

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-408

PHARMACOLOGY REVIEW(S)

Based on currently available information, I do not concur with the some of the details of the review regulatory conclusions regarding adequacy of some studies and the need for future studies. This memo also includes comments from B. Hill, acting supervisory pharmacologist.

1. Safety pharm conclusion: Although the conclusion says that cardiovascular or respiratory function was not affected, this is misleading since elsewhere it is reported that that metabolite M1 increased respiratory rate and M2 produced a transient decrease in heart rate. M1, M2 and M3 are reported to decrease heart rates in rats. M1 increased hexobarbital sleeping time. The M1 metabolite is more acutely toxic than butenafine and accounts for most of the orally absorbed material in rats. This metabolite (naphthoic acid) is shared with terbinafine as is the pharmacologic target.
2. Only 1-3% of the oral or subcutaneous dose was reportedly absorbed in rats or rabbits. Butenafine is not as extensively metabolized in humans as in rats (similar to terbinafine). Therefore, the multiple of parent butenafine may be much lower than indicated by mg/m^2 comparisons. AUC values of parent should be informative. These values will need to be corrected for protein binding, which differs among rats, dogs, and humans.
3. Twelve patients with severe tinea versicolor applied a range of 14 to 49 grams of Mentax® - TC Cream, 1% to cover each lesion and four inches of clear skin surrounding the margins of the lesions once daily for 7 days. The maximum amount of Mentax-TC cream applied in this study was 49 grams/day. If the MRHD is based on the maximum amount of Mentax-TC cream used in the clinical pharmacokinetic study, then the MRHD would be $300 \text{ mg}/\text{m}^2/\text{day}$ for a 60 kg individual ($490 \text{ mg}/\text{day} \div 60 \text{ kg} = 8.2 \text{ mg}/\text{kg}/\text{day}$; $8.2 \text{ mg}/\text{kg}/\text{day} \times 37 = 303 \text{ mg}/\text{m}^2/\text{day}$). In the primary pharm/tox review for Mentax-TC cream, it is stated that the human pharmacokinetic study was conducted at $260 \text{ mg}/\text{m}^2/\text{day}$. This MRHD was calculated based on a 70 kg individual ($490 \text{ mg}/\text{day} \div 70 \text{ kg} = 7 \text{ mg}/\text{kg}/\text{day}$; $7 \text{ mg}/\text{kg}/\text{day} \times 37 = 259 \text{ mg}/\text{m}^2/\text{day}$). However, it is preferable to use a 60 kg individual for the multiples of human exposure calculations per the pharm/tox start dose document and current practice. This value should be used to calculate multiples of the human, throughout the review and for labeling.
4. Repro/developmental toxicity studies. The doses in these studies did not achieve any maternal toxicity. These studies should be conducted at a maximum feasible dose or an MTD. The product should be labeled as Category C until adequate studies are conducted. Another reason for using category C is that the multiple of the human exposure is low. All reference to a _____ has been deleted from the label. No mention of this study can be found in the primary Pharm/Tox review for this NDA. Description of a peri-postnatal study should be added to labelin g.
5. A tg.AC carcinogenicity study is currently being conducted with the _____ formulation. If that study is adequate for evaluation and yields negative results, a dermal carcinogenicity study will not need to be conducted for this formulation
6. A phase 4 study should be conducted to evaluate the long-term effects in light. This would be consistent with Division and CDER practice and CDER guidance for a chronic intermittent indication.
7. Throughout the review it is not clear what dermal formulation is being studied.
8. Labeling recommendations:

Recommended revisions to the Pharm/Tox portions of the Mentax-TC label are provided below with ~~strikeout~~ text recommended for deletion and highlighted text recommended for addition to the label.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies to evaluate the carcinogenic potential of Mentax® - TC Cream, 1%, have not been conducted. Two *in vitro* assays (bacterial reverse mutation test and chromosome aberration test in Chinese

hamster lymphocytes) and one *in vivo* study (rat micronucleus bioassay) revealed no mutagenic or clastogenic potential for butenafine.

In subcutaneous fertility studies conducted in rats at dose levels up to 25 mg/kg/day 0.5 times the maximum recommended dose in humans for tinea versicolor based on body surface area comparisons) butenafine did not produce any adverse effects on male or female fertility.

Pregnancy

Teratogenic Effects: Pregnancy Category - C

Subcutaneous doses of butenafine (dose levels up to 25 mg/kg/day administered during organogenesis) (equivalent to 0.5 times the maximum recommended dose in humans for tinea versicolor based on body surface area comparisons) were not teratogenic in rats. In an oral embryofetal developmental study in rabbits dose levels up to 400 mg butenafine HCl/kg/day administered during organogenesis) (equivalent to 16 times the maximum recommended dose in humans for tinea versicolor based on body surface area comparisons), no treatment-related external, visceral, or skeletal malformations or variations were observed.

In an oral peri- and post-natal developmental study in rats (dose levels up to 125 mg butenafine HCl/kg/day) (equivalent to 2.5 times the maximum recommended dose in humans for tinea versicolor based on body surface area comparisons), no treatment-related effects on postnatal survival, development of the F1 generation or their subsequent maturation and fertility were observed.

There are, however, no adequate and well-controlled studies that have been conducted of topically applied butenafine in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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/s/

Abby Jacobs
7/8/02 08:41:22 AM
PHARMACOLOGIST

Jonathan Wilkin
7/21/02 06:26:23 PM
MEDICAL OFFICER

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The chemistry reviewer sent the following information to the pharm/tox group on
7/10/02:

"The specifications were found to be higher for degradation products than those reported in the release specifications for Mentax Cream (NDA 20-524). Specifically, the acceptance criterion for the total degradation products was proposed at _____ of butenafine HCl. The acceptance criteria for the individual degradation products were proposed at _____ of butenafine HCl for each of _____ In NDA 20-524, these acceptance criteria for total degradation products and the individual impurities at _____ and _____ of butenafine HCl for _____ and _____, respectively. The higher concentration of these impurities is unacceptable unless they have been qualified at the higher levels, and that the Division's Pharmacologist has reviewed the data and found the amounts acceptable. The original toxicity profile for a lower concentration of these impurities was reviewed by the Division's Pharmacologist and found acceptable (see Pharmacology review dated 8/24/95; NDA 20-524).

The specifications reported _____ new degradation products than those reported for Mentax Cream. They are _____ Acceptance criteria for the individual degradation products were proposed at _____ of butenafine HCl, respectively.

Note: It should be noted that clinical batch (e.g. Lot # PEGF-2) placed on stability studies (25°C/60% RH) revealed these degradation products at levels of _____ after _____ No degradation of butenafine HCl cream was reported at the _____ test station"

My comments and recommendations:

1. The degradants that were present in earlier formulations are considered to be qualified per ICH Q3B.
2. _____ should be qualified before a shelf life of greater than _____ is approved.
3. For a shelf life of greater than _____, the sponsor should propose how it will qualify the degradants _____
4. Toxicities of interest for these _____ include genotoxicity, contact sensitization, and general and dermal toxicity after repeated dose application (e.g., 28 days). Results of these studies will determine the need for further studies.

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Abby Jacobs
10/16/02 12:26:14 PM
PHARMACOLOGIST

Jonathan Wilkin
10/17/02 11:15:25 AM
MEDICAL OFFICER

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PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-408

Review number: 01

Sequence number/date/type of submission: 000/12-19-2001

Information to sponsor: Yes () No (X)

Sponsor and/or agent: Bertek Pharmaceuticals Inc.

P. O. Box 14149

Research Triangle Park, NC 27709-4149

Manufacturer for drug substance: DPT Laboratories, Inc.

307 E. Josephine Street

San Antonio, TX 78215

Reviewer name: Kumar D. Mainigi

Division name: Dermatologic and Dental Drug Products

HFD #: 540

Review completion date:

Drug:

Trade name: **Mentax^R-TC (butenafine HCl) Cream 1%**

Generic name (list alphabetically): None

Code name: KP-363

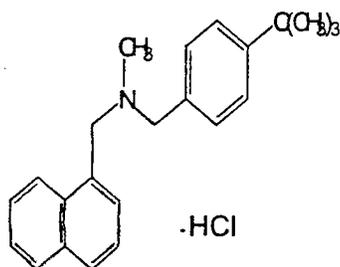
Chemical name: *N*-4-*tert*-Butylbenzyl-*N*-methyl-1-naphthalenemethylamine Hydrochloride

CAS registry number: 101827-46-7

Mole file number:

Molecular formula/molecular weight: C₂₃H₂₇N.HCl / 353.93

Structure:



Butenafine HCl

Relevant INDs / NDAs / DMFs:

IND 42,762 Butenafine HCl Skin Formulations

IND 57,959: Mentax Cream 1%

IND 60,471: Butenafine HCl Optimized Cream 1%

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NDA: 20-524: Mentax (butenafine HCl) Cream 1% for the treatment of tinea pedis
(approved 10/18/96)

NDA 20-663: Mentax (butenafine HCl) Cream 1% for the treatment of tinea corporis and
tinea cruris (approved 12/31/96)

Drug class: Antifungal

Indication: Tinea versicolor

Clinical formulations:

<u>Ingredients</u>	<u>Mentax^R-TC Cream, 1%</u>	<u>Mentax^R Cream, 1%</u>
	(New formulation)	(Marketed formulation)
	<u>Percentage (w/w)</u>	
Butenafine HCl	1.00	1.00
Purified water USP	/	/
Propylene glycol dicaprylate	/	/
Propylene glycol USP	/	0.00
Glycerin USP	/	/
Glyceryl monostearate,	/	/
Cetyl alcohol NF	/	/
White petrolatum USP	/	/
Stearic acid NF	/	/
Polyoxyethylene (23) cetyl ether	/	/
Polyolprepolymer-2	/	0.00
Benzyl alcohol NF	/	—
Trolamine NF	—	0.00
Diethanolamine	0.00	/
Sodium benzoate NF	—	/
Total	100.00	100.00

Route of administration: Topical

Proposed use: Treatment of Tinea versicolor

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Studies reviewed within this submission: None

Studies submitted but not reviewed within this submission: None

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Studies reviewed in the previous submissions:

Pharmacology

1. General pharmacology: subcutaneous studies of butenafine HCl in rat, dog, mouse, rabbit and guinea pig (E-14).
2. Blood hormone levels in rats subcutaneously treated with butenafine HCl (E-15).
3. General pharmacology of butenafine metabolites and degradation products
4. in mouse, rat, and guinea pig (E-16).
5. Effect of butenafine on the experimental tinea pedis in guinea pigs (PHA 010-009).
6. Irwin multidimensional test in rat (PHA 010-001).
7. Effect on gastric emptying in rat (PHA010-004).
8. Effects on the cardiovascular system in dog (PHA 010-002).
9. Effect on action potential in sheep Purkinje fiber (PHA010-003).

Biodisposition:

1. Single dose ADME studies in rats, guinea pigs and dogs (F-1).
2. Multiple dose ADME study in rats (F-2).
3. Skin penetration of butenafine in guinea pigs (F-3).
4. Absorption of gel and solution formulation.
5. Biotransformation in rat after the i.v.dose (F-4).
6. Percutaneous study of degradation products (TOX 010-037).
7. 28-Day oral toxicokinetic study in rat (TOX 010-071).
8. Cytochrome P-450 in rats and dogs (PHA 010-007).
9. In vitro inhibition of human cytochrome P-450 enzymes (PHA 010-008).
10. In vitro metabolism in rats, dogs and human (PHA 010-010).
11. Enzyme studies in human and rat hepatocytes (PHA 010-006).
12. Plasma protein binding (PHA 010-005).
13. In vivo protein binding in rat and dog (PHA 010-012).
14. Biodisposition in fed and fasted rats (PHA 010-011).
15. Butenafine HCl: Skin permeability and adsorption to horny materials (E-7).
16. ADME in rat, guinea pig, and dog after single dose (F-1).
17. ADME in rat after repeated doses (F-2).
18. Penetration in skin of guinea pig (F-3).
19. Metabolism in rat (F-4).

Acute toxicity

1. Oral toxicity in rats (TOX 010-001).
2. Oral toxicity in rats (TOX 010-A-003).
3. Oral toxicity of metabolites (TOX 010-038).
4. Oral toxicity in rats (TOX 010-043).
5. Oral study in rats (TOX 010-058).
6. Oral study in rats (TOX 010-061).
7. Oral study in rats (TOX 010-069).
8. Oral study in mice (TOX 010-009).
9. I.V. study in mice (TOX 010-010).
10. Topical study in mice (TOX 010-012).

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11. Intravenous study in rats (TOX 010-014).
12. Subcutaneous study in rats (TOX 010-015).
13. Dermal study in rats (TOX 010-016).
14. Oral study in dogs (TOX 010-017).
15. Topical study in dogs (TOX 010-018).
16. Topical study in rats with ———— degradates (TOX-010-037).
17. IP. study in rat with metabolites M1, M2, and M3 (TOX 010-038).
18. Oral study in rats (TOX 010-064).
19. Acute oral toxicity screen in rat (TOX 010-052).
20. Oral study in rats (NT200013).
21. Oral toxicity in rats (SLI 3133.787).
22. Oral study in rats (SLI 3133.78).

Short-term Toxicity

1. 21-day dermal (—) in mice in Tg.AC mice (TOX 010-063).
2. 14-day cumulative irritation in rabbit (TOX 010-025).
3. 21-day dermal study in rats (TOX 010-056).
4. 28-Day oral study in dogs (TOX 010-072).
5. 21-Day dermal irritation study in TG.AC mice and rats (TOX 010-062).
6. 7-Day oral study in rat (TOX 010-065).
7. 14-Day oral study in rat (TOX 010-074).
8. 14-Day intraperitoneal study in rat (D4).
9. 28-Day oral in rats (TOX 010-071).
10. 28-Day oral study in rat (TOX 010-070).
11. 28-day dermal in mice (TOX 010-063).
12. 7-Day oral study in dog (TOX 010—066).
13. 14-Day intraperitoneal study in rat (D4).

Subchronic Toxicity:

1. Three-month topical in rats with one month recovery (TOX 010-020).
2. Three-month subcutaneous in rats with one month recovery (TOX 010-019).
3. Three-month percutaneous study in rat (TOX 010-020).
4. Three-month topical in dogs with one month recovery (TOX 010-021).

Chronic Toxicity:

1. Six-month subcutaneous in rat with one month recovery (TOX 010-022).
2. A 12-month dermal study in dog (TOX 010-023).
3. 9-Month oral toxicity study in dogs (TOX 010-076).

Reproductive and Developmental Toxicity

1. Segment I subcutaneous in rats (TOX 010-031).
2. Segment II subcutaneous in rats (TOX 010-032).
3. Segment III subcutaneous in rats (TOX 010-033).
4. Segment II subcutaneous study in rat (TOX 010-034).
5. Segment II in rabbit (TOX 010-072).
6. Segment I and segment III oral studies in rats (TOX 010-081).

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Primary Irritation:

1. Eye irritation testing in rabbits (TOX 010-044).
2. Primary irritation test in rabbits (TOX 010-060).
3. Skin irritation testing in rabbits (TOX 010-045).
4. Dermal irritation testing with deteriorated drug in rabbits (D-18).
5. Primary eye irritation in rabbits (TOX 010-068).
6. Primary skin irritation in rabbits (TOX 010-067).
7. Primary skin irritation (solution 1%) in rabbits (TOX-010-077).
8. Primary eye irritation (solution 1%) in rabbits (TOX 010-078).
9. Primary skin irritation test (TOX 010-059).
10. Primary eye irritation test (TOX 010-057).
11. Primary skin irritation in rabbit (TOX 010-002).
12. Primary dermal irritation in rabbit (TOX 010-024).
13. Primary ocular irritation in rabbit (TOX 010-026).
14. Primary skin irritation in rabbit (TOX 010-053).
15. Primary eye irritation in rabbit (TOX 010-054).
16. Primary eye irritation in rabbit (TOX 010-055).
17. Primary eye irritation in rabbit (NT200013).
18. Primary eye irritation in rabbit (SLI 3133.78).

Genotoxicity:

1. Rat micronucleus assay (TOX -010-046).
2. Reverse mutation test in bacteria (TOX 010-035).
3. Chromosomal aberration assay in Chinese hamster lung fibroblasts (TOX 010-036).

Immunotoxicity:

1. Contact allergenicity in guinea pig (TOX-010-027).
2. Phototoxicity in guinea pig (TOX 010-028).
3. Photocontactallergenicity in guinea pig (TOX 010-029).
4. Antigenicity test in guinea pig and rat (TOX 010-030).

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Executive summary

I. Recommendations

A. Recommendation on Approvability: From the non-clinical point of view this new drug application is approvable.

B. Recommendation for Nonclinical Studies: All the required non-clinical studies were conducted, and the safety profile is complete.

C. Recommendations on Labeling: All the required data for labeling are available, and the non-clinical portion of the label is approvable.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings: Butenafine HCl has been extensively evaluated in its various formulations at concentrations ranging from 0.5 to 10%. The proposed drug product (an optimized cream formulation) Mentax^R-TC (butenafine HCl) Cream, 1%, is a slightly modified form of marketed Mentax Cream 1% (NDAs 20-524 and 20-663).

Only four basic toxicology studies were conducted with Mentax²-TC cream, its safety profile is primarily supported by the studies conducted with the cream, — formulations of butenafine hydrochloride. In rat acute oral toxicity study, no deaths or clinical signs of toxicity were observed at a dose level of 5g optimized cream/kg. The formulation tested as a mild dermal irritant but not as an ocular irritant in primary rabbit assays. In a 21-day cumulative dermal irritation assay in rats (4mg butenafine HCl/kg/day), no drug-related dermal lesions were observed.

In a 12-month topical dog study (25, 50, and 100mg/kg/day) conducted at 5-21 times (mg/m²/day) the maximum expected clinical dose of 95mg/m², only incidences of mild reversible erythema, papule and scabs were observed. No systemic toxicity was exhibited at any dose level. The NOELs for the local and systemic toxicity were established at 5 and 21(mg/m²) time the maximum expected clinical dose, respectively.

In a 9-month oral dog study (40, 160, 480mg/kg/day) conducted at 8-101 times (mg/m²) the maximum expected human dose, the significant drug-related effects at the mid- and high dose levels included decreased body weight and food consumption, dehydration, convulsions, and post-dose vomiting. The NOEL for systemic toxicity was established at 27 times the maximum recommended human dose in terms of mg/m² (40mg/kg/day).

A rat subcutaneous study conducted approximately at 2 times the maximum expected human dose did not affect fertility, fetal development, sexual maturation, reproductive function, or postnatal differentiation. In the rabbit oral teratogenicity study conducted at 50 times (mg/m²/day) the expected clinical dose, no drug-related external, visceral, or skeletal malformations were observed.

Butenafine tested nonmutagenic and nonclastogenic in bacterial and animal assays. It also tested negative in a photosensitization test in rats and guinea pigs. None of the butenafine formulations at 1% strength were phototoxic to guinea pigs.

In rats, one hour after the oral (0.2mg/kg) or subcutaneous (1mg/kg) radioactive dose, approximately 1.5-3.0% of the administered drug was absorbed. In an oral subchronic dog study (5-1000mg/kg/day), butenafine was well absorbed and the values of Cmax at 0.5 hour post-dose after the first dose ranged from 50 to 7596ng/mL of plasma. Drug is rapidly biotransformed in the animals and humans into several identical metabolites, which are mostly excreted as conjugates in the bile. Animals exhibited biphasic elimination of drug with a terminal half-life ranging from 15 to 36 hours.

B. Pharmacologic Activity: Butenafine inhibits the activity of squalene epoxidase, a key enzyme involved in the microsomal ergosterol synthesis in the fungi. This action leads to the rising level of squalene and falling level of the end-product ergosterol, required for membrane formation in the fungi. The accumulation of squalene in *C. albicans* treated with butenafine HCl has been demonstrated. It is suggested that accumulation of squalene cause an increase in membrane permeability resulting into disruption of cellular organization. The drug adsorbs to the stratum corneum and persists in the top layers of the skin where pathogenic fungi reside. Depending upon the test organism and drug concentration, butenafine can be fungistatic as well as fungicidal.

In a guinea pig model for experimental dermatomycosis, ten daily oral doses of 10mg butenafine HCl/kg/day significantly reduced the infection and provided cure.

C. Nonclinical Safety Issues Relevant to Clinical Use: None

III. Administrative

A. Reviewer signature-----

B. Supervisor signature: Concurrence-----

Non-concurrence-----
(see memo attached)

C. cc:list:

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PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

Pharmacology summary/conclusions: Like several other antifungal agents (e.g. terbinafine and naftifine), butenafine also inhibits the microsomal ergosterol synthesis in the fungi. However, in this case, the formation of the steroid nucleus is blocked at an earlier step of squalene epoxide, leading to a reduced level of end-product ergosterol required for membrane formation in the fungi. Following butenafine treatment, accumulation of squalene was observed in *C. albicans*. It has also been demonstrated that depending upon the test organism and drug concentration, butenafine can be fungistatic as well as fungicidal. In a guinea pig model for experimental dermatomycosis, ten daily oral doses of 10mg butenafine HCl/kg were efficacious both in reducing the intensity of infection as well as providing a significant cure.

In animals, three major metabolites of butenafine (M1, M2, and M3) were pharmacologically active (see names and structures on the next page). Thus, M1 raised the respiratory rate in rats, and prolonged the sleep time in mice; M2 produced a transient decrease in blood pressure in rats; and M3 decreased the heart rate in rats. However, it must be mentioned that these secondary pharmacodynamic (unintended) effects were observed at the intravenous dose levels (30-100mg test substance/kg) much greater than the maximum expected therapeutic dose of approximately 2.6mg/kg/day.

II. SAFETY PHARMACOLOGY:

Neurological effects: The subcutaneous (up to 100 mg/kg) and the topical (up to 3%) doses of butenafine HCl to guinea pigs and mice did not affect the somatic, and central and autonomic systems, respectively. At dosing time, convulsions were observed in 2/4 male dogs at 1000mg/kg dose level (at 210 times the maximum expected clinical dose in mg/m²), no such incidence occurred in females. At an intravenous dose of 100mg/kg metabolite M1, prolonged the hexobarbital-induced sleep time in mice.

Cardiovascular effects: A single oral dose of 100mg/kg butenafine HCl to dogs, did not affect the systolic and diastolic and mean arterial blood pressures, heart rate, QA, P-R, QRS, R-R intervals, and electrocardiograms. The heart rate in rats was decreased following the intravenous doses of metabolites M2 (30mg/kg), and M3 (100mg/kg).

Pulmonary effects: In dogs, the intravenous administration of 100mg/kg drug caused a slight increase in the respiratory rate, however, the lower doses were ineffective. An intravenous dose of metabolite M1 (100mg/kg) increased the respiratory rate in rats.

Renal effects: The renal functions in the butenafine treated animals were not evaluated.

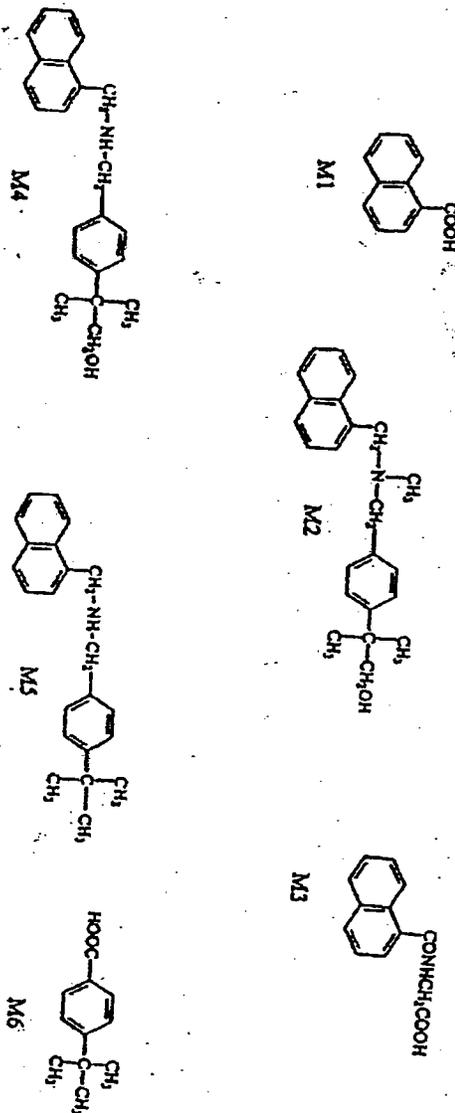
Gastrointestinal effects: In rats, an oral dose of 25mg butenafine HCl produced a marked ($p < 0.01$) decrease in the gastric emptying time, lower doses of 1 and 5mg/kg were ineffective. In mice, the drug did not affect the intestinal transport when treated with oral doses up to 100mg/kg.

Abuse liability: None

Other: In rat Irwin test model, single orals dose (5, 25, and 100mg/kg/day) of butenafine HCl did not affect any behavioral or physiological parameters. The coagulation process in mice was not affected by subcutaneous doses up to 100mg/kg. The daily subcutaneous doses of 25mg butenafine HCl/kg in rats produced no change in the blood levels of FSH,

- M1 = 1-naphthoic acid
- M2 = N-4-(2-hydroxy-1,1-dimethylethyl) benzyl-N-methyl-1-naphthalenemethylamine
- M3 = N-1-naphthoglycine
- M4 = N-4-(2-hydroxy-1,1-dimethylethyl)-1-naphthalenemethylamine
- M5 = N-tert-butylbenzyl-N-1-naphthalenemethylamine
- M6 = 4-tert-butyl-benzoic acid

METABOLITES OF BUTENAFINE



LH, ACTH, estradiol, progesterone, testosterone, and cortisterone. however, a slight hypertrophy of the adrenal glands was observed in females.

Safety pharmacology summary/conclusions: Butenafin (ssuming 100% systemic absorption), did not affect the functions of cardiovascular, somatic, central, and autonomic, and respiratory systems at dose levels ranging from 2-21 times the maximum recommended clinical dose of approximately 95mg butenafine HCl /m². In rats, a slight

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decrease in gastric emptying time was observed at approximately 2 times the maximum clinical dose.

Drug also did not cause any changes in the process of coagulation, intestinal transport, behavior, plasma pharmacokinetics, and hormone levels. At concentrations (30-100mg/kg) much higher than the expected topical clinical dose, intravenous doses of pharmacologically active metabolites of butenafine (M1, M2, M3) affected the blood pressure, heart and respiratory rates, and sleep time in rodents.

PHARMACOKINETICS/TOXICOKINETICS:

PK parameters: In various multi-species, multi-route, single and repeated dose studies, several pharmacokinetic parameters such as C_{max}, T_{max}, AUC, AUC_i, K_{EL}, and C_{ss} etc. were determined.

Absorption: In rats, one hour after the oral (0.2mg/kg) or subcutaneous (1mg/kg) doses of butenafine, approximately 1.5-3.0% of the administered dose was absorbed. Butenafine was well absorbed after the first dose in a 28-day oral dog study (5-1000mg/kg/day), and at 1/2 hour, the group values of C_{max} ranged from 50 to 7596ng/mL of plasma. In fed and fasted rats, oral butenafine (5mg/animal) was rapidly absorbed; however, food accelerated the rate of absorption, but not the extent of absorption.

Distribution: In a single oral dose rat (5mg) study, butenafine was widely distributed in the body with residence time ranging from 32 to 47%. In single oral (0.2mg/kg) or subcutaneous dose (1mg/kg) studies in rats, more than 90% of the radioactivity was bound to serum proteins. In a 4-week oral (5-1000mg/kg/day) study in dogs, the values of C_{max}, AUC, AUC_i, T_{max}, T_{1/2}, and K_{EL} increased in a nonlinear fashion with the dose. A moderate accumulation of parent drug was observed at all doses. In rats, butenafine and its metabolites were primarily found in the gut, liver, pancreas, and adrenals.

Metabolism: Subcutaneously administered butenafine is rapidly biotransformed by methylation, dealkylation, and hydroxylation into a number of metabolites designated as M1 to M6 etc. Only low concentrations of parent drug are found in the plasma and liver. The pharmacologically active metabolites (M1, M2, and M3) were rapidly excreted in the urine and feces. Compared to other metabolites, M2 is found at much higher concentration in the plasma, and therefore, was considered a major drug equivalent. In rats, about 60% of the administered dose was found in the bile, entirely in the conjugated forms of M1, M2, and M3. In a 28-day oral dog study, the combined plasma concentration of metabolites M5 and M2 was below 5% of the plasma concentration of butenafine.

Excretion: In single dose oral and subcutaneous rat studies, a biphasic elimination of butenafine with a terminal half-life ranging from 15 to 36 hours was recorded. The long half-life was attributed to a wide distribution of drug and its slow elimination from the adipose tissue. In rats, dogs, and humans, metabolite M2 is mainly excreted in the bile, with a minimum amount present in the urine. The primary urine metabolites are M1 and M3. In the urine, metabolites M1, M2, and M4 are mainly found as conjugates.

Other studies: In an oral rat study, approximately 3% of the administered dose was absorbed, however, less than 0.03% of the parent drug was found in the plasma within 4 hours of dosing, indicating a significant first-pass metabolism.

In a 9-month oral (40-and 480mg/kg/day) dog study, following 90 daily doses, the plasma concentration of the parent drug and its M2 metabolite was substantially reduced, suggesting a probable alteration in absorption and or auto-induction of drug metabolizing enzymes.

In a 12-month topical dog study with butenafine HCl solution (100mg/kg/day), the mean plasma concentrations of the parent drug at six and 12 months were 284 ± 81 and 252 ± 95 ng/mL, respectively. These peak levels achieved at 21 times (mg/m²) of the maximum expected clinical dose were not associated with any systemic toxicity.

A low level of drug is transferred through the placenta, however, the tissue distribution of drug in the fetus was similar to the maternal distribution. Butenafine is extensively excreted in the milk, reaching a peak level six-fold greater than the plasma level within three hours of a single subcutaneous dose.

PK/TK summary/ conclusions: In the oral non-clinical studies, approximately 1.5-3% of the administered butenafine radioactivity appeared in the plasma. However, within the first 4 hours, only 1/100 of the parent drug was found in the plasma, indicating a significant first-pass metabolism. The amounts of butenafine bound to plasma proteins in man, rat, and dog were 77-80, 89-91, and 93-100%, respectively. Only after seven daily oral doses (1200-1550 mg/kg) to dogs and rats, the parent drug and its metabolites in the plasma were detected. However, the highest amount of parent drug in the plasma never exceeded 8ng/mL. In rats, butenafine and its metabolites were primarily found in the gut, liver, pancreas, and adrenals. No systemic toxicity was observed in a 12-month topical dog study conducted at 21 times the maximum expected clinical dose.

Butenafine is rapidly metabolized by methylation, dealkylation, and hydroxylation. In rats, the parent drug and its metabolites are primarily found in the gut, liver, pancreas, and adrenals of rats. About 60% of the administered dose was found in the bile, almost entirely in the form of conjugated forms of major metabolites.

IV. GENERAL TOXICOLOGY:

Toxicology summary conclusions:

Single-dose studies: The oral LD₅₀ in rats, mice, and dogs exceeded 4000mg butenafine HCl/kg. The intravenous and subcutaneous LD_{50s} in mice and rats ranged between 100-200mg/kg. The primary systemic and local adverse effects of acute doses such as decreased body weight, soft feces, diarrhea, rough coats, hunched posture, reduced mobility, and erythema or swelling at the site of administration, were reversed during the 14 days observation period. At necropsy, no drug-induced gross lesions were found.

Subchronic studies: In a 28-day oral rat study (5-320mg/kg/day), increased liver weights were associated with hepatocyte hypertrophy and necrosis, and mixed inflammatory infiltrates in 80mg/kg females and in both sexes at 320mg/kg level. The microscopic lesions in the lungs of high dose females included histiocytic infiltrates. The NOAELs of 80 and 20mg/kg/day were established in male and female, respectively.

In a 28-day oral dog study (5-1000mg/kg/day), the adverse effects restricted to the high-dose groups (210 times the maximum expected clinical dose) included blue/pale mucous membranes, vomitus, decreased activity, and salivation within two hours of drug administration. At the time of dosing, tremors and convulsions were only observed in (2/4) males. Other drug-related lesions in males included the bone marrow hypocellularity, lbuminous degeneration and hepatocyte vacuolation in the liver, and lymphoid depletion in the lymph nodes and thymus. The NOAEL for both the sexes was considered to be 160mg/kg/day.

Chronic studies: Following subcutaneous injections of butenafine HCl to rats at doses up to 25mg/kg/day for three months, and at 5mg/kg for six months, animals in all groups including controls exhibited thickening of the skin and nodule formation at the site of drug administration. These changes were associated with microscopic lesions of intradermal hemorrhage and abscess. The severity of these lesions was markedly reduced during the one-month recovery period. The clinical signs for systemic toxicity restricted to the high-dose groups included decreased body weights and food consumption, changes in a few clinical pathology parameters, and increased absolute weights of liver and spleen.

In a 12-month topical dog study (25, 50, 100mg/kg/day), only incidences of mild reversible erythema, papule and scabs were observed. No systemic toxicity was exhibited. The NOELs for local and systemic toxicity were established at 25 and 100mg/kg/day, respectively.

In a 9-month oral (40, 160, and 480mg/kg/day) dog study, significant drug-related changes at the mid- and high-dose levels included decreased body weight and food consumption, dehydration, convulsions, few feces, pale mucous membrane and vomiting. The necropsy findings of two high-dose animals sacrificed on humane ground (male on day 45, female on day 54) exhibited more severe symptoms of the same type. The NOEL was established at 40mg/kg/day.

In general, butenafine at concentrations appropriately greater than the maximum expected therapeutic dose did not cause any serious or life threatening local or systemic toxicity in animals.

V. GENETIC TOXICOLOGY:

Genetic toxicology summary/ conclusions: In two *in vitro* assays (Ames reverse mutation, and chromosomal aberration test in Chinese hamster lymphocytes) and *in vivo* micronucleus assay in rats indicated that butenafine HCl was non-mutagenic and non-clastogenic.

Labeling recommendations: Genotoxicity profile is complete. Same data were used in the label for approved NDAs.

VI. CARCINOGENICITY:

Carcinogenicity summary/conclusions: For Mentax^R Cream, 1%, with a dosing regimen of 2-4 weeks, no carcinogenicity or photocarcinogenicity studies were required. Apparently, no such studies are warranted for Mentax^R-TC, 1%, with a dosing regimen of only 7 days.

Labeling Recommendations: It is mentioned in the label that no carcinogenicity studies were conducted with the Mentax^R-TC (butenafine HCl) Cream 1%.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Reproductive and developmental toxicology summary/conclusions:

The subcutaneous doses of 0.25, 2.5 or 25.0 mg/kg butenafine HCl (up to 2 times the maximum expected clinical dose in mg/m²) to rats, did not affect fertility, fetal development, sexual maturity, reproductive function, or postnatal differentiation. In rabbit oral teratogenicity study conducted at 80-400mg/kg/day dose level (up to 50 times the maximum expected human dose in mg/m²), no treatment related external, or skeletal malformations or variations were observed.

In combined segment I and segment III rat studies conducted at oral doses of 5, 20, and 125mg butenafine HCl/kg/day (up to 8 times the maximum expected clinical dose in mg/m²), treatment of F₀ animals had no effect on fertility, sperm morphology and counts, reproductive functions and litter data. In the F₁ generation, drug did not affect the body weights, development (surface righting, auditory startle, vaginal opening and perpetual separation), neurological assessment (motor activity and passive avoidance), vaginal cytology, fertility, and the litter data.

Labeling recommendations: To date, the sponsor has conducted 7 reproductive and developmental toxicity studies in rats and rabbits using subcutaneous and oral routes. These have included two segment I, three segment II, and two segment III studies. In general, the mid- and high-doses used in these studies were greater than the maximum expected clinical dose. In addition, with the same data, NDAs for topical butenafine preparations have been approved.

VIII. SPECIAL TOXICOLOGY STUDIES: In guinea pig assays, the cream, lotion, and solution formulations of 1% butenafine did not indicate any sensitizing or antigenic, phototoxic or photosensitizing activities. The 10% butenafine HCl solution was slightly phototoxic.

In a set of experiments, the effects of — decomposition products of butenafine, _____ on hexobarbital-induced sleep time (mice), blood pressure, heart rate and respiration (rats), and isolated ileum (guinea pigs),

were investigated. The intravenous administration of 10 and 100mg/kg of — to rats decreased the heart rate and respiratory rate, respectively. — at concentrations ranging from 10^{-3} M to 10^{-7} M suppressed the contraction of ileum induced by histamine and serotonin.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions: The safety of Mentax (butenafine HCl) Cream 1% (NDAs 20-524 and 20-663) has been well established in non-clinical and clinical studies, and the product is in the US market since 1996. The new optimized cream formulation Mentax^R-TC (butenafine HCl) Cream 1% is a modified form of Mentax Cream, 1%. It contains two additional ingredients, propylene glycol (PG) and polyolprepolymer-2 (PP-2). In addition, because diethanolamine (comparatively at very high-dose levels) tested carcinogenic in rodents, in the new formulation it is replaced with — trolamine — (see compositions on page ii). The active ingredient butenafine HCl has also been safely tested non-clinically at concentration ranging from 5% to 10% in its — formulation. Also in the same formulation, PG and PP-2 were tested at concentration levels of — respectively. In the optimized cream product, these ingredients are present at — concentration levels, respectively. PP-2 widely used in cosmetics and a number of marketed drug products (Vitoinin, Durascreen, Tretinoin Cream and Gel etc.) is also listed with the Cosmetics, Toiletries, and Fragrances Association since 1991.

According to the sponsor, the maximum expected clinical dose of 18 grams (180mg butenafine HCl) cream formulation would cover one half of the body surface area (9000cm^2). Assuming 100% systemic absorption, it will provide approximately 95mg drug/m^2 for a 70kg person. In a 12-month topical dog study (25, 50, 100mg/kg/day), where no systemic toxicity was observed at any dose level, and mild erythema, scab, and skin irritation were observed at the mid- and high-dose levels, the NOELs for systemic and local toxicity were established at 100 and 25mg/kg/day, respectively. The margin of safety in this case will be 5-21(mg/m^2) times. In the same dog study, the mean plasma C_{max} at 12 month was 252ng/mL. In a human pharmacokinetic study (n=12 subjects with severe tinea versicolor) conducted at 260mg/m^2 (~1/8 the dose in dog study), the mean plasma C_{max} was only about 4ng/mL. Hypothetically, in case of equivalent percent absorption in the two species, C_{max} in humans would have been ~ 32 ng/mL. In human *in vitro* studies, only 1.3% of the applied radioactive dose penetrated through the skin. Therefore, considering the real systemic absorption in humans, the actual margin of safety will be many folds greater.

General Toxicology Issues: None

Recommendations: From the non-clinical point of view, I have no objection to the approval of this new drug application.

Labeling with basis for findings: For the safety calculations in the label, the sponsor has used a figure of — $\mu\text{g butenafine HCl/m}^2$ as the maximum recommended dose for a 50 kg subject. However, at the same time it is also stated that "The sponsor anticipates that a maximum clinical dosage for the new drug product might be approximately 18 grams daily for 7 days"(p 133, Vol.1.1). However, taking into consideration that in some

cases of tinea versicolor, 1/2 the body surface area might be affected, in this review, the expected maximum of 18 grams for a 70kg man is used to calculate the safety margin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies to evaluate the carcinogenic potential of Mentax^R-TC Cream, 1% have not been conducted. Two *in vitro* assays (bacterial reverse mutation test and chromosome aberration test in Chinese hamster lymphocytes) and one *in vivo* study (rat micronucleus bioassay) revealed no mutagenic or clastogenic potential for butenafine.

Pregnancy

Teratogenic effects: Pregnancy Category

X. APPENDIX/ATTACHMENTS:

Addendum to review:

Other relevant materials (Studies not reviewed, appended consults, etc.):

Any compliance issues:

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PHARMACOLOGIST
See my supervisory pharmacologist memo; I concur with approvability
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comments
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