onwards in one study and from Week 8 onwards in the other study. The proportion of patients who had at least some improvement in PGA reached a plateau after 8 weeks of treatment, however, the extent of improvement continued to increase throughout the 24-week study period with more subjects achieving at least marked improvement as the study progressed.

The secondary end points in both of these trials were the subject self-assessment questionnaire (SSAQ) and video image analysis (VIA) of the skin and hair of the treatment area.

The SSAQ consisted of six questions on the impact of facial hair on the quality of life. The subjects rated their responses to these questions on an analogue scale from 0-100mm (0=not bothered/uncomfortable: 100=extremely bothered/uncomfortable). In both studies scores at endpoint were significantly lower for all six questions in the eflornithine-treated group compared with the vehicle group.

VIA was performed using a video fibre optic microscope to collect images of the skin, including hair on the treatment sites. Images were transferred to an image analysis system to evaluate hair growth (length) and spatial mass (hair area). No significant differences were found between the eflornithine and vehicle groups in hair length (success defined as at least 50% reduction) in either of the two studies at 24 weeks. However, there was a statistically significant difference in favour of eflornithine in spatial mass in both studies. The European Medicines Agency's European Public Assessment Report, (EPAR), for Vaniqa® notes that the changes in the SSAQ and the video analysis data (hair length and hair mass) were parallel to improvement or lack of improvement of PGA.

Two open-label non-comparative long-term safety and tolerability studies of 6- and 12-months duration recruited women with at least 20 hairs on the chin and upper lip and a routine of at least twice weekly facial hair removal. The primary efficacy variable was success rate defined as clear/almost clear or marked improvement as measured by the PGA score. A total of 216 patients were included in the 12-month study. The success rate among patients who remained in the study at 20 weeks was 18% (32/174), and at 52 weeks was 24% (35/146). The six-month study enrolled a total of 754 patients. At the end of the treatment period, 47% (289/611) of patients who completed the six-month treatment phase had achieved treatment success.

In the 6- and 12-month studies 90% and 81% of subjects respectively showed some level of improvement, PGA of clear/almost clear, marked improvement or improved.

Summary of evidence on comparative safety

In excess of 2000 patients have been exposed to topical eflornithine in clinical trials comparing it with a vehicle containing all the formulation components with the exception of the active component. Systemic absorption of topically administered eflornithine is low (<1%) and most absorbed eflornithine is excreted unchanged in urine with no evidence of metabolism. The majority of adverse events reported during clinical trials were skin-related and mild in nature, with burning, tingling or stinging skin, erythema or rash more frequently reported in the eflornithine group. The most commonly reported adverse event in both the eflornithine and vehicle groups was acne, followed by pseudofolliculitis barbae.

The adverse event profile of the long-term trials was consistent with that reported in the shorter pivotal trials, however, the proportion of subjects reporting acne and folliculitis was lower and alopecia higher. During 2004, a Phase IV safety study will commence to investigate whether treatment with eflornithine is associated with any degree of skin atrophy.

Summary of clinical effectiveness issues

There are no data from direct comparisons between topical eflornithine and oral co-cyprindiol in the treatment of facial hirsutism. Thus, comparative safety and efficacy is uncertain.

The two pivotal phase III clinical trials recruited mainly white women. Subgroup analysis showed a difference in treatment success in favour of Caucasian vs. black women, 31% vs. 13% respectively in one study and 46% vs. 35% respectively in the other. Thus, in practice, black women may not achieve the response rates seen in the pivotal trials. Subgroup analysis also showed that 29% of obese women and 43% of normal-weight women showed a marked or better improvement indicating a less pronounced effect in obese women.

The summary of product characteristics for co-cyprindiol notes that use carries an increased risk of venous thromboembolism (VTE) and that certain factors such as severe obesity (body mass index (BMI) >30kg/m^2), increasing age, genetic predisposition to clotting or idiopathic VTE (where a family history refers to VTE in a sibling or parent at an early age). The last factor is a contra-indication to use of co-cyprindiol and the presence of severe or multiple risk factors for VTE may also constitute a contra-indication. Efficacy and safety of eflornithine cream have not been investigated specifically in patients who are unable to receive co-cyprindiol.

Summary of comparative health economic evidence

A cost utility model was presented which examined the cost-effectiveness of eflornithine in women with facial hirsutism in whom treatment with co-cyprindiol was contra-indicated. The comparator in the economic model was 'no treatment' other than the hair removal methods the women themselves used. The results were derived using a simple model looking at the costs and benefits of eflornithine treatment over a period of 40 years. Utility values for the analysis were obtained from a sample of women from general practice with facial hirsutism and contrasted with the values obtained from a sample of women without facial hirsutism selected from employees of the manufacturer and a consultancy company. From this analysis, the quality of life gain from effective treatment was 0.109 using European Quality of Life (EQ-5D) values.

Assuming a discount rate of 3.5% on costs and benefits and a 20% success rate with treatment, the resulting cost per QALY figure was £7165. If a success rate of 30% was achieved with eflornithine, the cost per QALY figures fell to £4745. Limited sensitivity analysis was provided, but if, for example, a tube of eflornithine lasted only one month instead of two, the cost per QALY increased to £14331 assuming a 20% success rate. It was, however, unclear what allowance was made in these calculations for patients in whom treatment was halted due to lack of efficacy.

In this analysis the comparator was justified for the group of women who would be unable to take the alternative licensed treatment of co-cyprindiol because of a contraindication or lack of clinical appropriateness e.g. high BMI. The modelling approach adopted was appropriate but it is possible that the quality of life gains with treatment are overstated given some potential biases in the way they were derived.

Budget impact

The manufacturer estimated a budget impact over the next five years, assuming an existing patient population of 1100 women and an incident population of 275 women per year thereafter. Assuming a rate of usage of half a tube of eflornithine per month, the estimated impact ranged from £172,000 for 1100 patients treated in year 1 to £343,000 for 2200 patients treated in year 5. If one tube of cream is used per patient per month the corresponding figures were £344,000 for year 1 and £686,000 for year 5.

Guidelines and protocols

There are currently no guidelines available for the treatment of female facial hirsutism.

Additional information

After consideration of a full submission, the Scottish Medicines Consortium issued advice in March 2005 that eflornithine 11.5% cream (Vaniqa) was not recommended for use within NHS Scotland for the treatment of facial hirsutism in woman. There was no evidence of its efficacy in comparison to existing treatments and it is substantially more expensive.

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.

This assessment is based on data submitted by the applicant company up to and including 8 July 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

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

EMEA. The European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products. Scientific discussion. Vaniqa www.emea.eu.int/humandocs/PDFs/EPAR/vaniqa/021201en6.pdf