

PRODUCT MONOGRAPH

VANIQA®

(Eflornithine Hydrochloride)
Cream 13.9 %

Hair Growth Inhibitor

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VANIQA®

(Eflornithine Hydrochloride)

Cream 13.9%

THERAPEUTIC CLASSIFICATION

Hair Growth Inhibitor

ACTION AND CLINICAL PHARMACOLOGY

VANIQA® irreversibly inhibits ornithine decarboxylase in vitro and in vivo. This enzyme is integral in hair shaft production by the follicle. In preclinical and clinical studies, eflornithine administered topically has been shown to reduce the rate of hair growth.

Pharmacokinetics

The steady-state cutaneous penetration of eflornithine hydrochloride is minimal (less than 1%) after multiple-dose topical application of VANIQA® to visibly intact facial skin of hirsute women. Absorption was determined under conditions of clinical use including shaving. Steady -state plasma levels are reached within four days of twice-daily application. The apparent plasma $t_{1/2}$ of eflornithine is approximately 8 hrs. The steady-state C_{max} , C_{trough} and $AUC_{12\text{ hr}}$, expressed in terms of the anhydrous free base, following twice-daily topical application of 0.5g of the VANIQA® cream are approximately 10 ng/ml, 5 ng/ml, and 92 ng•hr/ml, respectively. Eflornithine is not known to be metabolized and is excreted unchanged in the urine.

INDICATIONS AND CLINICAL USE

VANIQA® is indicated for slowing of the growth of unwanted facial hair in women. It is recommended as an adjunct to any hair removal technique.

VANIQA® Cream has only been studied on the face and neck of affected women. Usage should be limited to those areas.

CONTRAINDICATIONS

Hypersensitivity to eflornithine or to any of the excipients of VANIQA®.

WARNINGS

None.

PRECAUTIONS

General

VANIQA® is for topical use only. Avoid contact with eyes or mucous membranes (e.g., nose or mouth). Discontinue use if hypersensitivity occurs. If skin irritation or intolerance develops, the patient should be directed to temporarily reduce the frequency of application to once per day. If irritation continues, the patient should discontinue use of VANIQA® and

consult their physician.

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

Use in the elderly: Of the total number of patients in clinical trials with VANIQA[®] (n = 1370), approximately 6% were 65 years or older, while approximately 1% were 75 years or older. No overall differences in safety were observed between older and younger patients.

Use in children: The safety and effectiveness of this product in pediatric patients have not been established.

Adolescents: The safety and efficacy of this product in adolescent patients has not been established.

Nursing mothers: It is not known whether or not eflornithine hydrochloride is excreted in human milk. Caution should be exercised when VANIQA[®] cream is administered to a nursing woman.

Use in pregnancy: There are no well-controlled studies of VANIQA[®] Cream in pregnant women. Therefore, VANIQA[®] should be used during pregnancy only if the physician considers the potential benefits to outweigh the potential risks to the fetus.

Hepatic and Renal Impairment: Safety and efficacy of VANIQA[®] Cream in patients with hepatic or renal impairment have not been established. Considering the low systemic exposure after topical application, problems would not be expected.

Drug interaction: None known

INFORMATION FOR PATIENTS

Patients using VANIQA[®] cream should receive the following information and instructions:

1. This medication is not a depilatory, but rather appears to reduce 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.) in conjunction with VANIQA[®].
2. Onset of improvement may be seen after as little as 4-8 weeks of treatment. Further improvement may be seen with continued use. 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.

ADVERSE REACTIONS

Adverse reactions reported for most body systems occurred at similar frequencies in active and vehicle groups. The most frequent adverse reactions related to treatment with VANIQA[®]

Cream were skin related. The following table notes the skin-related adverse reactions that occurred in greater than 1% of patients treated with VANIQA® or vehicle in controlled studies.

**Incidence Attributed to Therapy
Percentage (%) of Patients**

Adverse reaction	VANIQA® 13.9% (N = 395)	Vehicle (N = 201)
Acne	21.3	21.4
Pseudofolliculitis barbae	16.2	15.4
Burning, stinging, tingling	14.2	5.0
Pruritus (itching)	3.8	4.0
Dry skin	1.8	3.0
Alopecia	1.5	2.5
Erythema (redness)	1.3	0
Skin irritation	1.3	1.0
Dermatitis	1.0	0.5
Rash	1.0	0

Treatment related skin adverse reactions that occurred in less than 1% of the subjects treated with VANIQA® Cream are: bleeding skin, cheilitis, contact dermatitis, edema face, edema mouth, folliculitis, hair ingrown, herpes simplex, numbness and rosacea.

Adverse reactions were primarily mild in intensity and generally resolved without medical treatment or discontinuation of VANIQA® Cream. No serious adverse reactions were related to treatment. Only 2% of subjects discontinued studies due to an adverse reaction related to use of VANIQA® Cream. The drug was generally well tolerated.

Laboratory Test Abnormalities

No laboratory test abnormalities have been found to be associated with VANIQA® Cream.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Dermal Administration

Given the minimal cutaneous penetration of this drug, overdose via the topical route is not expected (see clinical pharmacology). However, should very high topical doses (e.g. multiple tubes per day) or oral ingestion be encountered (e.g., a 60 g tube contains 9 g of eflornithine HCl), the patient should be monitored, and appropriate supportive measures administered as necessary.

Intravenous Administration

Adverse effects and laboratory abnormalities have been noted with intravenous administration of high doses of eflornithine hydrochloride (400 mg/kg/day or approximately 24 g/day) for the treatment of *Trypanosoma brucei gambiense* infection (African sleeping sickness). Adverse events have included hair loss, facial swelling, seizures, hearing impairment, stomach upset, loss of appetite, headache, weakness and dizziness. A variety of hematological toxicities, including anemia, thrombocytopenia and leukopenia have also been observed, but these were usually reversible upon discontinuation of treatment.

DOSAGE AND ADMINISTRATION

Apply a thin layer of VANIQA® Cream to affected areas of the face and neck and rub in thoroughly. The treated area should not be washed for at least 4 hours after application. VANIQA® should be used twice daily at least 8 hours apart. The product may be used alone or in conjunction with other hair removal techniques. VANIQA® may be applied 5 minutes after shaving or other hair removal techniques. Cosmetics or sunscreens may be applied over treated areas after cream has dried.

Elderly: No dosage adjustment is necessary.

PHARMACEUTICAL INFORMATION

I. DRUG SUBSTANCE

Trade name:	VANIQA®
Proper names:	eflornithine HCl; difluoromethylornithine
Chemical Name:	2-(difluoromethyl)- DL-ornithine monohydrochloride monohydrate
Empirical Formula:	$C_6H_{12}F_2N_2O_2 \cdot HCl \cdot H_2O$
Structural Formula:	
Molecular Weight:	236.65
Description:	Eflornithine is a white crystalline solid. It is soluble in methanol and soluble in water up to 436 g/L. It is slightly soluble in ether, chloroform, acetone and ethanol.

II. COMPOSITION

In addition to the active ingredient, eflornithine hydrochloride, the cream contains: water, glyceryl stearate, PEG-100 stearate, ceteryl alcohol, cetareth-20, mineral oil, stearyl alcohol, dimethicone, phenoxyethanol, methylparaben and propylparaben.

III. STORAGE

Store between 15 to 25°C. Use within 6 months of first opening the tube.

AVAILABILITY OF DOSAGE FORM

VANIQA® Cream is available in 15, 30 and 60 g plastic tubes. VANIQA® is formulated as a smooth white to off-white, fragrance-free cream containing 13.9% (139 mg/g) of anhydrous eflornithine hydrochloride. See tube crimp and carton end for expiration date and lot number.

INFORMATION FOR THE PATIENT

What is VANIQA®?

VANIQA® (pronounced "VAN-i-ka") is a prescription medication applied to the skin for the treatment of unwanted facial hair in women.

The active ingredient in VANIQA® is eflornithine hydrochloride. VANIQA® also contains water, glyceryl stearate, PEG-100 stearate, cetearyl alcohol, cetareth-20, mineral oil, stearyl alcohol, dimethicone, phenoxyethanol, methylparaben and propylparaben.

How does VANIQA® work?

VANIQA® interferes with a natural component of the skin needed for hair growth. This results in slower hair growth and improved appearance where VANIQA® is applied.

VANIQA® does not permanently remove hair or "cure" unwanted facial hair. It is not a depilatory. Your treatment program should include continuation of any hair removal technique you are currently using. VANIQA® will help you manage your condition and improve your appearance.

Improvement in the condition occurs gradually. Don't be discouraged if you see no immediate improvement. Be patient. While many people see improvement after 4 to 8 weeks of treatment, improvement may take longer in some individuals. Improvement should increase with continued use for up to 6 months. If no improvement is seen after 6 months of use, discontinue use. Clinical studies show that about 8 weeks after stopping treatment with VANIQA®, the hair will return to the same condition as before beginning treatment.

Who should not use VANIQA®?

You should not use VANIQA® if you are allergic to any of the ingredients in the cream. All ingredients are listed on the tube and at the beginning of this leaflet.

What should you tell your doctor before using VANIQA®?

If you are allergic to any of the ingredients, tell your doctor.

If you are pregnant or plan to become pregnant, discuss with your doctor whether you should use VANIQA® during pregnancy. No clinical studies have been performed in pregnant women.

If you are breast feeding, consult your doctor before using VANIQA®. It is not known if VANIQA® is passed to infants through breast milk.

If you are taking any prescription medicines, non-prescription medicines or using any facial or skin creams, check with your physician before use of VANIQA®.

How should I use VANIQA®?

Use VANIQA® only for the condition for which it was prescribed by your doctor. Do not give it to other people or allow other people to use it.

You will need to continue your normal procedures for hair removal. Once desired results have been achieved, you may be able to reduce the time spent in removing hair or the frequency of hair removal. VANIQA[®] is to be used twice daily, at least eight hours apart, or as directed by your doctor. It is a drug for external use only and is not a cosmetic preparation.

Follow the instructions for application of VANIQA[®] carefully. Apply a thin layer of VANIQA[®] Cream to the affected areas of the face and/or neck and rub in thoroughly. You should not wash the treatment areas for at least 4 hours after application of VANIQA[®].

VANIQA[®] may cause temporary redness, rash, burning, stinging or tingling, especially when the skin is damaged. If irritation continues, stop use of VANIQA[®] and contact your doctor. Avoid getting the medication in your eyes or inside your nose or mouth. If the product gets in your eyes, rinse thoroughly with water and contact your doctor.

If you forget or miss a dose of VANIQA[®] do not try to "make it up". Return to your normal application schedule as soon as you can.

You may use your normal cosmetics or sunscreen after applying VANIQA[®] but you should wait a few minutes to allow the treatment to be absorbed before applying them.

If your condition gets worse with treatment, stop use of VANIQA[®] and contact your doctor. What are the possible side effects of VANIQA[®]?

VANIQA[®] may cause temporary redness, stinging, burning, tingling or rash on areas of the skin where it is applied. If these persist, consult your doctor.

How should VANIQA[®] be stored?

VANIQA[®] should be stored between 15 and 25°C.
Use within 6 months of first opening the tube.

Keep this and all medicines out of the reach of children.

This medicine was prescribed for your particular condition. Do not use it for another condition or give it to anyone else.

This summary does not include everything there is to know about VANIQA[®] Cream. Medicines are sometimes prescribed for purposes other than those given in this leaflet. If you have questions or concerns, or want more information about VANIQA[®], your doctor and pharmacist have the complete prescribing information upon which this leaflet is based. You may want to read it and discuss it with your doctor or pharmacist. Remember, no written summary can replace careful discussion with your doctor or pharmacist.

PHARMACOLOGY

ANIMAL PHARMACOLOGY

Pharmacokinetics

The extent of oral absorption of BMS-203522 was found to be excellent in both rats (78% of dose) and dogs (100% of dose). In mice, the mean dermal absorption of BMS-203522 from a 15% cream formulation was less than 0.84%. The absorption of both oral and dermal doses of [¹⁴C]BMS-203522 was similar for male and female rats. The dermal absorption of BMS-203522 in rats, after twice-daily application for up to 5 days, ranged from 0.18% to 0.75%. The serum and tissue half-life of BMS-203522, following intravenous and oral doses, was estimated to be approximately 6 h in mice. In a study of [¹⁴O]-labeled dermal doses of eflornithine in mice, the terminal half-life of elimination of total radioactivity in blood of males and females was estimated to be 5.5 h and 8.3 h, respectively. BMS-203522 follows linear pharmacokinetics upon administration of a wide range of oral doses (10-2000 mg/kg) in mice.

CLINICAL TRIALS

In 2 multicenter, double-blind, vehicle controlled studies involving 596 hirsute women, treatment with eflornithine HCl significantly inhibited the growth of facial hair. Patients were treated with either eflornithine (N = 395) or vehicle (N = 201) twice daily for a duration of 24 weeks, in each of these studies. Physician's Global Assessment (PGA) evaluated the improvement or worsening from baseline observations, on a 4-point scale, 48 hours after shaving the treated areas.

Marked improvement was observed as early as 4-8 weeks after initiating treatment and continued throughout the course of treatment. The evidence of benefit from therapy receded to baseline levels within 8 weeks of discontinuing use.

Approximately 35% of patients showed marked improvement or greater (protocol definition of clinical success) after 24 weeks of treatment with VANIQA[®], compared to 9% with the vehicle. Nearly 70% of patients treated with VANIQA[®] showed at least improved status after 24 weeks of treatment. Combined results of these two trials through 24 weeks are presented below.

PGA* Outcome	VANIQA [®]	Vehicle
Clear / almost clear**	6%***	0%
Marked improvement	29%***	9%
Improved	35%	33%
No improvement / worse	30%	59%

* Physician's Global Assessment

**Clear/almost clear = no or nearly no visible evidence of facial hair on treated areas.

*** Indicates statistical significance (P≤0.001)

Subgroup analysis revealed a significantly higher success rate on PGA outcome for whites

than non-whites (39% vs. 27%).

About 12% of women in the clinical trials were postmenopausal. Significant improvement in PGA outcome with VANIQA[®] versus vehicle was seen in postmenopausal women.

Results from a subject self-assessment instrument showed that VANIQA[®] statistically significantly reduced psychological discomfort with the condition as compared to those patients exposed to vehicle-treatment alone. These patient-observable differences were seen as early as 8 weeks after initiating treatment. Benefits were no longer evident at 8 weeks after treatment withdrawal.

Close monitoring of VANIQA[®] use in approximately 1100 additional patients for six months or more demonstrated sustained efficacy and no unusual safety concerns. Clinical trials with VANIQA[®] Cream involved over 1370 hirsute women of skin types I-VI, of whom 68% were white, 18% black, 11% Hispanic-Latino and 2% Asian-Pacific Islander.

TOXICOLOGY

Acute Toxicity

Species/ Strain	Group/ Size	Route/ Duration	Observation Period	Dosage Level	Estimated Lethal Dose mg/kg	Principal Drug-Related Findings
Rabbit / New Zealand White	2/sex (one group)	Dermal/ Single Dose	14 days	5000 mg/kg (500 mg eflornithine/ kg)	The minimal lethal dose(LD) value of a 10% eflornithine solution was greater than 500 mg/kg of eflornithine	No mortality was observed and all animals gained weight. Dermal irritation consisting of very slight erythema and very slight edema was observed at 24 hours. A lower degree of irritation was observed in the vehicle control rabbits.
Rat/ Sprague Dawley	5/sex (one group)	Oral/ Single Dose	14 days	10 g/kg (1500 mg eflornithine/ kg)	The minimal lethal dose(LD) of eflornithine 15% cream was greater than 10 g/kg in rats, or >1500 mg/kg of eflornithine	No deaths occurred, and the only clinical observation was the formation of some loose stools.

Sub acute Toxicity

Species/ Strain	Group Size	Route/ Duration	Drug Form	Dose Range mg/kg/day	Principal Drug-Related Findings
Hamster/ Syrian Golden	6 males/ group	Dermal/ 5 days per week (13 applications)	5%, 10%, 15% Cream Vehicle cream	10 µl/hamster/ day applied to the clipped hamster flank	No treatment-related findings were observed in survival, clinical observation, dermal irritation, body weights, or gross and microscopic observations
Rabbit/ New Zealand White	2/ sex	Dermal/ 5 days	10% Solution Vehicle Solution	0.5 ml applications of solutions under 24-hour patch occlusion	Dermal irritation consisting of no to well-defined erythema (grade 2) was observed in both vehicle- and SP33-treated animals. Very slight edema (grade 1) was observed in the vehicle-treated skin sites with very slight to slight edema (grade 2) observed in the SP33-treated sites. The SP33 vehicle was considered to be mildly irritating and the SP33 (10% BMS-203522) solution was considered mildly to moderately irritating.
Rabbit/ New Zealand White	2/ sex	Dermal/ 5 days	5%, 10%, 15% Cream Vehicle cream	0.5 ml under 24- hour patch occlusion	Daily and cumulative primary irritation scores classified each test formulation as mild to moderate irritation potential.
Rabbit/ New Zealand White	2/ sex	Dermal/ 14 days	5%, 10%, 15% Cream Vehicle cream	0.5 ml unoccluded skin sites	Daily and cumulative primary irritation scores classified each test formulation as mild to moderate irritation potential.

Species/ Strain	Group Size	Route/ Duration	Drug Form	Dose Range mg/kg/day	Principal Drug-Related Findings
Rabbit/ New Zealand White	2/ sex	Dermal/ 14 days	15% cream 10% solution Vehicle cream & solution	125 µl twice daily to unoccluded skin sites	Daily and cumulative primary irritation scores classified the 15% cream, 10% solution, and vehicle cream formulations as minimal irritation potential. The vehicle solution formulation was classified as non-irritating.
Rabbit/ New Zealand White	2/ sex	Dermal/ 21 days	15% Cream Formulation Vehicle Cream Formulation	80 µl /site as a q.d. or b.i.d.dose to unoccluded skin sites	15% cream dosed once daily resulted in no dermal irritation. Twice daily dosing resulted in no to very slight erythema reaction; Vehicle cream applied once daily for 21 days resulted in no to very slight erythema reactions; twice-daily dosing resulted in no irritation effects.
Mouse/ hairless albino SKH:hr-1	5/ sex	Dermal/ 14 days	15% Lotion Formulation Vehicle Lotion Formulation	100 µl /mouse per day for 14 days	No mortalities, clinical signs, dermal irritation or body weight effects were observed during the study. The results indicated that a maximum dose volume of 100 ml/mouse/day should be well tolerated in a 12-month photocarcinogenicity study.
Mouse/ CD-1	8/ sex	Dermal/13 weeks	15% Cream Formulation Vehicle Cream Formulation	50 and 100 µl /mouse/ day Vehicle : 100µl /mouse/day Water: 100µl /mouse/day Untreated Control	No mortalities and no treatment-related systemic clinical signs or dermal toxicity or hematologic changes were observed. Microscopic examination of the tissues, including the skin of the test sites treated with SP106 (15% BMS-203522) formulation, did not reveal any evidence of dermal or systemic toxicity. Under the conditions of this study, SP106 (15% BMS-203522) at dose volumes of 50 and 100 ml are not dermally irritating or systemically toxic. These dose levels served to identify the Maximum Tolerated Dose (MTD) level selected in a 2-year dermal study in mice.

Chronic Toxicity

Species/ Strain	Group Size	Route/ duration	Drug Form	Dose Range mg/kg/day	Principal Drug-Related Findings
Rat/ Sprague Dawley	10/sex	Dermal/ 26week	15%cream 10% solution Vehicle cream & solution	15% cream: (54 mg/kg/day) 10% solution: (36 mg/kg/day) Vehicle Untreated control	No remarkable toxic or irritant effects in rats that were topically treated twice daily with treatment or vehicle. There were no treatment-related mortalities during the study. In general, the treatment site appeared normal in all animals; however, initial low incidence of transient very slight erythema was noted during weeks 1, 2 and/or 3 in several treatment and control. Plasma evaluation showed no detectable systemic exposure to drug. The findings of this study indicated no remarkable toxic or irritant effects in rats that were topically treated twice daily with SP106V, SP106A, SP33, or SP33V formulations for at least 26 weeks.
Rabbit/ New Zealand White	10/sex	Dermal/ 26 weeks(study discontinued after 11 days)	15% cream 10% cream Vehicle Cream	125 µl per animal twice daily; unoccluded application untreated control	Due to dose-limiting severe dermal irritation in all test and vehicle control groups, study discontinued after Day 11 of dosing. An additional dermal irritation study with the vehicle also resulted in the same dose limiting irritation effects. Rabbits were considered unacceptable and too sensitive of a species for a long-term repeat-dose study.
Swine/ Hanford Miniature Swine	5/sex	Dermal/1 year	15% lotion Vehicle lotion	15 and150 mg/kg/day) Vehicle	No mortalities or treatment-related systemic clinical signs occurred. There were no treatment-related dermal changes at the application site during the 52-week study. There were no BMS-203522-related effects on body weight, physical or ophthalmic parameters, organ weights, clinical pathology, or gross or histopathologic evaluations.

Reproduction and Teratology

Species/ Strain	Group Size	Route/ Duration	Drug Form	Dose Range mg/kg/day	Principal Drug-Related Findings
Rat/Sprague Dawley	25/ sex/ group, Male rats sacrificed after mating; females sacrificed Day 14 of gestation	Dermal/ daily for 28 days (♂) and 15 days (♀) prior to and through cohabitation; up to Day 7 of gestation (♀). All animals wore Elizabethan collars.	15% lotion Vehicle lotion	50, 150 or 450 mg/kg/ day of the 15% lotion Vehicle control at 3.0 ml/kg/ day	No mortalities or systemic effects were observed at any dose level. BMS-203522, at doses up to 450 mg/kg as a 15% lotion, produced dose- related signs of dermal irritation with no adverse effects on reproductive and developmental parameters. Based on the results of this study, BMS-203522 was not a reproductive toxicant. The no-observed-effect-level (NOEL) for systemic maternal and reproductive toxicity was greater than 450 mg/kg/day.
Rat/Sprague Dawley	25 pregnant females/ group (three groups, including controls)	Dermal/ applied twice daily from gestation Day 0 to gestation Day 19. The animals were not fitted with Elizabethan collars nor was the skin site covered during treatment	15% cream Tap water control	15% cream of 225 and 450 mg/kg/ day. The controls received 225 ml of water	Survival and pregnancy rates were 100% in all groups. However, the percent of live fetuses was 93.3, 25.4, and 5.4% for controls, low- and high- dose groups, respectively. In utero growth retardation, as evidenced by fetal weights and delayed ossification and development of the viscera, was noted in both the low- and high-dose groups. No measures were taken in this study to prevent access of the dams to the drug by covering the application sites or collaring the rats. The absence of dermal irritation at 225 and 450 mg/kg/day, as well as the systemic exposure detected at days 15 and 19 (3200- to 9600-fold higher than those obtained in hirsute women) supports a hypothesis that drug may have been ingested by the dams and that the adverse maternal and developmental effects may have resulted from oral, and not dermal, exposure.

Species/ Strain	Group Size	Route/ Duration	Drug Form	Dose Range mg/kg/day	Principal Drug-Related Findings
Rat/ Sprague Dawley	21-28 pregnant females/ group (four groups, including controls)	Dermal/ b.i.d. from gestation Day 6 to gestation Day 15. Elizabethan collars and covered application sites	15% lotion Vehicle lotion	15% lotion at doses of 90, 225 and 450 mg/kg/ day Vehicle	Levels of BMS-203522 in maternal plasma confirmed the limited absorption of the test article when given dermally. Drug-related increases in both the incidence and severity of erythema at the application site occurred in dams given 225 and 450 mg/kg/day. There were no drug- related changes in the fetuses at any dose tested. Under the conditions of this study, BMS-203522 was not teratogenic in rats.
Rabbits/ New Zealand White	20 females/ group, (four groups including one control group)	Dermal/ applied once daily from Day 6 to 18 of gestation. All animals wore Elizabethan collars during the 6-hour daily exposures, and the skin sites were covered	15% lotion Vehicle lotion	Dose levels of 30, 90, or 300 mg/kg/ day of 15% lotion Vehicle	A dermal dose level of 300 mg/kg/day of BMS-203522, as a 15% lotion, produced marked maternal toxicity consisting of severe dermal irritation, significantly reduced body weight and food consumption, abortions and mortality, and increased fetal resorption and reduced fetal weights. However, it cannot be ruled out that these effects may have also been related to possible ingestion or direct absorption through irritated skin of the test. The maternal and developmental no-observable-effect level (NOEL) was considered to be 90 mg/kg/day. On the basis of these data, BMS-203522 was not formulation. teratogenic in rabbits.

Species/ Strain	Group Size	Route/ Duration	Drug Form	Dose Range mg/kg/day	Principal Drug-Related Findings
Rat/ Sprague Dawley	20 females/ group F0 generation (four groups including controls)	Oral (drinking water) from day15 of gestation to day 22 of weaning	Test Material: Eflornithine HCl at concentrations of 0, 0.1, 0.3, and 1.0% in the drinking water	Dose levels: of 0.1, 0.3 and 1.0% corresponding to average daily dose levels of 223, 625 and 1698 mg/kg/ day of eflornithine HCl Vehicle control: water	Maternal body weight and food and water consumption were significantly reduced in the 0.3 and 1.0% groups, but there were no adverse effects on maternal reproductive parameters. Pup weights were significantly reduced in these two dose groups during the nursing period. This continued throughout the growth period after weaning in the female pups, but lasted for 5 weeks in high-dose males. These findings indicate a mild toxic effect in the dams and pups at these two dose levels. There were no significant effects on behavior, development, or reproductive function of the F1 offspring, except for a slightly reduced fertility index in the high dose group (76.5% vs. 89.5%), which was considered to be of questionable biological significance. The systemic maternal, neonatal and developmental no-observed-adverse effect level (NOAEL) was 0.1% (223 mg/kg). Eflornithine caused changes in the F1 generation offspring only at doses that also caused maternal toxicity.

Photocarcinogenicity, Carcinogenesis and Mutagenesis

In a 12-month photocarcinogenicity study in hairless albino mice, animals treated with the vehicle alone showed an increased incidence of skin tumors induced by exposure to ultraviolet (UVA/UVB) light, whereas mice treated topically with VANIQA[®] at doses up to 600 mg/kg (1800 mg/m²) showed an incidence of skin tumors equivalent to untreated-control animals. A two-year dermal carcinogenicity study in CD-1 mice with VANIQA[®] revealed no evidence of carcinogenicity at daily doses up to 600 mg/kg (1800 mg/m²). In this study, daily doses resulted in systemic exposures 200- to 1000-fold higher than systemic exposures (based on AUCs) following topical application in humans.

At maximal doses, eflornithine did not elicit mutagenic effects in an Ames reverse-mutation assay or clastogenicity in primary human lymphocytes, with and without metabolic activation. A dermal micronucleus assay at doses up to 900 mg/kg in rats also yielded no evidence of genotoxicity.

Teratology

In dermal teratology studies, no maternal or fetal toxicity or teratogenic effects were observed in rats at doses up to 450 mg/kg (180 times the human dose) or in rabbits at doses up to 90 mg/kg (36 times the human dose). Higher doses in both studies resulted in maternal and fetal toxicity without evidence of teratogenicity. Fetotoxicity in the absence of maternal toxicity has been reported in oral studies with eflornithine with fetal no-effect doses of 80 mg/kg in rats and 45 mg/kg in rabbits. In these studies, no evidence of teratogenicity was observed in rabbits given up to 135 mg/kg.

Other Studies

Eflornithine topical 15% cream was non-phototoxic and non-sensitizing in guinea pigs.

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