March 2017

New Medicine Assessment

Eflornithine (Vaniqa®)

Treatment of facial hirsutism

Recommendation: Black

Eflornithine cream is not recommended for use across the Lancashire NHS health economy for the treatment of facial hirsutism. There is limited evidence of efficacy and significant improvement in quality of life. Other cosmetic treatments exist for the management of this condition.

Summary of supporting evidence:

- Eflornithine is the only topical treatment licensed for the treatment of facial hirsutism in women.
- Patients may need to continue to use a hair removal method (e.g. shaving or plucking) in conjunction with eflornithine (Vaniqa®).
- Data from 2 double-blind, phase-III trials showed that there were no significant differences between the eflornithine (Vaniqa®) and vehicle groups in hair growth (length) at 24-weeks.
- There was a statistically significant difference in favour of eflornithine in spatial mass (hair area). [1] [5] [6]
- The high level of drop out in the 2 double-blind phase III trials confer a high risk of bias.
- In the studies of eflornithine as an adjunct to laser therapy, the data from both studies appear to indicate that the effect on hirsutism was mainly due to the laser treatment.
- The Scottish Medicines Consortium (SMC) has restricted use of eflornithine (Vaniqa®) within NHS Scotland for the treatment of facial hirsutism in women for whom alternative drug therapy is ineffective, contraindicated or considered inappropriate. [5]
- The economic analysis submitted to the SMC by the manufacturer indicated that the cost per QALY of eflornithine cream was **£7,165.**
- Assuming a rate of usage of half a tube of eflornithine per month, the estimated impact to the Lancashire health economy is estimated to be **£78,000** in year 1 and **£201,000** in year 5.

Details of Review

Name of medicine (generic & brand name)**:** [1]

Eflornithine (Vaniqa®).

Strength(s) and form(s): [1]

Eflornithine (as Eflornithine monohydrate chloride) 11.5% white to off white cream.

Dose and administration: [1]

Eflornithine cream should be applied to the affected area twice daily, at least 8-hours apart. Efficacy has only been demonstrated for affected areas of the face and under the chin. Application should be limited to these areas. Maximal applied doses used safely in clinical trials were up to 30-grams per month.

Improvement in the condition may be noticed within 8-weeks of starting treatment.

Continued treatment may result in further improvement and is necessary to maintain beneficial effects. The condition may return to pre-treatment levels within 8-weeks following discontinuation of treatment.

Use should be discontinued if no beneficial effects are noticed within 4-months of commencing therapy.

Patients may need to continue to use a hair removal method (e.g. shaving or plucking) in conjunction with eflornithine (Vaniqa®). In that case, the cream should be applied no sooner than 5-minutes after shaving or use of other hair removal methods, as increased stinging or burning may otherwise occur.

BNF therapeutic class / mode of action: [1]

Other dermatological preparations. Eflornithine irreversibly inhibits ornithine decarboxylase, an enzyme involved in the production of the hair shaft by the hair follicle and has been shown to reduce the rate of hair growth.

Licensed indication(s): [1]

Treatment of facial hirsutism in women.

Proposed use (if different from, or in addition to, licensed indication above):

Course and cost: [2]

£56.87 per 60-grams tube.
Example regimen – maximum 30-grams of Vaniqa® cream per month, annual cost = £341.22

Relevant NICE guidance:

NICE Clincal Knowledge Summary: Hirsutism [3]

- Encourage weight loss in women who are overweight or obese
- Discuss methods of hair reduction and removal (such as shaving and waxing), as these will

remain an important part of management

- If hirsutism is mild and does not significantly impact on the woman's quality of life, reassure and advise that no additional treatment is required
- If additional treatment is required:
  - For women with facial hirsutism, offer topical eflornithine (depending on local prescribing policies)
    - If no benefit is seen within 4-months of starting treatment, discontinue treatment and refer the woman to secondary care
    - If improvement is seen, continued treatment is necessary to maintain the benefits; once the cream is discontinued, hair growth returns to pre-treatment levels within about 8-weeks
    - Do not prescribe topical eflornithine to pregnant or breastfeeding women, or women younger than 19-years of age
    - For all other women with hirsutism, offer Dianette® (co-cyprindiol) provided there are no contraindications, such as uncontrolled hypertension and current breast cancer
    - Advise the woman that this is a licensed use of Dianette®, which is a COC containing ethinylestradiol and the anti-androgen cyproterone acetate
    - Discuss the risks associated with the use of Dianette®, for example venous thromboembolism (VTE)
    - Because of an increased risk of VTE, stop treatment with Dianette® 3–4 months after the woman's hirsutism has completely resolved
- If a relapse occurs when Dianette® is stopped, consider the following options:
  - Intermittent use of Dianette® — that is, stopping treatment after resolution occurs, and starting again if symptoms reappear (licensed use)
  - Switching to a COC containing drospirenone (Yasmin®, unlicensed use)
- If COCs are contraindicated or have not worked (after treatment for 6-months or more), refer the woman to secondary care for initiation of a specialist treatment, such as anti-androgens, insulin-sensitizing drugs, or gonadotrophin-releasing hormone analogues

Background and context

Hirsutism is the presence of excess terminal hair growth on the face, chest, linea alba (midline of the abdomen), lower back, buttocks and anterior thighs in women and should not be considered, by itself, a disease. Excess hair growth occurs as a result of increased androgen production, increased skin sensitivity to androgens, or both. [1] [3] [5]

Although the condition may indicate an underlying disorder of androgen production e.g. polycystic ovary syndrome (PCOS), in most cases hirsutism results from a combination of mildly increased androgen production and increased skin sensitivity to androgens (‘idiopathic’ hirsutism). Not all hirsutism is androgen-dependent. Some hair growth in androgen dependent areas is normal, and there is no clear cut-off for defining excessive hair growth. It is important to differentiate between terminal hair (which is dark, thick, and coarse) and vellus hair (which is soft, fine, and unpigmented), as vellus hair does not indicate hirsutism. Androgen-independent hirsutism can be inherited as a familial trait. In addition, drugs such as steroids, cyclosporin, diazoxide and phenytoin, can cause hirsutism. [1] [3] [5]

In premenopausal women, PCOS is the most common cause of hirsutism (more than 70% of cases). No apparent underlying cause is found in about a quarter of women. Androgen secreting tumours, congenital adrenal hyperplasia, Cushing’s syndrome, acromegaly and drugs are less common causes of hirsutism. [1] [3] [5]

In postmenopausal women, a reduction in ovarian oestradiol production with relatively stable levels of testosterone production can lead to an increase in hair growth. In some women, increasing concentrations of luteinizing hormone lead to stromal hyperplasia, high testosterone levels and severe hirsutism. [1] [3] [5]

There are many levels of hirsutism severity. If of minor severity, it is often considered to be a costmetic problem. However, if of sufficient severity, it may have social and psychological influences. The amount of hair a woman will tolerate before it becomes unwanted varies considerably both culturally and racially. Women of Indian or Afro-Carribean origin tend to have less facial or body hair compaired with Caucasians. Among Caucasians, women of Mediterranean origin tend to have a heavier hair growth than those of Nordic origin. [1] [3] [5]

The usual forms of treatment are mechanical hair removal (shaving, plucking, waxing and depilatory creams) and medical treatment. Electrolyis and laser therapy are expensive but effective methods of permanent hair removal. Mechanical methods alleviate the problem temporarily but may result in local irritation. Medical treatment consists mainly of suppressing ovarian (oral contraceptives) or adrenal androgen secretion or of blocking androgen in the skin (e.g cyproterone acetate). The potential for systemic side effects, limits the use of of these treatments. [1] [3] [5]

An underlying cause should be looked for. In women with mild hirsutism and no other signs of PCOS or other underlying condition, investigations are not usually necessary.

In women with moderate-to-severe hirsutism and no other signs of PCOS or other underlying condition, plasma testosterone should be measured. If the testosterone level is greater than 4 nmol/L, referral to endocrinology should be arranged to exclude conditions such as Cushing's syndrome and an androgen-secreting tumour. [1] [3] [5]

Management options in primary care for premenopausal women include: [1] [3] [5]

- Weight loss (if obese or overweight).
- Hair reduction and removal treatments (such as shaving, waxing, electrolysis, or laser treatment)
- A combined oral contraceptive (COC), provided there are no contraindications (such as uncontrolled hypertension and current breast cancer)

Management options in primary care for postmenopausal women include: [1] [3] [5]

- Cosmetic hair reduction and removal
- Weight loss (if obese or overweight)

Referral to a specialist is recommended if: [1] [3] [5]

- There are clinical features suggestive of an androgen-secreting tumour (such as recent onset and rapid progression of hair growth, signs of virilization, very severe hirsutism, or an abdominal or pelvic mass)
- There are clinical features suggestive of Cushing's syndrome (such as facial weight gain [moon face]; weight gain in the neck, upper back, and torso; stretch marks; easy bruising and proximal muscle weakness)
- Hair growth worsens despite treatment
- Treatment has not been effective after at least 6 months' trial

Pharmacology and pharmacokinetics [4]

Eflornithine hydrochloride monohydrate, an amino acid analogue, is intended for the treatment of facial hirsutism in women and is to be applied to the affected areas twice daily. The drug is an irreversible inhibitor of the enzyme ornithine decarboxylase (ODC). ODC is responsible for the catalysis of ornithine to putrescene and is a critical enzyme for cell proliferation and function. Follicular cell proliferation and synthetic functions are important factors in hair growth. As ODC is

present in the hair follicle and implicated in the growth process, eflornithine has been developed as a topical product to treat facial hirsuitism in women. In view of the reported rapid turnover of ODC and the short half-life of eflornithine, continuous treatment is required. [1] [3] [5]

Steady state cutaneous penetration of eflornithine on facial skin of shaving women was 0.8%. The steady state plasma half-life of eflornithine was approximately 8-hours. Steady state was reached within 4-days. The steady state peak and trough plasma concentrations of eflornithine were approximately 10ng/ml and 5ng/ml respectively. The steady state 12-hour area under the plasma concentration versus time curve was 92.5ng.hr/ml. [1] [3] [5]

Eflornithine is not known to be metabolised and is eliminated primarily in the urine. [1] [3] [5]

Summary of evidence

Summary of efficacy data in proposed use:

Randomised-controlled Trials

Two studies evaluated the efficacy of eflornithine as a monotherapy and two studies evaluatated the efficacy of eflornithine as an adjunct to laser therapy.

Monotherapy elflornithine

Wolf et al 2007 conducted two identical double-blind, phase III trials. They 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 (VIA). Each particpipant had 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 8-weeks. [6]

The primary efficacy variable in both studies was the Physician's Global Assessment (PGA) recording improvement or worsening of the patient's facial hirsutism from baseline as assessed by the study investigators. The assessment was 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). Intention to treat analysis was performed and subjects who withdrew from the trials had their last observation carried forward. Data from each study was analysed separately and there was no pooling of the data from the two trials.

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, 24.4% [CI 95% 18.0; 32.0, p≤0.001], than the vehicle group, 4.3% [CI 95% 1.2; 11.0, p≤0.001]. The corresponding 24-week success rate in the second study was also significantly greater in the eflornithine group, 44% [CI 95% 37.0; 51.0, p≤0.001], than the vehicle group, 13% [CI95% 7.0; 21.0, p≤0.001]. The treatment effects were reversed during the 8-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. [6]

Elfornithine as an adjunct to laser therapy

Hamzavi et al 2007 conducted a 6 month randomised, double-blind, placebo-controlled, right-left comparison study comparing eflornithine cream combined with laser treatment versus laser alone for treating unwanted hair on the upper lip in 31 women. Laser treatments were performed every 4 weeks for up to 6 sessions. Each patient also applied either eflornithine or placebo cream twice daily to each side of the upper lip in a double-blinded manner. Subjects were evaluated for safety by recording adverse events and for efficacy via Investigator Global Scoring (primary outcome), patient self assessment and hair count analysis (secondary outcomes). The results for each of the outcomes were as follows:

- Based on the investigator global assessments complete or almost complete hair removal was achieved in 29 of 31 [93.5%] of the eflornithine-laser-treated sites versus 21 of 31 [67.9%] for the placebo cream-laser-treated sites [P =0.021].
- Statistically significant differences in favour of eflornithine were likewise demonstrated at the final assessment through blinded patient self assessment (13/31 patients [41.9%] thought that the eflornithine was superior to placebo, [P =0.029]).
- Hair counts with eflornithine were 7.9% [CI 95%, 2.4; 13.3, P< 0.01] lower than placebo.[7]

Smith et al 2006 conducted a 34 week randomised double-blind study of 64 women comparing elfornithine with a placebo vehicle. Subjects were randomized to treatment with eflornithine on one side of the face and vehicle on the contralateral side for 34 weeks. Subjects received laser therapy to both sides of the face at Weeks 2 and 10. Blinded evaluations included left to right comparisons and appearance relative to baseline by patients (primary outcome). For the primary outcome 60% (32/54) of the 54 participants that finished the treatment preferred the eflornithine treated side compared to 20% (11/54). Ten out of the 64 (15.6%) participants did not complete the study.[8]

Reviews

The Scottish Medicines consortium (SMC) undertook an assessment of the use of eflornithine for the treatment of facial hirsutism in women and advised restricted use of the product within NHS Scotland in patients for whom alternative drug therapy is ineffective, contraindicated or considered inappropriate. However, it concluded that 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. [5]

PrescQIPP Bulletin 57 (DROP List) suggested that there is limited evidence for efficacy and patient satisfaction with eflorithine. [9]

The Midlands Therapeutic Review and Advisory Committee (MTRAC), states that the evidence for the safety and efficacy of eflornithine was considered to be weak. Although eflornithine is the only topical treatment available for hirsutism, it was considered to have a low place in therapy, as the long term safety of the drug has not been evaluated and has not been compared with the only other licensed therapy, co-cyprindiol. [10]

Other efficacy data:

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 6-month study enrolled a

total of 754-patients. At the end of the treatment period, 47% (289/611) of patients who completed the 6-month treatment phase had achieved treatment success. [5]

In the 6- and 12-month studies 90% and 81% of subjects respectively showed some level of improvement. [5]

Summary of safety data:

Preclinical safety data

According to the SPC for Vaniqa® non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity, genotoxicity and carcinogenic potential, including one photocarcinogenicity study in mice. In a dermal fertility study in rats, no adverse effects on fertility were observed at up to 180 times the human dose. In dermal teratology studies, no teratogenic effects were observed in rats and rabbits at doses up to 180 and 36 times the human dose, respectively. Higher doses resulted in maternal and foetal toxicity without evidence of teratogenicity. [1]

Clinical safety

In excess of 2,000-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 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. [5]

Table 1 : Number (%) of Subjects with Treatment Related Skin and Appendages Adverse Events [4]

	Eflornithine (N=395) n (%)	Vehicle (N=201) n (%)
Acne	84 (21.3)	43 (21.4)
Pseudofolliculitis barbae	64 (16.2)	31 (15.4)
Burning, stinging, tingling skin	56 (14.2)	10 (5.0)
Pruritis	15 (3.8)	8 (4.0)
Rash, Papular rash	8 (2.0)	0 (0.0)
Dry Skin	7 (1.8)	6 (3.0)
Alopecia	6 (1.5)	5 (2.5)
Erythema	5 (1.3)	0 (0.0)
Skin irritation	5 (1.3)	2 (1.0)
Dermatitis	4 (1.0)	1 (0.5)

Interaction with other medicinal products

No interaction studies have been performed with Vaniqa® since it is a product for topical use and the systemic exposure to the drug is low. However, the company submitted results to the EMA from *in vitro* inhibition studies of eflornithine with recombinant human cytochrome P450 isoenzymes. The studies showed that eflornithine is not an inhibitor of metabolism by these enzymes and the likelihood of drug-drug interactions of eflornithine with their respective substrates is low. [1]

Pregnancy

Throughout clinical trials, data from a limited number of exposed pregnancies (22) indicate that there is no clinical evidence that treatment with Vaniqa® adversely affects mothers or foetuses. Among the 22 pregnancies that occurred during the trials, only 19 pregnancies occurred while the patient was using Vaniqa®. Of these 19 pregnancies, there were 9 healthy infants, 5 elective abortions, 4 spontaneous abortions and 1 birth defect (Down's Syndrome to a 35-year old). To date, no other relevant epidemiological data are available. Animal studies have shown reproductive toxicity, although the potential risk to humans is unknown. Therefore, women who are pregnant or planning pregnancy should use an alternative means to manage facial hair. [1]

Breastfeeding

It is not known if eflornithine is excreted in human milk, however women should not use Vaniqa® whilst breastfeeding. [1]

Fertility

There are no data available. [1]

Strengths and limitations of the evidence:

Strengths

1. The SMC concluded that 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. [5]
2. 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 second study. [1] [5] [6]
3. Studies have been conducted of eflornithine in combination with laser surgery which may reflect the use of eflornithine in clinical practice. [12]
4. Adverse effects observed in the studies were mild and confined to the skin.

Limitations

1. Limited data is available regarding the efficacy of eflornithine from six relatively small studies totalling 907 patients.
2. The largest study **Wolf et al 2007** had a high drop out rate of 153 from the initial 596 women randomised representing a high risk of bias. [6]
3. In the studies of eflornithine as an adjunct to laser therapy, the authors suggest the data from both studies indicate that the effect on hair removal is mainly due to the laser treatment. [8]
4. Eflornithine has not been evaluated or compared with the only other licensed therapy for hirsutism, co-cyprindiol. [7]
5. PrescQIPP Bulletin 57 (DROP List) suggested that there is limited evidence for efficacy and patient satisfaction with eflorithine. [9]

Summary of evidence on cost effectiveness:

A cost utility model was presented to the SMC examining 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. [5]

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. [5]

In the 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. [5]

Prescribing and risk management issues:

None

Commissioning considerations:

Table 2: Comparative Unit Costs: [1] [2] [11]

Drug	Example regimen	Pack cost	Cost per year given 30g usage per month (ex VAT)
Eflornithine 11.5% cream	Maximum 30g per month	£56.87 ¥ per 60g tube	£341.22
Co-cyprindiol 2mg / 35micrograms	1 daily for 21-days	£5.70 ¥ per 63-tablets	£22.80

This table does not imply therapeutic equivalence of drugs or doses. ¥ Prices: NHS Electronic Drug Tariff (December 2016).

Based on data available from PrescQIPP DROP-List Scorecard [9], the total spend on eflornithine over a 12-month period between Nov15 – Oct16 across the Lancashire health economy was **£47,832.** The total spend on co-cyprindol for the treatment of hirsutism can not be ascertained due to its use in the treatment of moderate to severe acne.

Associated additional costs or available discounts:

There are no known currently available manufacturer discounts.

Productivity, service delivery, implementation:

Most women presenting with facial hirsutism should be managed by a GP in primary care. However, referral to a Specialist is recommended if:

- there are clinical features suggestive of an androgen-secreting tumour (sudden onset or rapid progression of hair growth, severe hirsutism, signs of virilisation, a pelvic or abdominal mass) or Cushing's syndrome (weight gain in the neck, upper back and torso, moon face, stretch marks, easy bruising, proximal muscle weakness)
- hair growth worsens despite treatment
- serum total testosterone concentration ≥ 4 nanomol/L, refer urgently (within 2-weeks) if testosterone level is ≥ 6-7 nanomol/L
- elevated 17-hydroxyprogesterone levels

Anticipated patient numbers and net budget impact:

Based on the data from prescQIPP of the total spend on Vaniqa® and the cost per year of Vaniqa® per patient, the equivalent of 140 patients receive treatment with Vaniqa® over a 1 year period in the Lancashire health economy.

Using assumptions from the economic model presented to the SMC it would be expected that an additional 90 patients per year would require treatment with Vaniqa® thereafter.

Assuming a rate of usage of half a tube of eflornithine per month, the estimated impact ranged from **£78,000** for 230 patients treated in year 1 to **£201,000** for 590 patients treated in year 5.

If one tube of cream is used per patient per month the corresponding figures were **£156,000** for year 1 and **£402,000** for year 5.

Innovation, need, equity:

Eflornithine is the only topical treatment licensed for the treatment of facial hirsutism in women. Self-funded cosmetic treatments for reduction in hair growth or hair removal (e.g. shaving, plucking, laser treatment, electrolysis) are available and may be required irrespective of eflornithine use.

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