PRODUCT MONOGRAPH

Tinactin® **Once-A-Day**™ Cream

BUTENAFINE HYDROCHLORIDE CREAM 1%

Topical Antifungal Agent

Distributed by: Bayer Inc., Consumer Care
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Mississauga, ON
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Date of Preparation: March 9, 2015

Submission Control No: 182252

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BUTENAFINE HYDROCHLORIDE CREAM 1%

Topical Antifungal Agent

ACTION

Butenafine hydrochloride is a benzylamine derivative with a chemical structure and mode of action similar to that of the allylamine class of antifungal drugs. In common with the azole class of antifungal drugs, allylamine antifungal drugs act by suppressing the biosynthesis of ergosterol, an essential component of fungal cell membranes. Allylamines act at an earlier stage of the ergosterol pathway than azoles, independent of cytochrome P-450, by inhibiting squalene epoxidase. In addition to decreasing the production of ergosterol, inhibition of the epoxidation of squalene also results in an increased squalene content within the fungal cells. The squalene accumulation causes an increased membrane permeability and a subsequent disruption of cellular organization. Depending on the concentration of the drug and the fungal species tested, the antifungal allylamines and benzylamines are not only fungistatic, but also fungicidal. Cell death is probably due to accumulation of squalene rather than ergosterol deficiency.

INDICATIONS

Tinactin® Once-A-Day™ Cream is indicated for the topical treatment of tinea pedis caused by *Trichophyton rubrum, T. mentagrophytes, and Epidermophyton floccosum.*

CONTRAINDICATIONS

Tinactin® Once-A-Day™ Cream is contraindicated in persons who have shown hypersensitivity to the active or excipient ingredients of this formulation or to the other allylamines, e.g., naftifine.

WARNINGS

Tinactin® Once-A-Day™ Cream should never be used for the treatment of infections of the eye.

PRECAUTIONS

If a reaction suggesting sensitivity or chemical irritation should occur, use of Tinactin® Once-A-Day™ Cream should be promptly discontinued and appropriate therapy instituted. **Tinactin® Once-A-Day™ Cream should not be used during pregnancy or by a nursing mother except on the advice of a physician.**

Tinactin® Once-A-Day™ Cream is not suitable for treating fungal infections of the nail or scalp. Occlusive dressings should not be applied over Tinactin® Once-A-Day™ Cream unless directed by a physician. **For adults and children over 12 years of age. Do not use on children under 12 years of age unless under the advice of a physician.**

ADVERSE REACTIONS

Short-term studies indicate that Tinactin® Once-A-Day™ Cream is well tolerated by the skin. During clinical trials conducted in Japan, 23 (2.56%) of 898 patients treated with butenafine cream reported side effects consisting mainly of irritation, pruritus and stinging. During North American clinical trials with Tinactin® Once-A-Day™ Cream, no patient discontinued therapy due to adverse events and 2/137 patients reported local adverse reactions judged by the investigator to be possibly, probably, or definitely related to drug therapy. The incidence of local adverse reactions was 0.7%.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There has been no experience with overdosage of Tinactin® Once-A-Day™ Cream. Treatment should include general supportive measures.

DOSAGE AND ADMINISTRATION

When clinically warranted, therapy with Tinactin® Once-A-Day™ Cream may be initiated while results of culture and susceptibility tests are pending. Treatment should be adjusted according to the findings.

A thin layer of Tinactin® Once-A-Day™ Cream should be applied (to avoid macerating effects) to the affected and immediate surrounding area in patients with the following condition:

Condition	Frequency	Duration
Tinea Pedis	Once daily	4 weeks

The full course of therapy should be followed to reduce the possibility of recurrence. However, if there is no response within the recommended treatment period, the diagnosis should be re-evaluated.

The safety of Tinactin® Once-A-Day™ Cream has not been established with treatment periods exceeding those recommended. Therefore, treatment must not exceed the recommended duration of therapy indicated above.

1. Dosage Directions:

   a. Cleanse the skin with soap and water and dry thoroughly.

   b. Rub in a thin layer on affected (and immediately surrounding) area once daily.

   c. In applying medication, pay special attention to spaces between toes.

   d. Wear well fitting, ventilated shoes and cotton socks.

2. Warnings

   a. For external use only.

   b. Do not use for infections of the scalp or nails.

   c. **Do not use while pregnant or nursing except on the advice of a physician.**

   d. Do not exceed recommended dosage.

   e. **Do not use on children under 12 years of age unless under the advice of a physician.**

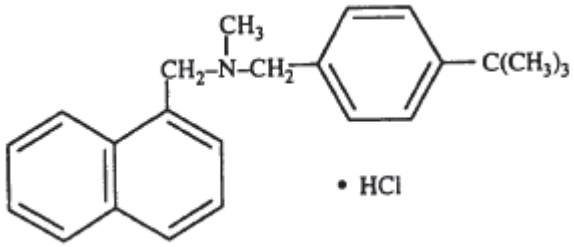
PHARMACOLOGICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Butenafine Hydrochloride

Chemical Name: N-4-tert-Butylbenzyl-N-methyl-1 naphthalenemethylamine Hydrochloride

Structural Formula:



Code Name: KP-363

Molecular Formula: $C_{23}H_{27}N$-AHCl

Molecular Weight: 353.93

Description: White crystals or crystalline powder, odorless or with a faint characteristic odor

Melting Point: 210° to 217°C

Stability and Storage Recommendations:

Keep container closed when not in use. Store in a cool dry place between 15° and 30° C.

DRUG PRODUCT

Composition

Tinactin® Once-A-Day™ Cream contains: Butenafine hydrochloride; propylene glycol dicaprylate; glycerin; cetyl alcohol; glyceryl monostearate; white petrolatum; stearic acid; polyoxyethylene cetyl ether; benzyl alcohol; diethanolamine; sodium benzoate; purified water.

AVAILABILITY OF DOSAGE FORMS

Each gram of smooth, white cream contains 10 mg butenafine hydrochloride. It is available in a 24-gram tube.

INFORMATION FOR THE CONSUMER

1. Treatment should be continued for one to two weeks after symptoms have disappeared (up to a maximum of four weeks of treatment). If no improvement is seen within two weeks, a physician should be consulted.

2. Use Tinactin® Once-A-Day™ Cream for the full treatment period even though symptoms have subsided.

3. Notify the physician if the area of application reveals signs of increased irritation (redness, itching, burning, swelling or oozing).

4. 4 Keep Tinactin® Once-A-Day™ Cream away from the eyes, nose, mouth, and other mucous membranes. If contact with the eyes occurs, rinse thoroughly with water.

5. Dosage Directions:

a. Cleanse the skin with soap and water and dry thoroughly.

b. Apply a thin layer on affected (and immediately surrounding) area once daily.

c. In applying medication, pay special attention to spaces between toes.

d. Wear well fitting, ventilated shoes and cotton socks.

6. Warnings:

a. For external use only.

b. Do not use for infections of the scalp or nails.

c. Do not use while pregnant or nursing except on the advice of a physician.

d. Do not exceed recommended dosage.

e. Do not use on children under 12 years of age unless under the advice of a physician.

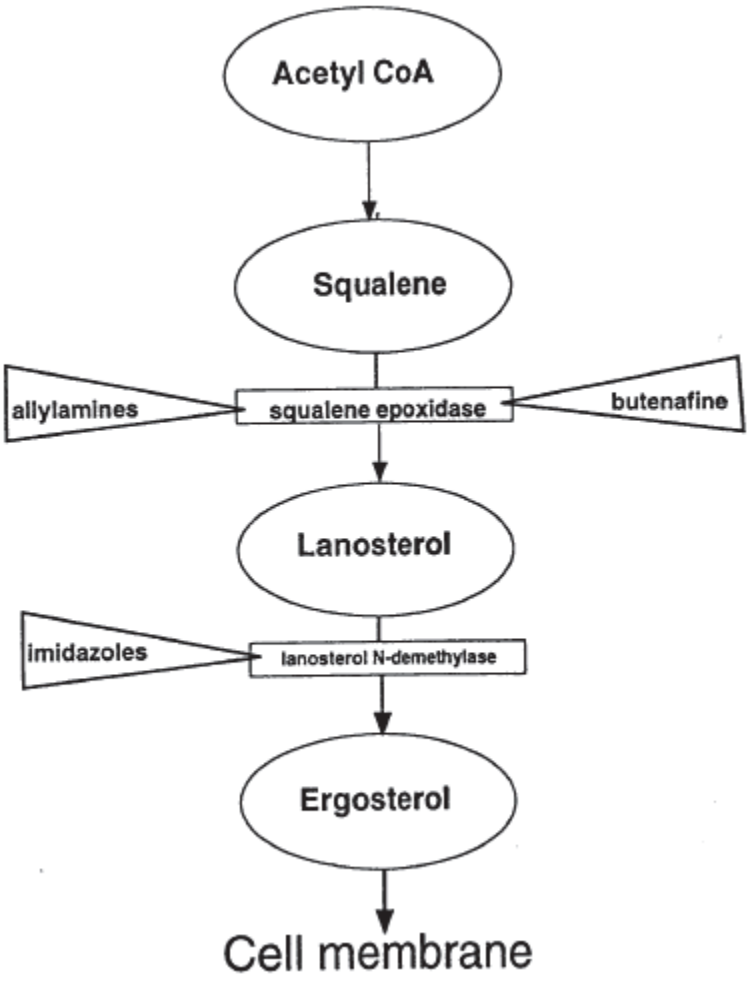
PHARMACOLOGY

ACTION AND CLINICAL PHARMACOLOGY

Butenafine is a potent, broad spectrum antifungal that is fungicidal against dermatophytes and molds. The mechanism of action of butenafine most likely involves specific inhibition of fungal ergosterol biosynthesis at the point of squalene epoxidation, leading to a deficiency of this essential component of the fungal cell membranes and to intracellular accumulation of the precursor squalene (Figure 1).

FIGURE 1

Synthesis Pathway for Ergosterol Biosynthesis and Sites of Inhibition by Allylamines, Imidazoles and Butenafine



PHARMACOLOGICAL EFFECTS

Animal Studies

Numerous *in vivo* and *in vitro* studies were performed to assess the pharmacological effects of butenafine HCl. Butenafine HCl was administered subcutaneously in 50% aqueous Macrogol 400; intravenously in Macrogol 400 or 40% propylene glycol; topically in 0.5% carboxymethyl cellulose; and dissolved in either Macrogol 400 or propylene glycol for in *vitro* studies. The results are summarized below.

- Effects on the Central and Peripheral Nervous Systems:

Subcutaneous administration of 1-100 mg/kg butenafine HCl to mice had no effect on the central and autonomic nervous systems. Topical administration of 0.3-3.0% butenafine HCl solutions to guinea pigs had no effect on the somatic nervous system.

A 10^{-4} M solution of butenafine HCl produced no autonomic or smooth muscle effects *in vitro* when added to isolated ileum or trachea from guinea pig, jejunum or aorta from rabbit, and vas deferens or uterus from rat. This solution also produced no effects on the somatic nervous system of the rat when added to phrenic nerve diaphragm preparations.

- Effect on Respiratory and Cardiovascular Systems:

Intravenous administration of 1-30 mg/kg butenafine HCl to rats caused a transient decrease in heart rate with a 10 mg/kg dose and a transient decrease in respiratory rate with a 30 mg/kg dose. A decrease in blood pressure was observed in rats with subcutaneous administration of 10 mg/kg. No effect was seen on isolated atrial muscle from guinea pigs when a 10^{-4} M solution of butenafine HCl was applied.

In dogs, an intravenous dose of 100 mg/kg, the highest dose administered, caused a slight increase in respiratory rate.

- Effect on the Gastrointestinal System:

Butenafine HCl had no effect on intestinal transport when given subcutaneously to mice at 1-100 mg/kg.

- Effect on the Urogenital System:

No diuretic effect was observed when butenafine HCl was given subcutaneously to mice at 1-100 mg/kg.

- Effect on the Endocrine System:

Butenafine HCl, at doses of 1-25 mg/kg, given to rats subcutaneously for six weeks had no effect on hormone levels or kinetics. A slight hypertrophy of the adrenal glands was observed in females.

- Effect on the Hematological System:

Mice and rats dosed subcutaneously with 1-100 mg/kg butenafine HCl showed no effect on blood coagulation. No hemolysis or effects on plasma were observed when blood from rabbits was exposed to 10^{-4} M butenafine HCl, *in vitro*.

Other

Three of the primary metabolites of butenafine HCl (defined as M1, M2, M3) were isolated from the bile and urine of rats dosed with butenafine HCl subcutaneously. Degradants (D1, D2, D3) of butenafine HCl were produced by irradiation (D1) and heating (D2 and D3) of butenafine HCl at 215^{o} C for 20 minutes. The metabolites and degradants were administered intraperitoneally and subcutaneously, respectively. Doses of 10 and 100 mg/kg produced no effects on spontaneous movement in mice; however, M1 prolonged hexobarbital-induced sleeping time. Rats dosed intravenously with 1-100 mg/kg of butenafine HCl metabolites or degradants showed transient decrease in blood pressure with M2 (100 mg/kg), decreased heart rate with M2 (30 mg/kg), M3 (100 mg/kg), and D2 (10 mg/kg), and increased respiratory rate with M1 and D2 (100 mg/kg). *In vitro* administration of M1 (10^{-5} M), D1 (10^{-5} M), and D2 (10^{-4} M) to isolated guinea pig ileum, inhibited the contraction of smooth muscle induced by various agonists.

ABSORPTION, DISTRIBUTION , METABOLISM, AND EXCRETION

The absorption of butenafine HCl is very slow and minimal following topical application to the skin. The drug remains in the skin predominantly in the unmetabolized (parent) form and is retained preferentially in the stratum corneum. Systemically absorbed drug is bound extensively to plasma proteins and is rapidly and nearly completely metabolized by methylation, dealkylation, and hydroxylation into five major metabolites which are characteristic for drugs of this class. The tissue concentration of parent compound and metabolites after subcutaneous administration was very high in intestinal contents and distributed primarily to liver, adrenals, pancreas, and fat. It is excreted predominantly as conjugated metabolites in the feces and urine, and high concentration in milk.

SUMMARY OF ANIMAL ADME STUDIES

Species	Strains	Group Size	Study Type	Route	Dose (Radiolabeled)	Results
Rat	Wistar	3M + 3F per study	Plasma conc.	Topical	20 mg/kg for 7 days	Plasma conc. peaked (25 ng/ ml) 24 hr. after admin. Elimination slower than when admin. systemically. No sex differences.
Rat	Wistar	3M + 3F(D) 4/M (PC) 5M (E)	Plasma conc. Distribution Urinary and fecal excretion	Topical	10 mg/kg for 7 days	Plasma conc. peaked (53 ng/ml) 24 hr. after admin. Elimination slower than when admin. systemically.
Rat	Wistar	3M per group	Distribution	Topical	10 mg/kg for 6 hours on intact and abraded skin	After 6 hours 89% (intact) and 79% (abraded) remained at the skin dosing site. Skin tissue conc. max of 17.8 µg/g (intact) and 173 µg/g (abraded). Excretion rate in urine and feces after 4 days was 4% (intact) and 25% (abraded). Partitioning into subcutaneous layer low. Max. plasma conc. 50-55 ng/ml (intact) and 245-271 ng/ml (abraded) after 10 hrs.
Rat	Wistar	3-4 M per study	Plasma conc. Distribution	Topical (occluded)	2 mg/kg/day for 7 days	Plasma conc. Increased during Day 1 and 2, then reached a constant value (23.4 ng/ml) until dosing ceased, $T_{1/2}$ - 31.9 hr. (similar to single admin.). Amount remaining on skin was higher than after single administration.
Rat	Wistar	5M per dose	Skin distribution	Topical	50, 500 mg/kg/day for 3 months (Non-labeled)	Dose response conc. not seen in skin. After 1 month recovery, skin conc. decreased to 1/150 (50 mg/kg). Amount transferred to systemic circulation did not increase sig. following repeated admin. due to stratum corneum acting as barrier and reservoir.
Rat	Wistar	5M per dose	Plasma/Fat distribution	Topical	1, 25 mg/kg/day for 3 months (Non-labeled)	Levels of butenafine in plasma and fat measurable and proportional to dose one day after last dose. In high dose group, plasma levels decreased 1/6 and fat levels decreased 1/9 one month after recovery (25 mg/kg).
Rat	Wistar	3M + 3F per study	Plasma conc. Urinary, fecal and resp. excretion.	Oral	0.2 mg/kg	Peak plasma conc. (156 ng/ ml) at 1 hr. after dosing. Total excretion after 1 week was >90% (approx. 60% was in feces). Resp. excretion was <0.2% during 3 days. $t_{1/2}$: 3.6 hr. α-phase, 14.8 hr. ß-phase.

Species	Strains	Group Size	Study Type	Route	Dose (Radiolabeled)	Results
Rat	Wistar	3M + 3F per study	Plasma conc. Protein binding Urinary and fecal excretion.	IV	0.2 mg/kg	Biphasic decline. Protein binding 90%. Total excretion after 1 week was 90% (>60% was in feces). No sex differences. $t_{1/2}$: 1.9 hr. α -phase, 21.9 hr. - ß -phase (male); $t_{1/2}$: 1.8 hr.- α -phase, 24.6 hr. ß-phase (female).
Rat	Wistar	3M + 3F	Autoradiograph	IV	1.0 mg/kg	High conc. in intestine, liver, adrenal, pancreas and brown fat. Low levels in blood.
Rat	Wistar	3F (pregnant)	Distribution	SC	0.2 mg/kg	6 hrs. after admin. the transfer to fetus was low, 0.01%/embryo (organogenic period) and 0.1%/fetus (perinatal period).
Rat	Wistar	3M + 3F per study	Plasma conc. Protein binding Urinary & fecal excretion.	SC	0.2 mg/kg	Peak conc. at 30 min. (82 ng/ml). Total excretion after 1 week was about 90% (>60% was in feces). No sex differences. Elimination from fat slow. $t_{1/2}$: 2.6 hr.α -phase, 26.9 hr. ß- phase.
Rat	Wistar	3M + 3F per study	Plasma Conc. Protein Binding	SC	1.0 mg/kg	Peak conc. at 30 min. (234 ng/ml). Protein binding 90%. $t_{1/2}$: 4.5 hr. α-phase, 36.4 hr. ß-phase.
Rat	Wistar	3F (Lactating dams and neonates)	Plasma conc. Distribution	SC	1.0 mg/kg	Peak conc. in milk at 3 hr. (13320 ng/ml - 6x plasma conc.). Conc. decreased 1/7, one day after/Conc. in neonate tissue about half of mother's after one day.
Rat	Wistar	3M + 3F	Distribution Autoradiograph	SC	2.5 mg/kg	Almost completely absorbed in 2 days. High conc. in intestinal contents, liver, adrenal, pancreas, brown fat, mesenterium, and harderian gland. Distribution pattern did not vary from IV and topical admin. 80.9% excreted in feces and urine after 4 days.
Rat	Wistar	5M	Biliary excretion & enterohepatic circulation	SC	0.2 mg/kg	25.3% excreted in bile 4 hours after admin. and 44% after 24 hours.
Rat	Wistar	3-4M per study	Plasma conc., Distribution, Excretion	SC	0.2 mg/kg/day for 7 days	Distribution pattern similar to that for single dose. Plasma conc. (150 ng/ml) several times higher and elimination from fat was slow. Total excretion in urine plus feces was 69% one day post- admin., 93%7 days post-admin., and 97% 14 days post- admin (>60% excreted in feces).

Species	Strains	Group Size	Study Type	Route	Dose (Radiolabeled)	Results
Guinea Pig	Hartley	3M per study	Penetration and retention time on skin.	Topical (occluded and non-occluded)	2 mg/animal in 0.2 ml for 72 hrs.	High conc. in 50 µm deep (250-500 µg/g, epidermis containing stratum corneum) and in 100-200 µm (70-250 µg/g) at 24 hr. Low levels in 1300-1600 µm.
Guinea Pig	Hartley	3M	Conc. in skin, Adsorption	Topical	2 mg/animal	After 6 hours 50 µg/g in top 300 µm layer, including stratum corneum and <0.5 µg/g in 1000-2500 µm skin layer. Elimination from skin slow and retention in stratum corneum high.
Dog	Beagle	3M	Plasma conc.	Topical	1 mg/kg topically for 6 hours	Max. plasma conc. 3.3 ng/ml after 6-24 hours.
Dog	Beagle	8M + 8F	Plasma conc. Skin Conc. Distribution to adipose tissue	Topical	25 and 100 mg/kg/day for 12 months	Plasma conc. 229±118 (6th month) and 148±47 (12th month) ng/ml at 25 mg/kg. Plasma conc. 284±81 (6th month) and 352±95 (12th month) at 100mg/kg. Skin levels 319±207 (25mg/kg) and 1086±707 (100 mg/kg) µg/g after 12 months. Adipose tissue levels 35.6±24.7 (25 mg/kg) and 95.3±32.0 (100 mg/kg) µg/g after 12 months.
Dog	Beagle	3M	Plasma conc. Urinary and fecal excretion	IV	0.2 mg/kg	Total excretion rate after 1week was 85.1%, slightly slower than that of rat. Biphasic decline. $t_{1/2}$: 1.1 hr. α- phase, 58.7 hr. ß-phase
Dog	Beagle	3M	Protein Binding	IV	0.1 mg/kg	Protein binding 93%
Rat	Wistar	3 per dose	Biotransformation	Topical	10 mg/kg	Little metabolism detected in skin
Rat	Wistar	3 per dose	Biotransformation	Oral	115, 500mg/kg	N-demethylation and N-dealkylation of benzylamines and oxidation of tert-butyl group were the main metabolic route.
Rat	Wistar	3 per dose	Biotransformation	IV	5 mg/kg	Unchanged butenafine not observed in urine and bile.
Rat	Wistar	3 per dose	Biotransformation	SC	0.2, 2.5 mg/kg	Metabolized rapidly and little unchanged drug observed in plasma.

HUMAN PHARMACOKINETICS

Studies in humans showed that absorption of butenafine through the skin of normal male volunteers is very low. In multiple dose studies utilizing exaggerated doses of 5 grams/day for seven days, the highest detectable plasma concentration of butenafine was 7.6 ng/ml.

CLINICAL STUDIES

Butenafine has been studied in tinea pedis in two North American clinical trials. In these studies, effective treatment was tabulated as a combination of laboratory results and clinical improvement. In the table below, the term "Mycological Cure" is defined as both negative KOH and negative culture. "Effective Clinical Response" is defined as a Physician Global Assessment of "Cleared" or "Excellent". "Effective Treatment" is defined as a patient having both a "Mycological Cure" and a Physician Global Assessment of "Cleared" or "Excellent".

The combined results of two North American vehicle-controlled studies of Tinactin® Once-A-Day™ Cream used once daily for four week in the treatment of tinea pedis are presented in the following table.

Patient Outcome Category	Week 8 (Four Weeks After Cessation of Therapy)	
	Butenafine Vehicle	Vehicle
Mycological Cure	85% (75/88)	38% (31/81)
Effective Clinical Response	75% (66/88)	36% (29/81)
Effective Treatment	69% (69/88)	26% (21/81)

MICROBIOLOGY

IN VITRO

In *in vitro* susceptibility tests, butenafine HCl showed antimicrobial activity against a broad range of fungi including dermatophytes, filamentous and dematiaceous fungi, dimorphic fungi and yeast. Butenafine exhibited particularly strong antifungal activity against dermatophytes. Tinactin® Once-A-Day™ Cream exhibits *in vitro* antifungal activity against a broad spectrum of organisms, although the clinical significance of these data is unknown. Fungicidal activity has been demonstrated *in vitro* against *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, Trichophyton tonsurans, Microsporum canis* and fungistatic activity against *Candida albicans.*

MIC Values of Butenafine Hydroxhloride

for Several Pathogenic Fungi Circulation on

Sabouraud's Dextrose Agar Medium at 27°C or 37°C (Yeasts)

Micro-Organisms	Number of Strains	Geometric Means	MIC (µg/ml) Range
Dermatophytes			
T. mentagrophytes	22	0.012	0.006-0.025
T. rubrum	41	0.007	0.0015-0.025
M. canis	14	0.024	0.0125-0.05
M. gypseum	7	0.014	0.006-0.025
E. floccosum	3	0.016	0.006-0.025
Molds			
Aspergillus fumigatus	3	0.65	0.39-0.78
Aspergillus flavus	5	0.125	0.025-0.1
Aspergillus niger	4	0.19	0.05-0.39
Aspergillus terreus	2	0.2	
Aspergillus nidulans	1	0.2	
Sporothrix schenckii	1	0.78	
Nocardia asteroides	1	>100	
Actinomadura madurae	1	6.25	
Yeasts			
Candida albicans	57	>100	
Candida albicans pH 5.0*	57	27.07	3.13-50
Candida tropicalis	4	6.25, >100, >100,>100	
Candida krusei	2	25, >100	
Candida parapsilosis	2	3.13, 6.25	
Cryptococcus neoforms	4	1.17	0.78-1.56
Others	3	6.25, 6.25, >100	

* Growth medium adjusted to pH 5.0 through addition of 5N HCl.

IN VIVO

The therapeutic effects of butenafine HCl in various models of dermatophytosis in the guinea pig was compared with that of other antifungals and are summarized in Primary Therapeutic Studies in Animals. In all but one of the studies reported below, the butenafine HCl solution used consisted of butenafine HCl dissolved in Macrogol 400:ethanol (75:25). The adsorption study employed 14Clabeled butenafine HCl initially dissolved in Tween 80 and then incorporated in a mixture of Macrogol 400: ethanol:water (30:20:50).

- **Effects on Tinea Dorsalis:**

In guinea pigs with tinea dorsalis caused by *Trichophyton mentagrophytes*, *Microsporum canis* or *Candida albicans*, 1.0% butenafine HCl was compared with naftifine, tolnaftate, clotrimazole, miconazole and bifonazole for efficacy. A 0.5% butenafine HCl cream applied twice a day and a 1.0% butenafine cream applied once a day had cure rates of 100% against *T. mentagrophytes*. Once percent naftifine and 1.0% tolnaftate creams when applied once a day had cure rates of 82% and 64%, respectively. Butenafine HCl, naftifine and tolnaftate had equal efficacy against *M. canis* while clotrimazole had lower efficacy. One percent butenafine HCl had equal efficacy to bifonazole but less activity than miconazole against *C. albicans*.

- **Effects on Tinea Pedis:**

Butenafine HCl was tested in a guinea pig model of tinea pedis caused by *T. mantagrophytes*, a mycosis that does not heal spontaneously. Treatment with 0.2 to 2.0% butenafine HCl creams or solutions were started on the 10th day after infection and lasted for 20-40 days. Dose-related effectiveness was seen against tinea pedis with once-daily application of 1.0% butenafine solution, and showed higher potency than either 1.0% naftifine, tolnaftate or clotrimazole solutions.

- **Prophylactic Effects**:

To establish the prophylactic effect of 1.0% butenafine HCl solution relative to 1.0% bifonazole solution, each compound was applied to the skin of guinea pigs. After 24, 48 and 72 hours following application, the region was infected with *T. mentagrophytes*. Butenafine HCl effectively prevented infection up to 17 days after a 48-hour, pre-infection application, whereas lesions appeared after eight days following a 24-hour, pre-infection application of bifonazole.

- **Substantivity and Efficacy against *T. mentagrophytes***:

The permeability and retention (substantivity) of butenafine HCl in the skin of guinea pigs were examined following topical application of a 1.0% ^{14}C-labeled butenafine HCl solution for six hours to the dorsal skin of guinea pigs. At six hours post-application, 50 μg/g or more of butenafine HCl was observed in the epidermis, including the horny layer in which dermatophytes are commonly found. At 24 hours post-application, 10 μg/g or more of butenafine HCl still remained in the epidermis, indicating high affinity and long retention. The concentration of butenafine HCl in the epidermis 24 hours post-topical application of a 1.0% solution was enough to inhibit the growth of *T. mentagrophytes*.

MICROBIOLOGY

IN VIVO

Summary of Primary Therapeutic Studies in Animals

Species	Strain	Study Type	Group Size	Route	Dose and Mode of Administration	Results
Guinea Pigs	Hartley	*in vivo*-prophylactic effect on dermatophytosis, *T. mentagrophytes*	5M/ group	Topical	0.2 ml, 1% butenafine or B for 24, 48, 72 hrs. and observations for 17 days after infection.	Butenafine effective prophylactically for 17 days when applied *q.d.* 24 and 48 hr. pre-infection.
Guinea Pigs	Hartley	*in vivo*-effect on dermatophytosis, *T. mentagrophytes*	5M/ group	Topical	0.01, 0.1, 1.0% butenafine, N, T, or C; for 10 days (Day 2 post-infection).	1% solution of butenafine, N, T effective but not C. 0.1% and 0.01% were 94 and 60% effective, N and T were less.
Guinea Pigs	Hartley	*in vivo*-effect on dermatophytosis, *T. mentagrophytes*	5M/ group	Topical	1.0% butenafine, N or T once daily / 4 days (Day 2 post-infection)	Butenafine gave complete cure, N and T 82% and 64%.
Guinea Pigs	Hartley	*in vivo*-effect on dermatophytosis, *T. mentagrophytes*	5M/ group	Topical	1% butenafine or N, *q.d.* for 4-10 days (Day 3 and 4 post-infection)	Complete cure after 10 days
Guinea Pigs	Hartley	*in vivo*-effect on dermatophytosis, *T. mentagrophytes*	5M/ group	Topical	0.125, 0.25, 0.5 and 1.0% butenafine; *q.d.* or *b.i.d.* for 10 days (Day 4 post-infection).	100% cure with 0.5%, *b.i.d.* or 1%, *q.d.* No difference in efficacy seen between 1% *q.d.* and *b.i.d.*
Guinea Pigs	Hartley	*in vivo*-effect on dermatophytosis, *M. canis*	5M/ group	Topical	0.1, 1.0% butenafine, N, T or C; *q.d.* for 10 days (Day 10 post-infection).	C has lowest activity. All others equal efficacy.
Guinea Pigs	Hartley	*in vivo*-effect on Tinea pedis, *T. mentagrophytes*	8-10M	Topical	0.2, 0.5, 1.0% butenafine once daily for 20 days (Day10 post-infection)	Dose related effect seen. 92% cure with 1% butenafine
Guinea Pigs	Hartley	*in vivo*-effect on Tinea pedis, *T. mentagrophytes*	5M	Topical	0.25, 0.5, 1.0, 2.0% butenafine *q.d.* or *b.i.d.* for 20 days (Day 10 post-infection	Dose related effect from 0.25% - 1.0%. No differences between 1.0% and 2.0% or *q.d.* & *b.i.d.*

Species	Strain	Study Type	Group Size	Route	Dose and Mode of Administration	Results
Guinea Pigs	Hartley	*in vivo*-effect on Tinea pedis, *T. mentagrophytes*	5M	Topical	1.0% butenafine *q.d.* for 10, 20, or 40 days (Day 10 post-infection).	The longer the duration the better the efficacy.
Guinea Pigs	Hartley	Intracutaneous distribution		Topical	1% C^{14} labeled butenafine solution for 6 hours	50 µg/g of butenafine was observed in the epidermis.
Guinea Pigs	Hartley	*in vivo*-effect on dermatophytosis, *C. albicans*	6M	Topical	0.2 ml of 1.0% butenafine, M or B *b.i.d.* for 7 days (Day 1 post-infection).	Efficacy almost equal to B but less than M.

B: bifonazole

C: clotrimazole

M: miconazole

N: naftifine

T: tolnaftate

TOXICOLOGY

ACUTE TOXICOLOGY

Species	Route	Test Article	Doses (mg/kg)	Duration of Observation (Days)	Results
Rat	Topical	UV light degradate "D1"	0, 200, 2000, 5000 mg/kg for 24 hr.	14 Days	No mortality, signs of systemic toxicity or gross path. Erythema and scab at high dose. Sporadic soft feces.
Rat	Topical	Heat degradate "D2"	0, 20, 1000, 5000 mg/kg for 24 hr.	14 Days	No mortality or gross path. Erythema , scab, reduced weight gain and soft feces at high dose.
Rat	Topical	Heat degradate "D3"	0, 250, 500, 1000 mg/kg for 24 hr.	14 Days	No mortality, systemic toxicity, or gross path. Transient erythema and scab. Sporadic soft feces
Rat	IP	Dosing Metabolite "M1"	0, 700, 800, 1000, 1500, 2000 mg/kg	14 Days	Some mortality in all treated groups within 2 days. LD_{50} - M : 807 mg/kg, F: 748 mg/kg
Rat	IP	Dosing Metabolite "M2"	0, 500, 700, 1000, 1500 mg/kg	14 Days	Some mortality in 3 highest dose groups in day 1. LD_{50} - M : 942 mg/kg, F: 1129 mg/kg
Rat	IP	Dosing metabolite "M3"	0, 700, 800, 1000, 1500, 2000 mg/kg	14 Days	Some mortality in at top 3 doses in the first day. White fecal and urinary discharge in day 1. LD_{50} - M : 1146 mg/kg, F: 852 mg/kg

D1: 1-naphthalene methanol

D2: 1-(chloromethyl) naphthalene

D3: N-methyl-bis (1-naphthalenemethyl) aminehydrochloride

M1: 1-naphthoic acid

M2: N-4 (2-hydroxy-1,1-dimethylethyl) benzyl-N-methyl-1-naphthalenemethylamine

M3: N-1-naphthoxyl glycine 100

SUBCHRONIC TOXICITY STUDIES

Species	Route	Doses (mg/kg)	Duration	Results
Rat	SC	0, 0.2, 1, 5, 25 mg/kg daily for 90 days	90 day dosing + 30 day Recovery period	No effects on survival. Reversible changes; skin thickening and nodules (all groups) and hematology (5, 25 mg/kg). NOEL (systemic) – 1mg/kg/d
Rat	Topical	0, 15, 50, 150, 500 mg/kg daily for 90 days	90 day dosing + 30 day recovery period	No effects on survival or pathology. Reversible changes: erythema, blisters, WBC differential. Decreased food consumption (50 mg/kg males; 150 mg/kg females). NOEL (systemic & local) – 15 mg/kg/d
Dog	Topical	0, 25, 50, 100 mg/kg	90 day dosing + 30 day recovery period	No systemic toxicity. Reversible erythema, scab formation, papules at application site (all groups). NOEL (systemic) -> 100 mg/kg/d

CHRONIC STUDIES

Species	Route	Doses (mg/kg)	Duration	Results
Rat	SC	0, 0.05, 0.5, 5.0 mg/kg/d for 6 months	6 month dose + 1 month recovery	No mortality. Reversible changes: increased liver and spleen weights, blood chemistry and body weight gain at high dose. NOEL (systemic) - 0.5 mg/kg/day
Dog	Topical	0, 25, 50, 100 mg/kg/d for 12 months	12 months	No systemic toxicity observed. Erythema, scab, and skin irritation in all groups. NOEL (systemic) - 25 mg/kg/d

MUTAGENICITY

In vitro mutagenicity testing (bacteria reverse mutation and CHL chromosome aberration) revealed no specific mutagenic or genotoxic properties of butenafine

CARCINOGENICITY

Long-term animal studies to determine carcinogenic potential have not been performed.

REPRODUCTION STUDIES

Species	Route	Doses (mg/kg)	Segment	Results
Rat	SC	0, 0.25, 2.5, 25 mg/kg at least 60 days, before and during mating and 7th day of pregnancy for females	I: Fertility and reproductive performance	No abnormality in reproductive functions, or condition during pregnancy, or morphology of fetuses. Decreased food intake and body weight gain at 25.0 mg/kg. NOEL – 2.5 mg/kg dam NOEL – 25 mg/kg fetus
Rat	SC	0, 0.25, 2.5, 25 mg/kg, day 7 to 17 of gestation.	II: Teratogenic potential (Days 7 to 17)	No effect on fetal or postnatal development. NOEL – 2.5 mg/kg dam NOEL – 25 mg/kg fetus
Rabbit	Topical	0, 12.5, 25, 50 mg/kg from day 6 to day 18 of gestation.	II: Teratogenic potential (Days 6 to 18)	No effect on general toxicity, reproduction, survival, organogenesis or growth of the fetuses. NOEL – 50 mg/kg
Rat	SC	0, 0.25, 2.5, 25 mg/kg during peri and postnatal periods.	III: Peri and postnatal tox. (Days 7 to 21, postnatal)	No changes in survival rate, postnatal differentiation, sexual maturity test or reproductive function test in offspring or in F2 rat. NOEL – 25 mg/kg

SPECIAL TOXICITY STUDIES

Species	Route/Test	Doses Volume	Duration (Days)	Results
Rabbit	Topical, Eye	0.1 ml for 24 hrs.	5 days	Discharge and conjunctivitis in all groups. Reversible edema, iridial congestion and opacity. Normal by day 5.
Rabbit	Topical, Eye	0.1 ml for 24 hrs.	3 days	No positive corneal, iritic or conjunctival changes.
Rabbit	Topical, Skin (intact and abraded)	0.5 ml for 24 hrs.	3 days	Slight erythema and edema. Decreased to slight or none by 72 hrs.
Rabbit	Topical, Skin	0.5 ml for 24 hrs.	1 day test + 7 day recovery	No edema. Reversible erythema in all test groups and solution vehicle.
Rabbit	Topical, Skin	0.5 ml 6 hr/day for 14 days	14 day test + 7 day recovery	No edema. Reversible erythema (all groups) and eschar formation (3/6, high dose)
Guinea Pig	Topical, Contact allergenicity	50 µl for 24 hrs	14 day post challenge	No contact-allergic reaction.

Species	Route/Test	Doses Volume	Duration (Days)	Results
Guinea Pig	Topical, Phototoxicity	10 µl solution; 10 mg cream once	3 days	Slight phototoxicity with 10% solution. None with either formulation at 1%.
Guinea Pig	Topical, Photocontact allergenicity	0.1 ml solution; 0.1 g cream	5 days	No photocontact allergenicity.
Guinea Pig PCG model, Rat	Topical, SC Antigenicity – Active and passive cutaneous, systemic, anaphylaxis, PCA, PHA	Topical – 15, 50, 150, 500 mg/kg; S.C.-0.2, 1.0, 5.0, 25 mg/kg	variable	No antigenicity.

DERMAL SAFETY STUDIES IN MAN

Tinactin® Once-A-Day™ Cream is not a primary irritant and appears to be devoid of allergenic sensitization or phototoxic/photoallergy potential on topical application.

A challenge patch of 0.2 ml Tinactin® Once-A-Day™ Cream applied to the skin for 24 hours, 10 to 17 days after nine consecutive 24-hour patched applications of the same dose, did not product contact sensitization in 204 North American volunteers.

In 27 North American volunteers (22 female and 5 male) treated topically with Tinactin® Once-A-Day™ Cream, exposure to long-wave ultraviolet light did not produce any phototoxic reaction.

Thirty-one North American volunteers received a series of six applications (two per week) of 0.2 ml of Tinactin® Once-A-Day™ Cream on an occlusive dressing applied to the paraspinal area for 24 hours. Following removal of the patch, the skin was exposed to twice the subject's minimal erythema dose from a Xenon Solar Simulator. Fourteen days after the last exposure, the subjects were challenged with 0.2 ml Tinactin® Once-A-Day™ Cream applied to an untreated site of the skin for 24 hours and subsequently exposed to long ultraviolet light. Tinactin® Once-A-Day™ Cream was shown to be devoid of any detectable photocontact allergenic potential.

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