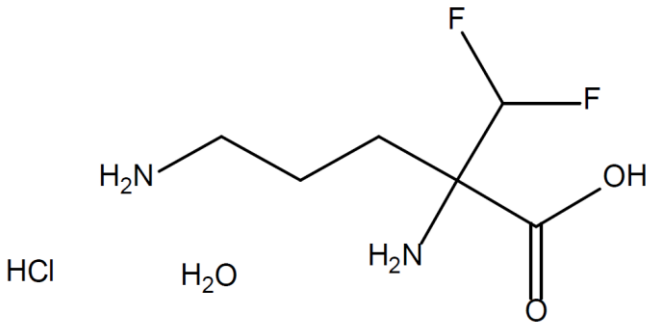
PRODUCT INFORMATION
VANIQA®
EFLORNITHINE CREAM, 11.5%

NAME OF THE MEDICINE

eflornithine hydrochloride

Chemically, eflornithine hydrochloride (±)-2-(difluoromethyl) ornithine monohydrochloride monohydrate.

Chemical Structure



Empirical formula: $C_6H_{12}F_2N_2O_2.HCl.H_2O$

Molecular weight: 236.65

CAS Number

96020-91-6

DESCRIPTION

Vaniqa is a cream containing 11.5% (115 mg/g) of eflornithine as eflornithine hydrochloride monohydrate (150 mg/g).

Vaniqa is supplied as a cream in a 30 gram tube.

Vaniqa contains the following inactive ingredients: ceteareth-20, cetostearyl alcohol, dimethicone 200, glyceryl monostearate, methyl hydroxybenzoate, paraffin – light liquid, PEG-100 stearate, phenoxyethanol, propyl hydroxybenzoate, stearyl alcohol, water and sodium hydroxide.

PHARMACOLOGY

Pharmacodynamics

There are no studies examining the inhibition of the enzyme ornithine decarboxylase (ODC) in human skin following the application of topical eflornithine. However, there are studies in the literature that report the inhibition of ODC activity in skin following oral eflornithine. It is postulated that topical eflornithine hydrochloride irreversibly inhibits skin ODC activity. This enzyme is necessary in the synthesis of polyamines. Animal data indicate that inhibition of ornithine decarboxylase inhibits cell division and synthetic functions, which affect the rate of hair growth. Vaniqa has been shown to retard the rate of hair growth in non-clinical and clinical studies.

Eflornithine blocks the biosynthesis of polyamines by inhibiting the enzyme ornithine

decarboxylase (ODC). *In vivo* studies in hamsters have shown that eflornithine inhibits ODC in hair follicles when applied topically. Eflornithine penetrates the skin and inhibits ODC in a time-dependent manner. *In vivo* studies in mice and hamsters indicated that topically applied eflornithine suppresses hair growth, however suppression was not dose-dependent. There are studies in the literature that report the inhibition of ODC activity in skin following oral eflornithine. However, the ability of topically applied eflornithine to inhibit ODC in human skin has not been investigated.

Pharmacokinetics

Absorption.

The mean percutaneous absorption of eflornithine in women with unwanted facial hair, from a 13.9% w/w cream formulation, is < 1% of the radioactive dose. This follows either single or multiple doses under conditions of clinical use that included shaving within 2 hours before radiolabelled dose application in addition to other forms of cutting or plucking and tweezing to remove facial hair.

Distribution.

Steady-state was reached within four days of twice-daily application. The apparent steady-state plasma t1/2 of eflornithine was approximately 8 hours. Following twice-daily application of 0.5 g of the cream (total dose 1.0 g/day; 139 mg as anhydrous eflornithine hydrochloride), under conditions of clinical use in women with unwanted facial hair (n=10), the steady-state C_{max}, C_{trough} and AUC12hr were approximately 10 ng/mL, 5 ng/mL and 92 ng.hr/mL, respectively, expressed in terms of the anhydrous free base of eflornithine hydrochloride. At steady-state, the dose-normalised peak concentrations (C_{max}) and the extent of daily systemic exposure (AUC) of eflornithine following twice-daily application of 0.5 g of the cream (total dose 1.0 g/day) is estimated to be approximately 100- and 60-fold lower, respectively, when compared to 370 mg/day once-daily oral doses.

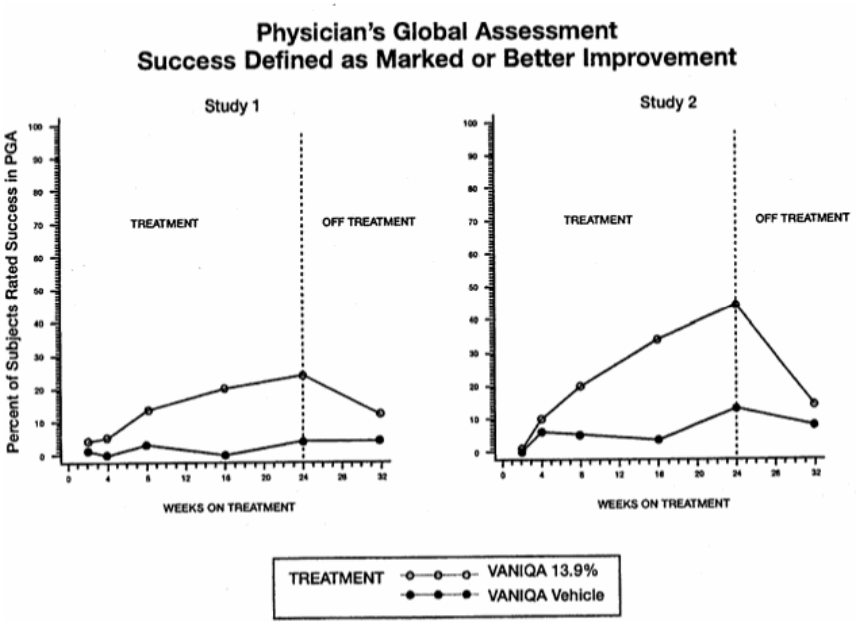
Metabolism and Excretion.

This compound is not known to be metabolised and is primarily excreted unchanged in the urine.

CLINICAL TRIALS

Results of topical dermal studies for contact sensitisation, photocontact sensitisation, and photocontact irritation reveal that under conditions of clinical use, Vaniqa is not expected to cause contact sensitisation, phototoxic, or photosensitisation reactions. Results of the topical dermal study for contact irritation did reveal that Vaniqa could cause irritation reactions in clinical use in susceptible individuals or under conditions of exaggerated use.

Two randomised double-blind studies, involving 594 female patients (393 treated with Vaniqa, 201 with vehicle) treated twice daily for up to 24 weeks, evaluated the efficacy of Vaniqa in the reduction of unwanted facial hair in women. Women in the trial had a customary frequency of removal of facial hair two or more times per week. Women with facial conditions such as severe inflammatory acne, who had recently used alternative hair removal techniques, who were receiving concomitant medication for the treatment of hirsutism or treatments that could exacerbate hirsutism, women who were pregnant, and nursing mothers were excluded from the studies. Physicians assessed the improvement or worsening from the baseline condition (Physician's Global Assessment [PGA]), 48 hours after shaving, of all treated areas. Statistically significant improvement for Vaniqa versus vehicle was seen in each of these studies for "marked improvement" or greater response (24-week time point; $p \leq 0.001$). Marked improvement was seen consistently at 8 weeks after initiation of treatment and continued throughout the 24 weeks of treatment. Hair growth was not significantly different from pre-treatment levels after 8 weeks of treatment withdrawal. The success rate over time is graphically presented below for each pivotal trial.



Combining the two trials, approximately 32% of patients showed marked improvement or greater (protocol definition of clinical success) after 24 weeks of treatment with Vaniqa, compared to 8% with the vehicle. Combined results of these two trials through 24 weeks are presented below.

PGA Outcome	Vaniqa	Vehicle
Clear/almost clear	5%	0%
Marked improvement	27%	8%
Improved	26%	26%
No improvement/worse/missing	42%	66%

Subgroup analyses appeared to suggest greater benefit for Whites than non-Whites (37% vs. 22% success, respectively; p=0.017). However, non-Whites, mostly Black subjects, did have significant treatment benefit with 22% graded as success on Vaniqa compared to 5% on vehicle.

About 12% of women in the clinical trials were postmenopausal. Significant improvement in PGA outcome versus vehicle was seen in postmenopausal women (38% compared to 0%, p≤0.001).

Vaniqa statistically significantly reduced how bothered patients felt by their facial hair and by the time spent removing, treating, or concealing facial hair. These patient-observable differences were seen as early as 8 weeks after initiating treatment. Hair growth approached pretreatment levels within 8 weeks of treatment withdrawal.

The combined experience in clinical trials with Vaniqa involved over 1370 women with unwanted facial hair of skin types I-VI, of whom 68% were White, 17% Black, 11% Hispanic-Latino, 2% Asian-Pacific Islander, 0.6% American Native and 1.3% other. The longest evaluation time of Vaniqa observed in a clinical trial was 52 weeks. One hundred and forty-two subjects completed this non-randomised, open-label study.

No studies have been conducted to compare Vaniqa to other treatments registered for the reduction of unwanted facial hair in women. Also, no data exists regarding the combined therapy of Vaniqa with orally administered treatments.

INDICATIONS

Vaniqa delays the regrowth of unwanted facial hair, following depilation, in women.

CONTRAINDICATIONS

Vaniqa is contraindicated in patients with a history of sensitivity to any components of the preparation.

Vaniqa is also contraindicated in patients with severe renal impairment.

PRECAUTIONS

Vaniqa has only been studied on the face and adjacent involved areas under the chin of affected individuals. Usage should be limited to these areas of involvement.

General:

For external use only.

Discontinue use if hypersensitivity occurs.

Transient stinging or burning may occur when applied to abraded or broken skin.

Information for Patients

Patients using Vaniqa should receive the following information and instructions:

1. This medication is not a depilatory, but rather appears to retard hair growth to improve the condition and the patient's appearance. Patients will likely need to continue using a hair removal method (e.g. shaving, plucking, etc.) until the desired level of hair reduction is achieved.
2. Onset of improvement was seen after as little as 4-8 weeks of treatment in the 24-week clinical trials. The condition may return to pretreatment levels 8 weeks after discontinuing treatment.
3. If skin irritation or intolerance develops, direct the patient to temporarily reduce the frequency of application (e.g. once a day). If irritation continues, the patient should discontinue use of the product.

Refer to the Consumer Medicine Information leaflet for additional important information and instructions.

Carcinogenicity

There were no treatment-related increases in tumour incidence in a two year carcinogenicity study in mice receiving topical doses of eflornithine up to 600 mg/kg/day. These doses resulted in exposures to eflornithine up to ~40 times the exposure anticipated clinically based on plasma AUC.

In a one year photo-co-carcinogenicity study, mice received topical doses of ethlornithine up to 600 mg/kg/day (~18 times anticipated clinical exposure based on BSA). The vehicle alone enhanced the tumourigenicity of ultraviolet light. Animals treated with eflornithine exhibited a tumour incidence similar to that of untreated controls.

Eflornithine was not genotoxic in assays for gene mutation in bacteria or clastogenicity in human lymphocytes in vitro. In an in vivo micronucleus test carried out in rats, 900 mg/kg of eflornithine applied topically (~50 times the exposure anticipated clinically based on BSA), the frequency of micronucleated polychromatic erythrocytes in bone marrow was unaffected. Systemic absorption of eflornithine in rats following topical administration is below 1%, and thus it is unlikely that adequate levels of eflornithine were attained in the bone marrow of rats to clearly demonstrate a lack of genotoxicity in vivo.

Use in pregnancy (category B3)

There are no adequate or well-controlled studies of eflornithine in pregnant women.

In a fertility and early embryonic development study in rats treated topically with eflornithine, there were no adverse effects on fertility at doses up to 450 mg/kg (~25 times the anticipated clinical expose based on BSA). In a peri- and postnatal study in rats, eflornithine administered in the drinking water was associated with maternal toxicity and reduced pup weights at doses ≥480 mg/kg (~30 times the anticipated clinical exposure based on BSA). The fertility of the F1 generation was reduced by the treatment of the F0 dams at 1330 mg/kg (~80 times the anticipated clinical exposure based on BSA). In the latter study, the multiples of human exposure are likely to be much higher, since eflornithine is well absorbed orally in rats, whereas minimal absorption occurs in humans treated topically.

In pregnant rats, suspected of oral ingestion of eflornithine during days 0 to 19 of gestation, maternal toxicity and fetel effects including reduced numbers of live fetuses, decreased fetal

weights, and delayed ossification and development of the viscera were observed at doses ≥225 mg/kg/day (~18 times the anticipated clinical exposure based on BSA) of eflornithine topically. In rabbits, topical administration of 15% eflornithine at a dose of 30 mg/kg from day 6 through 18 of gestation adversely affected maternal body weight and weight gain and both absolute and relative feed consumption. Post-implantation loss was also significantly higher than the control at this dose. The NO AEL in rabbits was 90 mg/kg/day, which is approximately 15 times the exposure (based on B SA), anticipated clinically.

Effects on fertility

In a dermal fertility and early embryonic development study in rats treated with Vaniqa there were no adverse reproductive effects at doses up to 450 mg/kg (29 times the MRHD based on BSA). In a peri- and postnatal study in rats, eflornithine administered in the drinking water was associated with maternal toxicity and reduced pup weights at doses of at least 625 mg/kg (40 times the MRHD based on BSA) and a slightly reduced fertility index, which was considered to be of questionable biological significance, at 1698 mg/kg (110 times the MRHD based on BSA). No effects were seen with an oral dose of 223 mg/kg (14 times the MRHD based on BSA). In the latter study, the multiples of the human exposure are likely to be much higher, since eflornithine is well absorbed in rats, whereas minimal absorption occurs in humans treated topically.

Use in lactation

It is not known whether or not eflornithine hydrochloride is excreted in human milk. Caution should be exercised when Vaniqa is administered to a nursing woman.

Paediatric Use

The safety and effectiveness of this product have not been established in paediatric patients less than 12 years of age.

Use in the elderly

Of the 1373 patients on active treatment in clinical studies of Vaniqa, approximately 7% were 65 years or older and approximately 1% were 75 or older. No apparent differences in safety were observed between older patients and younger patients.

Effect on laboratory tests

No laboratory test abnormalities have been consistently found to be associated with Vaniqa. In an open labelled study, some patients showed an increase in their transaminases; however, the clinical significance of these findings is not known.

INTERACTIONS WITH OTHER MEDICINES

It is not known if Vaniqa has any interaction with other topically applied drug products.

ADVERSE EFFECTS

Adverse events reported for most body systems occurred at similar frequencies in Vaniqa and vehicle control groups. The most frequent adverse events related to treatment with Vaniqa were skin-related. The following table notes the percentage of adverse events associated with the use of Vaniqa or its vehicle that occurred at greater than 1% in both the vehicle-controlled studies and the open-label safety studies after up to 1 year of continuous use.

Adverse Event Term	Vehicle-Controlled Studies		Vehicle-Controlled and Open-Label Studies
	VANIQA (n=393)	*Vehicle (n=201)*	*VANIQA (n=1373)*
Acne	21.3	21.4	10.8
Pseudofolliculitis Barbae	16.3	15.4	4.9
Stinging Skin	7.9	2.5	4.1
Headache	3.8	5.0	4.0
Burning Skin	4.3	2.0	3.5
Dry Skin	1.8	3.0	3.3
Pruritus (itching)	3.8	4.0	3.1
Erythema (redness)	1.3	0.0	2.5
Tingling Skin	3.6	1.5	2.2
Dyspepsia	2.5	2.0	1.9
Skin Irritation	1.0	1.0	1.8
Rash	2.8	0.0	1.5
Alopecia	1.5	2.5	1.3
Dizziness	1.5	1.5	1.3
Folliculitis	0.5	0.0	1.0
Hair Ingrown	0.3	2.0	0.9
Facial Edema	0.3	3.0	0.7
Anorexia	1.0	2.0	0.7
Nausea	0.5	1.0	0.7
Asthenia	0.0	1.0	0.3
Vertigo	0.3	1.0	0.1

In the controlled studies, skin adverse events which occurred with active treatment greater than that seen with vehicle (as shown in the table above) included stinging skin, burning skin, erythema, tingling skin and rash.

Adverse events were primarily mild in intensity and generally resolved without medical treatment or discontinuation of Vaniqa. Only 2% of subjects discontinued studies due to an adverse event related to the use of Vaniqa.

DOSAGE AND ADMINISTRATION

A thin layer of Vaniqa should be applied to affected areas of the face and adjacent involved areas under the chin, and rubbed in thoroughly. The treated areas should not be washed for at least 4 hours. Vaniqa should be used twice daily at least 8 hours apart or as directed by your doctor. The patient should continue to use hair removal techniques as needed in conjunction with Vaniqa. (Vaniqa should be applied at least 5 minutes after hair removal.) Cosmetics or sunscreens may be applied over treated areas after cream has dried.

OVERDOSAGE

Overdosage information with Vaniqa is unavailable. Given the low percutaneous penetration of this drug, overdosage via the topical route is not expected (see PHARMACOLOGY). However, should very high topical doses (e.g. multiple tubes per day) or oral ingestion be encountered (a 30 g tube contains 4.2 g of eflornithine hydrochloride), the patient should be monitored and appropriate supportive measures administered as necessary.

(Note: Use of an intravenous formulation of eflornithine hydrochloride at high doses (400 mg/kg/day or approximately 24 g/day) for the treatment of Trypanosoma brucei gambiense infection (African sleeping sickness) has been associated with adverse events

and laboratory abnormalities. Adverse events in this setting have included hair loss, facial swelling, seizures, hearing impairment, stomach upset, loss of appetite, headache, weakness and dizziness. A variety of haematological toxicities, including anaemia, thrombocytopenia and leukopenia have also been observed, but these were usually reversible upon discontinuation of treatment.)

PRESENTATION AND STORAGE CONDITIONS

Vaniqa is available as a 30 gram tube.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

A. Menarini Australia Pty Ltd
Level 8, 67 Albert Ave,
Chatswood NSW 2067
Australia

POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (S4)

AUSTRALIAN REGISTRATION NUMBER

AUST R 80167

DATE OF FIRST INCLUSION IN THE ARTG:

14 August 2002

DATE OF MOST RECENT AMENDMENT:

17 August 2016