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New Drug Spotlight

# Vaniqa – Eflornithine 13.9% Cream

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## ABSTRACT

*Eflornithine HCl 13.9% cream is the first topical prescription treatment to be approved by the US FDA for the reduction of unwanted facial hair in women. It irreversibly inhibits ornithine decarboxylase (ODC), an enzyme that catalyzes the rate-limiting step for follicular polyamine synthesis, which is necessary for hair growth. In clinical trials eflornithine cream slowed the growth of unwanted facial hair in up to 60% of women. Improvement occurs gradually over a period of 4–8 weeks or longer. Most reported adverse reactions consisted of minor skin irritation.*

**KEY WORDS:** *eflornithine, ornithine decarboxylase inhibitor, reduction of unwanted facial hair in women*

The first topical prescription treatment for the reduction of unwanted facial hair in women, eflornithine HCl 13.9% cream (*Vaniqa*, Bristol-Myers Squibb), was approved by the US FDA in August 2000. This product is an irreversible inhibitor of ornithine decarboxylase (ODC), an enzyme that is critical for the biosynthesis of cationic polyamines, which are necessary for cell growth. *Vaniqa* appears to be effective regardless of whether the unwanted facial hair is hereditary or whether it is due to medical conditions such as an androgen excess disorder, e.g., polycystic ovarian syndrome.

## The Hair Growth Cycle

All hair undergoes an intrinsic, rhythmic, cyclical growth pattern consisting of three phases. Periods of growth (anagen) are followed by periods in which the bulbar portion of the follicle is almost totally degraded through apoptosis (catagen), which is then followed by the resting phase (telogen). The duration of anagen on the face is usually 16 weeks, whereas on the scalp it typically continues for 150 weeks. Catagen lasts for 1 week on both the scalp and face, and telogen lasts for 6 weeks on the face, and 12 weeks on the scalp. Each hair follicle consists of a permanent and non-permanent portion with the lowermost aspect of the permanent portion located at the level of the insertion of the arrector pili muscle, also known as the "follicular bulge".

The rate of growth for hair is approximately 0.44mm/day on the scalp, and 0.27mm/day for beards. Seasonal variation does exist with a higher rate of growth in the summer (July/August), as compared to the winter months (Jan/Feb). This variability correlates with fluctuations in androgen levels where higher levels of testosterone occur during the summer months.

In principle, there are three ways to slow down hair growth: 1) decrease the anagen phase, 2) delay the onset of anagen following the telogen phase, or 3) prolong telogen. While neither the telogen phase, nor the onset of anagen can yet be prolonged pharmacologically, the anagen phase can be reduced.

## Ornithine Decarboxylase

ODC is an enzyme that is key to the formation of cationic polyamines, which in turn are necessary for cellular migration, differentiation and proliferation. Polyamines are low molecular weight, aliphatic, non-protein, nitrogenous bases that are predominantly found in proliferating tissues.

## The Polyamine Pathway

L-Ornithine → Putrescine → Spermidine → Spermine

**Ornithine decarboxylase**

ODC activity and its biosynthetic products, putrescine and spermidine are usually low in normal resting cells, but high in

proliferating cells, such as within anagen follicles. As well, ODC and putrescine were found to be higher in psoriatic skin, and putrescine is twice as high in the serum of psoriatic patients.[1]

In terms of hair growth, investigators reported that ODC activity increased in rodent skin within four hours after hair plucking. This is much sooner than the earliest reported increases in matrix cell labeling indices after hair plucking,[2–4] which implies that ODC activity increases prior to the onset of increased mitotic activity. In embryonic human epidermis, ODC was found to be expressed in the ectodermal cells at sites where follicles develop, and to persist in cells at the leading edge of the follicular placode. ODC is abundantly expressed in the proliferating bulb cells of anagen follicles, and entry of the follicle into catagen is accompanied by a down-regulation of ODC expression, which persists until the next follicular growth cycle is initiated. In animal vibrissae, ODC is expressed in a group of outer root sheath cells near the follicle bulge, which is the putative site of hair follicle stem cells.[5,6] ODC activity is particularly high at the level of the bulb.

Increased ODC activity, has thus been associated with prolongation of anagen, and conversely, when ODC is decreased, anagen is reduced, thereby slowing hair growth. ODC activity is also reduced during the telogen phase.[7]

## *Pharmacokinetics*

The mean percutaneous absorption for eflornithine 13.9% cream is less than 1%, and the steady-state peak serum concentration is less than 10ng/ml. It is not metabolized and is excreted unchanged in the urine. The time required to reach steady-state is 4 hours. The plasma half-life is 8 hours.[8]

Patients were seen at baseline, day 2, and weeks 2, 4, 8, 12, 16, 20, 24, and 32. At all visits a clinical assessment, self-assessment, video imaging, photographs and safety data were taken. Efficacy was determined by a Physician's Global Assessment using a 4-point scale: clear to almost clear, marked improvement, improved, no improvement. All clinical assessments were made 48 hours after shaving. Statistically and clinically significant improvement was noted in the eflornithine group as compared to the vehicle control group at 8 weeks and continued for 24 weeks. However, hair regrowth approached pretreatment levels within 8 weeks of treatment withdrawal.

The subject self-assessment showed marked improvement with the use of *Vaniqa*. The mean overall level of discomfort or bother was reduced by 33% for the eflornithine group after 24 weeks based on a self-assessment questionnaire and a visual analog scale. There were no significant differences for patients using the placebo vehicle in this same period of time.[10]

## *Adverse Events*

Skin related side effects such as stinging, burning and tingling occurred in a few patients, particularly when eflornithine was applied to broken or abraded skin. Only 2% discontinued eflornithine due to an adverse reaction in the United States. This drug is classified as a Pregnancy Category C agent, so risk to the fetus cannot be ruled out.

## *Dosage and Cost*

*Vaniqa* is supplied in a 30gm tube, and should be applied twice daily. The area should not be washed for 4 hours after application, but cosmetics and sunscreens can be applied over treated areas once the cream has dried. The cost is $50.00 USD for a 30gm tube.

| Outcome | *Eflornithine* | Vehicle |
|---|---|---|
| Clear/almost clear | 5% | 0 |
| Marked improvement | 27% | 8% |
| Improved | 26% | 26% |
| No improvement | 42% | 66% |

**Table 1**: 58% of *Vaniqa* group demonstrated improvement versus 34% of placebo (p <.001)

## *Clinical Trial Results*[9]

Two multi-center, double-blinded, vehicle controlled, randomized studies were carried out in the US and Europe. The first trial was conducted in 10 US centers: n=285 (189 *Vaniqa* cream/96 vehicle), and second took place at 8 centers in the US and 1 in Europe: n=309 (206 *Vaniqa*/103 vehicle). All ethnic groups and skin types were included, and all women were removing at least 5 hairs/cm$^2$ on the chin and upper lip at least twice/week prior to study entry.

The treatment regimen consisted of twice daily application of the creams for 24 weeks, followed by 8 weeks of no treatment.

## *Conclusion*

Eflornithine HCl 13.9% cream, used twice daily is effective for unwanted facial hair in women and complements other current hair removal methods by slowing the rate of hair regrowth. In order to prevent regrowth, eflornithine treatment must be continued indefinitely.

*continued on page 5*

# Treatment of *Toxicodendron* Dermatitis (Poison Ivy And Poison Oak)

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## ABSTRACT

Toxicodendron *dermatitis results from a reaction to an oil soluble oleoresin that is present in many parts of the poison ivy and poison oak plants. Prophylactic measures include avoidance, protective clothing, barrier creams and hyposensitization. Treatments include washing the area immediately with a solvent suitable for lipids and the use of anti-inflammatory agents, especially corticosteroids.*

**KEY WORDS:** *poison ivy, poison oak,* Toxicodendron *dermatitis*

Poison-ivy dermatitis, the prototype allergic contact dermatitis, is so common in North America that physicians at all levels of training usually recognize it. Approximately 61% of persons in the United States are patch-test positive, and another 31% seem to become sensitive after they are exposed.[1] The acute, often vesicular eczema typically appears in hand print and finger-mark patterns because it is often transferred from the hands to areas of skin that absorb more efficiently.[2] This results in the formation of "streaks" of vesicles and sometimes bullae that are recognized by physicians as "poison ivy" (dermatitis). The allergy is to an oil soluble oleoresin present in tiny "resin" canals in many parts of the plant. Chemically the antigenic material comprises alk(en)yl catechols with predominantly pentadec(en)yl catechols in poison ivy and heptadec(en)yl catechols in both eastern and western poison oak.[2,3] The mechanism is a classic delayed hypersensitivity-type allergic contact dermatitis mediated predominantly through the endogenous pathway by CD8+ T-cells. The basic mechanism is presented in two recent reviews.[2,4]

Prophylactic measures for *Toxicodendron* dermatitis include avoidance, protective clothing, barrier creams, hyposensitization, and cleansing the affected area right away with soap and water or a solvent suitable for lipids. Anti-inflammatory agents, especially corticosteroids are used for treatment.

## *Prophylaxis*

The most effective way to prevent contact dermatitis to poison ivy is avoidance of the plant, and this requires plant recognition in all four seasons. The method used for identification of poison ivy, poison oak and poison sumac is given in several published reviews.[5–7] Several suggestions are illustrated in Figure 1. When one is in doubt as to whether or not a plant is a *Toxicodendron*, the black-spot test[8] can be done by crushing sap from leaves onto a sheet of white paper, observing precautions. The resulting stain should darken on exposure to the air if it came from a *Toxicodendron*. However, this test employs only one quality of these plants, and should not be a substitute for other proved means of identification.[8]

For persons at risk, protective clothing is recommended. Vinyl (PVC) gloves are especially useful, but rubber gloves allow penetration of the antigen.[11] Contaminated fomites e.g., animal fur, garden tools and even clothing, can also transfer the antigen. If garments are only mildly to moderately soiled, they may be amenable to washing or better dry cleaning.

A number of barrier substances may reduce the severity of reactions from a standardized exposure. Examples include *Ivy Block*, quaternium-18 bentonite cream,[12-14] or *Stokogard cream*.[15] The last product contains multiple amino groups that are intended to prevent absorption by binding the antigen on the skin surface.[15] It is applied prophylactically and washed off within a few hours. *Ivy Block* is an OTC preparation that has been approved by the U.S. Food and Drug Administration. It reduces experimental patch test reactions. A number of creams have some efficacy,[16] but some products marketed for this purpose, while possessing some benefit, are somewhat less potent.[17]

## *Hyposensitization*

Oral and injectable urushiol has been administered to achieve a form of hyposensitization. Earlier investigators such as Shelmire[18] were able to produce reduced reactivity with relatively crude preparations. This usually involved administration of progressively increasing doses of the causative antigen by mouth or by injection, over a period of many months.[19,20] However, sometimes complications were severe.[18] The degree of hyposensitization in modern times has usually been less dramatic, but still useful. The earlier reports of greater success probably were achieved at somewhat greater risk of complication, and today the antigens available are, for the most part, too weak to be effective at the dosages recommended.[21] Interestingly, people who are exposed daily in their workplace tend to develop a form of individual tolerance called "hardening." A classic example occurs in workers applying Japanese lacquer.[22] It is also seen in patients treated for alopecia areata and other conditions where contact dermatitis is repeatedly produced therapeutically.[23] The kits that were once used for oral hyposensitization are no longer available. The reason for such oral hyposensitization seems to be induced by anti-idiotypic antibodies.[24]

*continued on page 4*

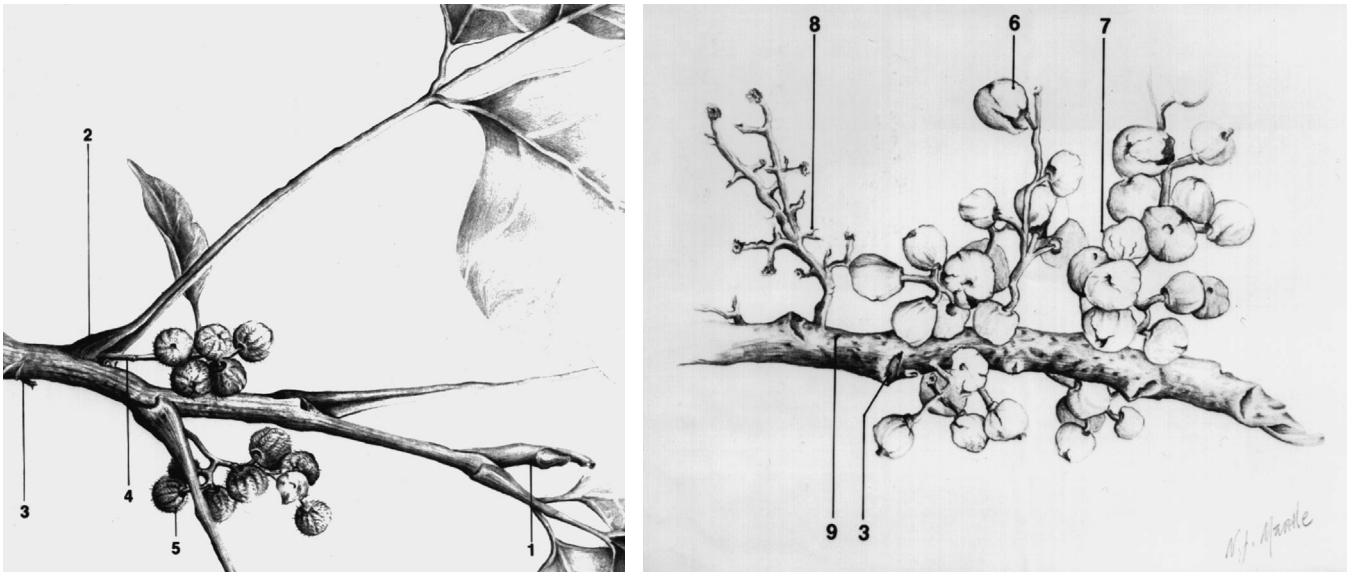


**Figure 1:** Reprinted from *Clinics in Dermatology*, Volume 4(2), Guin JD, Beaman JH, *Toxicodendrons* of the United States, pp 137–48, 1986, with permission from Elsevier Science.

*Toxicodendrons* have a number of characteristic features that help in recognition, some in all seasons.

1. Buds are not terminal, i.e., they do not arise at the end of the twig. Consequently, new growth is in a different direction from the previous year. Therefore most twigs are not straight (western poison oak may be an exception), but appear gnarled.
2. The petiole (from which the three leaflets of poison ivy and poison oak arise) is enlarged where it is attached, and it is grooved on its dorsal surface.
3. The leaf scar is U- or V-shaped because of the grooved petiole.
4. Fruit (in female plants) and flowers (in male and female plants) are in panicles, borne in the axillary position.
5. Trichomes on the exocarp (outer layer) of fruits of poison oak and some subspecies of poison ivy.
6. The exocarp peels off in winter.
7. After the exocarp peels off, one sees a chalk-white mesocarp often with black lines (the toxic resin canals) resembling longitudinal lines on a globe.
8. Female plants may exhibit empty fruit stalks from the previous season.
9. Pores in the bark called lenticles give the wood a characteristic texture typical of *Toxicodendrons*.

The urushiol from the plant is readily absorbed through the skin, so people who are highly allergic should try to remove the antigen within a few minutes of exposure.[9] Soap and water are helpful, but any solvent suitable for lipids would likely be satisfactory, provided it is used immediately. Moderately sensitive people probably have a bit longer, about 30 minutes, to try to remove most of the antigen.[9] When none of these is available, water alone can be beneficial.[9,10]

Bathing with a contaminated hand can be a problem because of possible spread of the antigen, so some measure of common sense must be employed.

## *Corticosteroid Treament of* Toxicodendron *Dermatitis*

Oral therapy is usually effective if the patient is given an adequate dosage for a sufficient period of time. In an adult, one usually starts with 30-60mg of prednisone per day over 14–21 days.[25]

Treatment is normally continued for at least fourteen days after the initial exposure. Injectable (TM) corticosteroids are also effective, but they seem to have little advantage, and the repository forms do not allow day-to-day control. In some cases where systemic therapy is contraindicated or where distribution is limited, moderately potent topical corticosteroids can be used with 24-hour occlusion. This method uses category II to V topical corticosteroids under occlusion for at least two 24-hour applications, usually with a day of rest between. Absorption is more efficient using a 1–3 day application than it is for periods of less than 24 hours.[26] Use of the less complex formulations such as a corticosteroid in petrolatum (only) may help reduce the increase in new allergies caused by the broadening of the allergic base (extended allergen syndrome). In very small areas intradermal triamcinolone acetonide or diacetate 2 mg/ml can be quite effective. Higher concentrations are usually unnecessary and in some areas may induce atrophy.

## Conclusion

Poison Ivy dermatitis is better prevented than treated, and recognition of the plant is the best method of prevention. Barrier creams, protective clothing and especially disposable vinyl gloves are useful in reducing exposure. Treatment is with systemic corticosteroid therapy unless there is a contraindication. In the latter case, topical corticosteroids with 24-hour occlusion are beneficial.

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*continued from page 2*

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# Update on Drugs

| Class | Name/Company | Approval Dates and Comments |
|---|---|---|
| *Oncologic Agent* | **Arsenic Trioxide**<br>*Trisenox*<br>Cell Therapeutics | The European Commission (EMEA) granted orphan medicinal product designation in April 2001, for the treatment of multiple myeloma and myelodysplastic syndromes. |
| *Hormonal Preparation* | **Transdermal 17-Beta Estradiol**<br>*Estradot*<br>Noven Pharmaceuticals | The regulatory authorities in the Netherlands approved this transdermal therapy in March 2001, for the treatment of menopausal symptoms and for the prevention of postmenopausal osteoporosis. |
| *Antimetabolite Agent* | **Methotrexate**<br>*Trexall*<br>Barr Laboratories/<br>DuPont Pharmaceuticals | The US FDA approved this proprietary product in March 2001, for the treatment of neoplastic disease, psoriasis and rheumatoid arthritis. *Trexall* represents new dosage strengths in 5, 7.5, 10, and 15mg tablets. |

## Drug News

| | |
|---|---|
| *OTC Product* | The US FDA sent letters to four internet retailers in March 2001, to caution them that advertising and selling colloidal silver as a cure for conditions ranging from sunburn to sinus infections and allergies violates the agency's regulations, since the products have not undergone the FDA approval process for new drugs. They cannot be considered dietary supplements if they claim to prevent, diagnose, mitigate, treat or cure a disease. Furthermore, dietary supplements are, by law, ingestible, so that promotion of colloidal silver in topical formulations for conditions such as sunburn, acne and rashes further invalidates the products' status as supplements. Four of the sites to receive letters from the FDA are Synergy Systems, Soul Healer, survival.com, and rawhealth.net. |
| *Antibacterial Agent* | Preliminary phase III data for the antibacterial product *Cidecin* (Daptomycin for injection, Cubist Pharmaceuticals) has shown it to be as effective as comparable agents in treating complicated skin and soft tissue infection resulting from gram-positive bacteria. |
| *Antipruritic Agent* | Researchers at the University of Muenster in Germany report that capsaicin, an herb that inhibits a peptide transmitter involved in pain transmission (substance P), relieved pruritus and promoted the healing of skin lesions in 33 patients with prurigo nodularis.* Pruritus was completely eliminated in all patients by day 12 of treatment. However, it returned within 2 months after the treatment was discontinued.<br>**J Am Acad Dermatol* 44:471–78 (2001) |
| *Leprosy* | With assistance from the World Bank of $30 million USD, India is launching the second phase of its national leprosy elimination project. Over 2/3 of the world's leprosy patients live in India, and officials from the World Health Organization (WHO) say that India's role for global leprosy elimination is absolutely critical. The project will assist in identifying new cases early, providing appropriate uninterrupted multi-drug therapy to prevent disabilities, and helping to locate and treat patients among previously inaccessible groups. |

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