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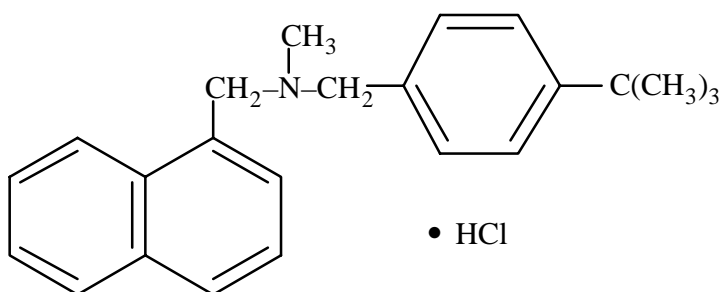
Mentax[®] (butenafine HCl cream) Cream, 1%

Rx Only

DESCRIPTION

Mentax[®] Cream, 1%, contains the synthetic antifungal agent, butenafine hydrochloride. Butenafine is a member of the class of antifungal compounds known as benzylamines which are structurally related to the allylamines.

Butenafine HCl is designated chemically as *N*-4-*tert*-butylbenzyl-*N*-methyl-1-naphthalenemethylamine hydrochloride. The compound has the empirical formula C₂₃H₂₇N•HCl, a molecular weight of 353.93, and the following structural formula:



Butenafine HCl is a white, odorless, crystalline powder. It is freely soluble in methanol, ethanol, and chloroform, and slightly soluble in water. Each gram of Mentax[®] Cream, 1%, contains 10 mg of butenafine HCl in a white cream base of purified water USP, propylene glycol dicaprylate, glycerin USP, cetyl alcohol NF, glyceryl monostearate SE, white petrolatum USP, stearic acid NF, polyoxyethylene (23) cetyl ether, benzyl alcohol NF, diethanolamine NF, and sodium benzoate NF.

CLINICAL PHARMACOLOGY

Pharmacokinetics

In one study conducted in healthy subjects for 14 days, 6 grams of Mentax[®] Cream, 1%, was applied once daily to the dorsal skin (3,000 cm²) of 7 subjects, and 20 grams of the cream was applied once daily to the arms, trunk and groin areas (10,000 cm²) of another 12 subjects. After 14 days of topical applications, the 6-gram dose group yielded a mean peak plasma butenafine HCl concentration, C_{max}, of 1.4 ± 0.8 ng/mL, occurring at a mean time to the peak plasma concentration, T_{max}, of 15 ± 8 hours, and a mean area under the plasma concentration-time curve, AUC_{0-24 hrs} of 23.9 ± 11.3 ng-hr/mL. For the 20-gram dose group, the mean C_{max} was 5.0 ± 2.0 ng/mL, occurring at a mean T_{max} of 6 ± 6 hours, and the mean AUC_{0-24 hrs} was 87.8 ± 45.3 ng-hr/mL. A biphasic decline of plasma butenafine HCl concentrations was observed with the half-lives estimated to be 35 hours and > 150 hours, respectively.

At 72 hours after the last dose application, the mean plasma concentrations decreased to 0.3 ± 0.2 ng/mL for the 6-gram dose group and 1.1 ± 0.9 ng/mL for the 20-gram dose group. Low levels

of butenafine HCl remained in the plasma 7 days after the last dose application (mean: 0.1 ± 0.2 ng/mL for the 6-gram dose group, and 0.7 ± 0.5 ng/mL for the 20-gram dose group). The total amount (or % dose) of butenafine HCl absorbed through the skin into the systemic circulation has not been quantitated. It was determined that the primary metabolite in urine was formed through hydroxylation at the terminal *t*-butyl side-chain.

In 11 patients with tinea pedis, Mentax[®] Cream, 1%, was applied by the patients to cover the affected and immediately surrounding skin area once daily for 4 weeks and a single blood sample was collected between 10 and 20 hours following dosing at 1, 2 and 4 weeks after treatment. The plasma butenafine HCl concentration ranged from undetectable to 0.3 ng/mL.

In 24 patients with tinea cruris, Mentax[®] Cream, 1%, was applied by the patients to cover the affected and immediately surrounding skin area once daily for 2 weeks (mean average daily dose: 1.3 ± 0.2 g). A single blood sample was collected between 0.5 and 65 hours after the last dose, and the plasma butenafine HCl concentration ranged from undetectable to 2.52 ng/mL (mean \pm SD: 0.91 ± 0.15 ng/mL). Four weeks after cessation of treatment, the plasma butenafine HCl concentration ranged from undetectable to 0.28 ng/mL.

Microbiology

Butenafine HCl is a benzylamine derivative with a mode of action similar to that of the allylamine class of antifungal drugs. Butenafine HCl is hypothesized to act by inhibiting the epoxidation of squalene, thus blocking the biosynthesis of ergosterol, an essential component of fungal cell membranes. The benzylamine derivatives, like the allylamines, act an earlier step in the ergosterol biosynthesis pathway than the azole class of antifungal drugs. Depending on the concentration of the drug and the fungal species tested, butenafine HCl may be fungicidal or fungistatic in vitro. However, the clinical significance of these in vitro data is unknown.

Butenafine HCl has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in the INDICATIONS AND USAGE section:

Epidermophyton floccosum
Malassezia furfur
Trichophyton mentagrophytes
Trichophyton rubrum
Trichophyton tonsurans

CLINICAL STUDIES

Interdigital Tinea Pedis

Once Daily Four Week Dosing

In the following data presentations, patients with interdigital tinea pedis in the absence of moccasin-type tinea pedis and onychomycosis were studied. The term “**Mycological Cure**” is defined as both negative KOH and culture. The term “**Effective Treatment**” refers to patients who had a “Mycological Cure” **and** an Investigator’s Global of either “Excellent” (80% to 99% improvement) **or** “Cleared” (100% improvement). The term “**Overall Cure**” refers to patients who had both a “Mycological Cure” **and** an Investigator’s Global Assessment of “Cleared”(100% improvement).

Data from the two controlled studies in which Mentax[®] Cream, 1%, was used once daily for 4 weeks have been combined in the table below. Patients were treated for 4 weeks and evaluated 4 weeks post-treatment. In the “per protocol” analysis shown in the table below, statistical significance (Mentax[®] vs. vehicle) was assessed 4 weeks post-treatment.

Interdigital Tinea Pedis: 4-Week Dosing Regimen

Patient Outcome Category	WEEK 4 (End of Treatment)		WEEK 8 (4 Weeks Post-Treatment)	
	Butenafine	Vehicle	Butenafine	Vehicle
Mycological Cure	89% (83/93)	57% (51/90)	90% (66/73)	38% (25/66)
Effective Treatment	57% (53/93)	28% (25/90)	74% (54/73)	26% (17/66)
Overall Cure	15% (14/93)	8% (7/90)	25% (18/73)	9% (6/66)

Twice-Daily One Week Dosing

In the following data presentations, patients with interdigital tinea pedis in the absence of moccasin-type tinea pedis were studied. Patients with concurrent onychomycosis were not excluded. The term “**Mycological Cure**” is defined as both negative KOH and culture. The term “**Effective Treatment**” refers to patients who had a “Mycological Cure” **and** an Investigator’s Global of either “Excellent” (90% to 99% improvement) **or** “Cleared” (100% improvement). The term “**Overall Cure**” refers to patients who had both a “Mycological Cure” **and** an Investigator’s Global Assessment of “Cleared” (100% improvement).

Data from the two controlled studies in which Mentax[®] Cream, 1%, was used twice daily for 1 week have been combined in the table below. Patients were treated for 1 week and evaluated 5 weeks post-treatment. In the “modified-intent-to-treat” analysis shown in the table below, statistical significance (Mentax[®] vs. vehicle) was assessed 5 weeks post-treatment.

Interdigital Tinea Pedis: 1-Week Dosing Regimen

Patient Outcome Category	WEEK 1 (End of Treatment)		WEEK 6 (5 Weeks Post-Treatment)	
	Butenafine	Vehicle	Butenafine	Vehicle
Mycological Cure	44% (111/253)	28% (75/265)	79% (200/253)	20% (54/265)
Effective Treatment	5% (12/253)	3% (7/265)	38% (95/253)	7% (18/265)
Overall Cure	0.4% (1/253)	0.4% (1/265)	*15% (37/253)	0.7% (2/265)

* The Overall Cure Rate of 15% is calculated from a 9% rate in one trial and a 20% rate in the second trial.

Tinea Corporis and Tinea Cruris

In the following data presentations, patients with tinea corporis or tinea cruris were studied. The term “**Mycological Cure**” is defined as both negative KOH and culture. The term “**Effective Treatment**” refers to patients who had a “Mycological Cure” **and** an Investigator’s Global of either “Excellent” (90% to 99% improvement) **or** “Cleared” (100% improvement). The term “**Overall Cure**” refers to patients who had both a “Mycological Cure” **and** an Investigator’s Global Assessment of “Cleared”(100% improvement).

Separate studies compared Mentax[®] Cream to vehicle applied once daily for 2 weeks in the treatment of tinea corporis and tinea cruris. Patients were treated for 2 weeks and evaluated 4 weeks post-treatment. All subjects with a positive baseline exam (including positive culture and KOH) and who were dispensed medication were included in the “modified intent-to-treat” analysis shown in the table below. Statistical significance (Mentax[®] vs. vehicle) was achieved for all patient outcome categories at Week 2 (end of treatment) and Week 6 (4 weeks post-treatment).

Tinea Corporis

Patient Outcome Category	WEEK 2 (End of Treatment)		WEEK 6 (4 Weeks Post-Treatment)	
	Butenafine	Vehicle	Butenafine	Vehicle
Mycological Cure	88% (37/42)	28% (10/36)	88% (37/42)	17% (6/36)
Effective Treatment	60% (25/42)	17% (6/36)	81% (34/42)	14% (5/36)
Overall Cure	31% (13/42)	3% (1/36)	67% (28/42)	14% (5/36)

Tinea Cruris

Patient Outcome Category	WEEK 2 (End of Treatment)		WEEK 6 (4 Weeks Post-Treatment)	
	Butenafine	Vehicle	Butenafine	Vehicle
Mycological Cure	78% (29/37)	11% (4/38)	81% (30/37)	13% (5/39)
Effective Treatment	57% (21/37)	8% (3/39)	73% (27/37)	5% (2/39)
Overall cure	32% (12/37)	8% (3/39)	62% (23/37)	3% (1/39)

Tinea (pityriasis) versicolor

In the following data presentations, patients with tinea (pityriasis) versicolor were studied. The term “**Negative Mycology**” is defined as absence of hyphae in a KOH preparation of skin scrapings, i.e.; no fungal forms seen or the presence of yeast cells (blastospores) only. The term “**Effective Treatment**” is defined as Negative Mycology plus total signs and symptoms score (on a scale from zero to three) for erythema, scaling, and pruritus equal to or less than 1 at Week 8. The term “**Complete Cure**” refers to patients who had negative mycology plus sign/symptoms scores of zero for erythema, scaling, and pruritus.

Two separate studies compared Mentax[®] Cream to vehicle applied once daily for 2 weeks in the treatment of tinea (pityriasis) versicolor. Patients were treated for 2 weeks and were evaluated at the following weeks post-treatment: 2 (Week 4) and 6 (Week 8). All subjects with a positive baseline KOH and who were dispensed medications were included in the “intent-to-treat” analysis shown in the table below. Statistical significance (Mentax[®] vs. vehicle) was achieved for Effective Treatment, but not Complete Cure at 6 weeks post-treatment in Study 31. Marginal statistical significance ($p = 0.051$) (Mentax[®] vs. vehicle) was achieved for Effective Treatment but not Complete Cure at 6 weeks post-treatment in Study 32. Data from these two controlled studies are presented in the table below.

Tinea Vericolor

Proportion (%) of responders in pivotal clinical trials (all randomized patients)					
Patient Response Category	Week [®]	Study 31		Study 32	
		Butenafine	Vehicle	Butenafine	Vehicle
Complete Cure *	2	41/87 (47%)	11/40 (28%)	29/85 (34%)	12/41 (29%)
	4	43/86 (50%)	15/42 (36%)	36/83 (43%)	13/41 (32%)
	8	44/87 (51%)	15/42 (36%)	30/86 (35%)	10/43 (23%)
Effective Treatment**	2	56/87 (64%)	16/40 (40%)	46/85 (54%)	16/41 (39%)
	4	50/86 (58%)	19/42 (45%)	45/83 (54%)	16/41 (39%)
	8	48/87 (55%)	15/42 (36%)	37/86 (43%)	11/43 (26%)
Negative Mycology ***	2	57/87 (66%)	20/40 (50%)	57/85 (67%)	21/41 (51%)
	4	51/86 (59%)	20/42 (48%)	52/83 (63%)	18/41 (44%)
	8	48/87 (55%)	15/42 (36%)	43/86 (50%)	12/43 (28%)

[®] Week 2 (end of treatment), Week 4 (2 weeks post-treatment), and Week 8 (6 weeks post-treatment)
 * Negative Mycology plus absence of erythema, scaling, and pruritus
 ** Negative Mycology plus no or minimal involvement of erythema, scaling, or pruritus
 *** Absence of hyphae in a KOH preparation of skin scrapings, i.e., no fungal forms seen or the presence of yeast cells (blastospores) only

Tinea (pityriasis) versicolor is a superficial, chronically recurring infection of the glabrous skin caused by *Malassezia furfur* (formerly *Pityrosporum orbiculare*). The commensal organism is part of the normal skin flora. In susceptible individuals the condition may give rise to hyperpigmented or hypopigmented patches on the trunk which may extend to the neck, arms and upper thighs. Treatment of the infection may not be immediately result in restoration of pigment to the affected sites. Normalization of pigment following successful therapy is variable and may take months, depending upon individual skin type and incidental sun exposure. The rate of recurrence of infection is variable.

INDICATIONS AND USAGE

Mentax[®] (butenafine HCl cream), 1%, is indicated for the topical treatment of the following dermatologic infections: tinea (pityriasis) versicolor due to *M. furfur* (formerly *P. orbiculare*), interdigital tinea pedis (athlete's foot), tinea corporis (ringworm) and tinea cruris (jock itch) due to *E. floccosum*, *T. mentagrophytes*, *T. rubrum*, and *T. tonsurans*. Butenafine HCl cream was not studied in immunocompromised patients. (See DOSAGE AND ADMINISTRATION Section).

CONTRAINDICATIONS

Mentax[®] (butenafine HCl cream) Cream, 1%, is contraindicated in individuals who have known or suspected sensitivity to Mentax[®] Cream, 1%, or any of its components.

WARNINGS

Mentax[®] (butenafine HCl cream) Cream, 1%, is not for ophthalmic, oral, or intravaginal use.

PRECAUTIONS

General

Mentax[®] Cream, 1%, is for external use only. If irritation or sensitivity develops with the use of Mentax[®] Cream, 1%, treatment should be discontinued and appropriate therapy instituted. Diagnosis of the disease should be confirmed either by culture on an appropriate medium, [except *M. furfur* (formerly *P. orbiculare*)] or by direct microscopic examination of infected superficial epidermal tissue in a solution of potassium hydroxide-

Patients who are known to be sensitive to allylamine antifungals should use Mentax[®] (butenafine HCl cream) Cream, 1%, with caution, since cross-reactivity may occur.

Use Mentax[®] Cream, 1%, as directed by the physician, and avoid contact with the eyes, nose, and mouth, and other mucous membranes.

Information for Patients

The patient should be instructed to:

1. Use Mentax[®] Cream, 1%, as directed by the physician. The hands should be washed after applying the medication to the affected area(s). Avoid contact with the eyes, nose, mouth, and other mucous membranes. Mentax[®] Cream, 1%, is for external use only.
2. Dry the affected area(s) thoroughly before application, if you wish to apply Mentax[®] Cream, 1%, after bathing.
3. Use the medication for the full treatment time recommended by the physician, even though symptoms may have improved. Notify the physician if there is no improvement after the end of the prescribed treatment period, or sooner, if the condition worsens (see below).
4. Inform the physician if the area of application shows signs of increased irritation, redness, itching, burning, blistering, swelling, or oozing.
5. Avoid the use of occlusive dressings unless otherwise directed by the physician.
6. Do not use this medication for any disorder other than that for which it was prescribed.

Drug Interactions

Potential drug interactions between Mentax[®] (butenafine HCl cream) Cream, 1%, and other drugs have not been systematically evaluated.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies to evaluate the carcinogenic potential of Mentax[®] 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 reproductive studies in rats at 25 mg/kg/day (6 times the maximum possible systemic dose) in humans based on a mg/m² comparison) dose level, butenafine did not produce any adverse effects on male or female fertility.

Pregnancy

Teratogenic effects: Pregnancy Category B

Subcutaneous or topical doses of butenafine (25 to 50 mg/kg/day) (equivalent to 5 to 20 times the maximum possible systemic dose in humans based on a mg/m² comparison) were not teratogenic in rats and rabbits. In an oral teratogenicity study in rabbits (80, 200, and 400 mg butenafine HCl/kg/day) (equivalent to 3 to 16 times the maximum possible systemic dose in humans based on a mg/m² comparison), no treatment-related external, visceral, or skeletal malformations or variations were observed. There are, however, no adequate and well-controlled studies that have been conducted with 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.

Nursing Mothers

It is not known if butenafine HCl is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised in prescribing Mentax[®] Cream, 1%, to a nursing woman. Nursing mothers should avoid application of Mentax[®] Cream, 1%, to the breast.

Pediatric Use

Safety and efficacy in pediatric patients below the age of 12 years have not been studied. Use of Mentax[®] Cream, 1%, in pediatric patients 12 to 16 years of age is supported by evidence from adequate and well-controlled studies of Mentax[®] Cream, 1%, in adults.

ADVERSE REACTIONS

In controlled clinical trials, 9 (approximately 1%) of 815 patients treated with Mentax[®] Cream, 1%, reported adverse events related to the skin. These included burning/stinging, itching, and worsening of the condition. No patient treated with Mentax[®] Cream, 1%, discontinued treatment due to an adverse event. In the vehicle-treated patients, two of 718 patients discontinued because of treatment-site adverse events, one of which was severe burning/stinging and itching at the site of application.

In uncontrolled clinical trials, the most frequently reported adverse events in patients treated with Mentax[®] Cream, 1%, were: contact dermatitis, erythema, irritation, and itching, each occurring in less than 2% of patients.

In provocative testing in over 200 subjects, there was no evidence of allergic contact sensitization for either the cream or the vehicle base for Mentax[®] Cream, 1%.

OVERDOSAGE

Overdosage of butenafine HCl in humans has not been reported to date.

DOSAGE AND ADMINISTRATION

Patients with tinea (pityriasis) versicolor should apply Mentax[®] once daily for two weeks. In the treatment of interdigital tinea pedis, Mentax[®] should be applied twice daily for 7 days OR once daily for 4 weeks (NOTE: in separate clinical trials, the 7-day dosing regimen was less efficacious than the 4-week regimen (see CLINICAL STUDIES Section). While the clinical significance of this difference is unknown, these data should be carefully considered before selecting the dosage regiment for patients at risk for the development of bacterial cellulitis of the lower extremity associated with interdigital cracking/fissuring).

Patients with tinea corporis or tinea cruris should apply Mentax[®] once daily for two weeks.

Sufficient Mentax[®] Cream should be applied to cover affected areas and immediately surrounding skin of patients with tinea versicolor, interdigital tinea pedis, tinea corporis, and tinea cruris. If a patient shows no clinical improvement after the treatment period, the diagnosis and therapy should be reviewed.

HOW SUPPLIED

Mentax[®] (butenafine HCl cream) Cream, 1%, is supplied in tubes in the following sizes:

15-gram tube (NDC 62794-151-02)

30-gram tube (NDC 62794-151-03)

STORE BETWEEN 5°C and 30°C (41° and 86°F).

Manufactured by: DPT Laboratories
San Antonio, TX 78215

Distributed by: BERTEK PHARMACEUTICALS INC.
Morgantown, WV 26505

June 6, 2001
PN341.02I

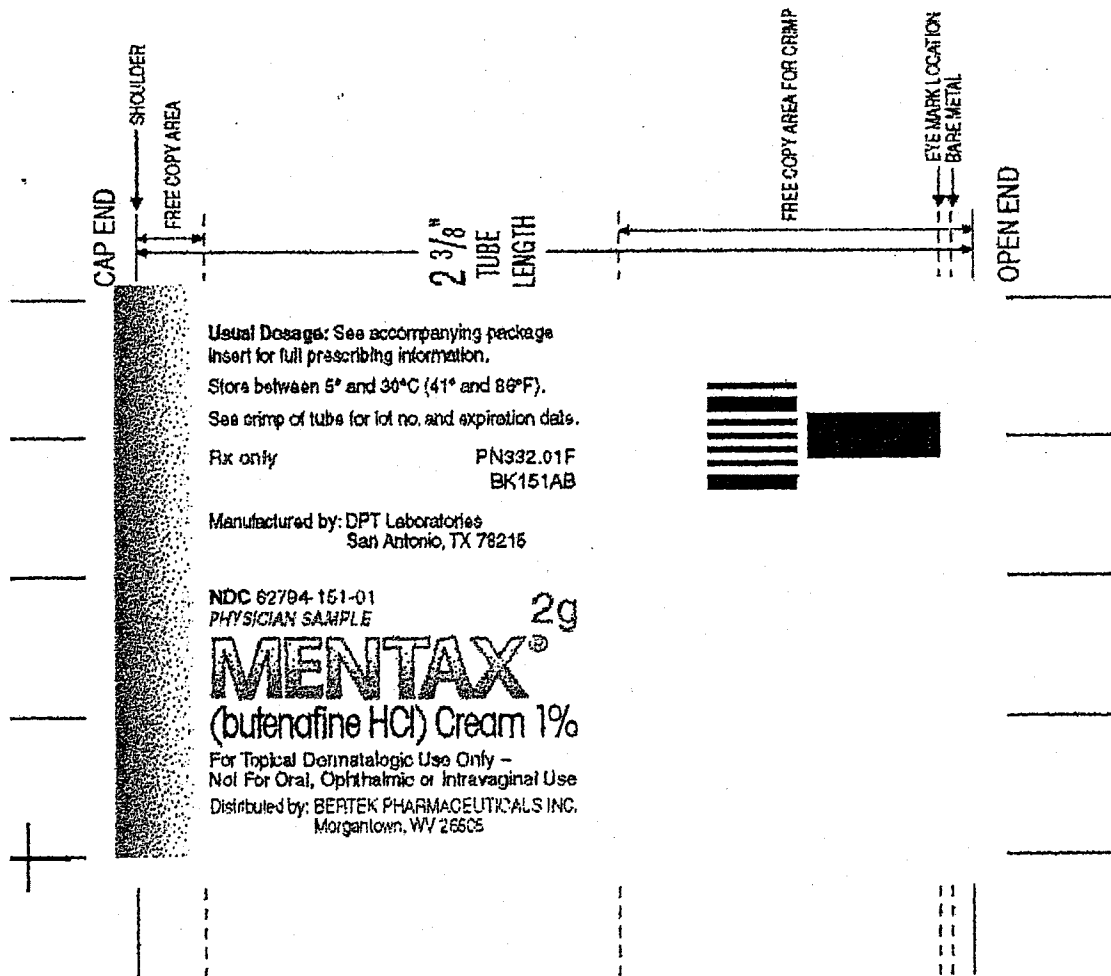
Approved NDA #20-524

Supplement #006/5

Mentax (butenafine HCl cream) Cream 1%

Final Printed Labeling

PN 332.01F: Tube, 2-gram



1-036

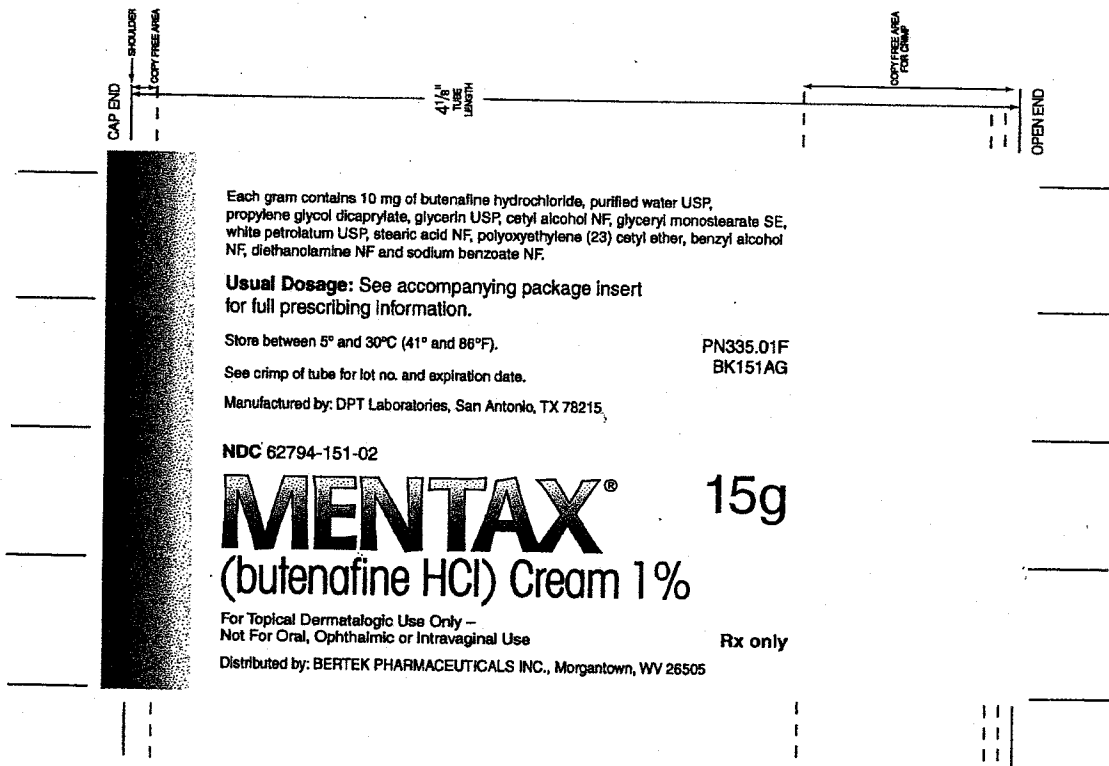
Approved NDA #20-524

Supplement #006/5

Mentax (butenafine HCl cream) Cream 1%

Final Printed Labeling

PN 335.01F: Tube, 15-gram



1- 037

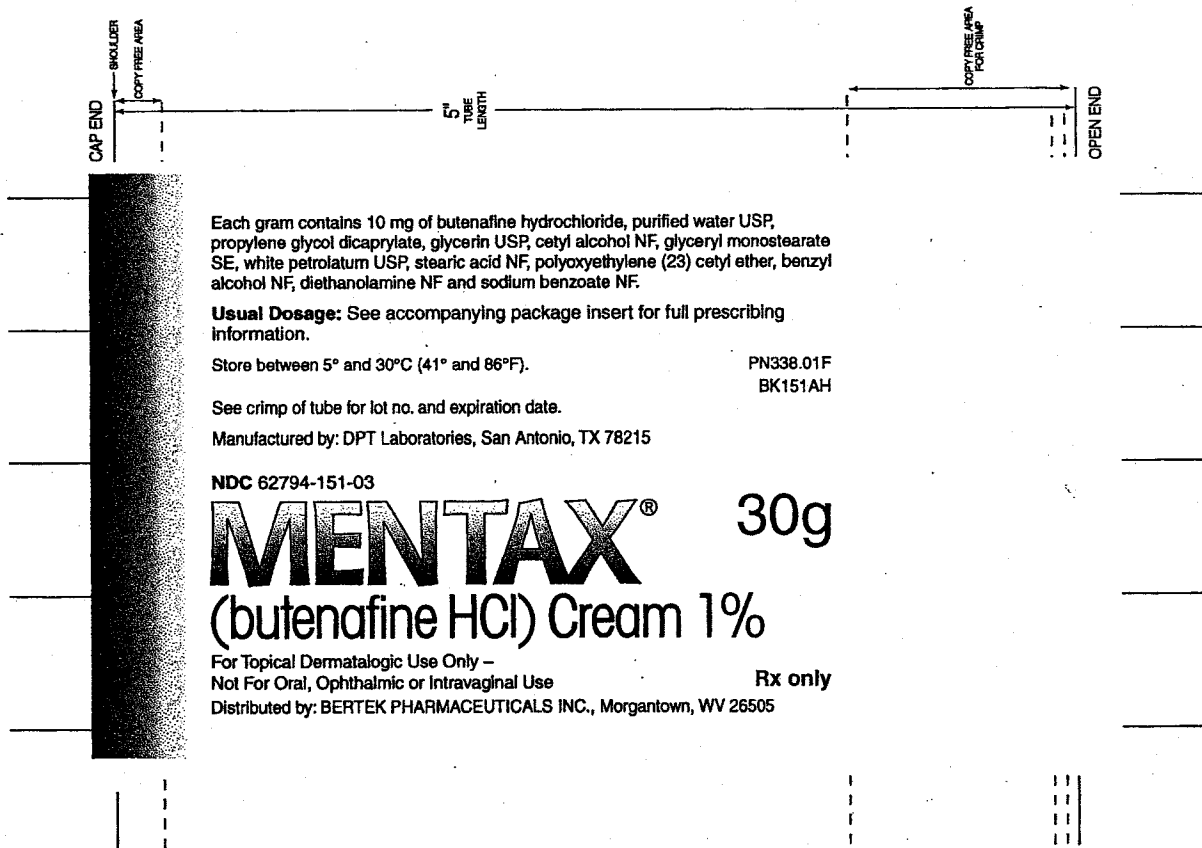
Approved NDA #20-524

Supplement #0065

Mentax (butenafine HCl cream) Cream 1%

Final Printed Labeling

PN 338.01F: Tube, 30-gram



1- 038

Approved NDA #20-524

Supplement #006/5

Mentax (butenafine HCl cream) Cream 1%

Final Printed Labeling

PN 480.01B: Carton, 2-gram tubes x 12, Physician Sample

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NDC 62794-151-04
Physician Sample
MENTAX[®]
(butenafine HCl) Cream 1%

MENTAX[®]
(butenafine HCl) Cream 1%

Topical Antifungal Cream 1%
Available for prescription in 15g and 30g tubes

Box contains 12, 2g tubes

Rx only

For topical Dermatologic Use Only-Not For Oral, Ophthalmic or Intravaginal Use

Store between 5° and 30°C (41° and 86°F)

Please see accompanying prescribing information.

Each gram contains 10 mg of butenafine hydrochloride, purified water, USP, propylene glycol dicaprylate, glycerin USP, cetyl alcohol NF, glyceryl monostearate SE, white petrolatum USP, stearic acid NF, polyoxyethylene (23) cetyl ether, benzyl alcohol NF, diethanolamine NF and sodium benzoate NF.

Distributed by: BERTEK PHARMACEUTICALS INC.

Morgantown, WV 26505

Manufactured by: DPT Laboratories

San Antonio, TX 78215

BK151-04-12C:R1S

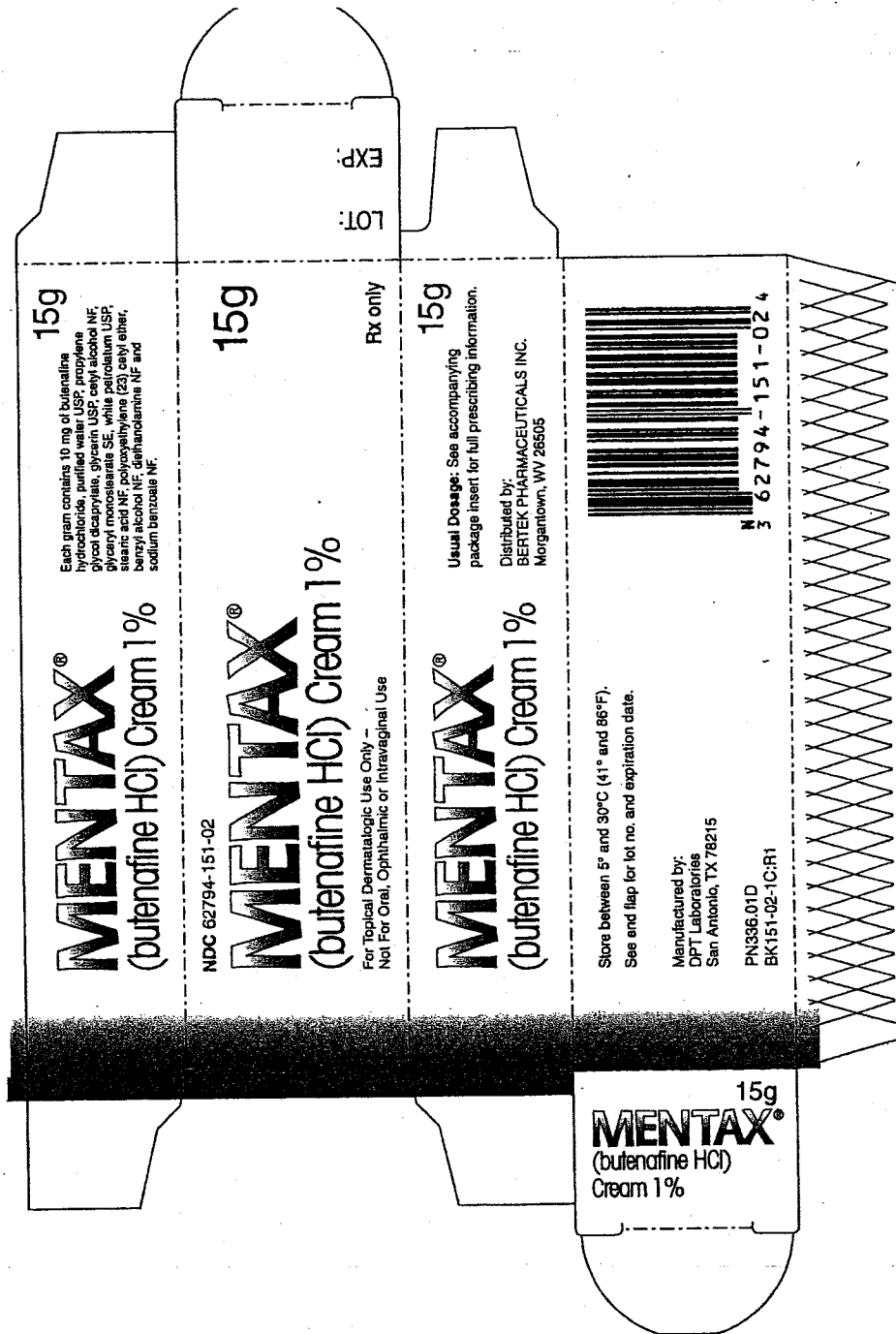
PN480.01B

LOT:

EXP:

1- 039

Mentax (butenafine HCl cream) Cream 1%
Final Printed Labeling
PN 336.01D: Carton, 15-gram tube



15g
Each gram contains 10 mg of butenafine hydrochloride, purified water USP, propylene glycol dicaprylate, glycerin USP, cetyl alcohol NF, glyceryl monostearate SE, white petrolatum USP, stearic acid NF, polyoxyethylene (23) cetyl ether, benzyl alcohol NF, dehydroalanine NF and sodium benzoate NF.

MENTAX[®]
(butenafine HCl) Cream 1%

NDC 62794-151-02

MENTAX[®]
(butenafine HCl) Cream 1%

For Topical Dermatologic Use Only -
Not For Oral, Ophthalmic or Intravaginal Use

15g

Rx only

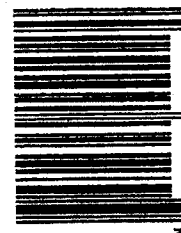
15g
Usual Dosage: See accompanying package insert for full prescribing information.
Distributed by:
BERTEK PHARMACEUTICALS INC.
Morgantown, WV 26505

MENTAX[®]
(butenafine HCl) Cream 1%

Store between 5° and 30°C (41° and 86°F).
See end flap for lot no. and expiration date.

Manufactured by:
DPT Laboratories
San Antonio, TX 78215

PN336.01D
BK151-02-1C:R1



15g
MENTAX[®]
(butenafine HCl)
Cream 1%

Approved NDA #20-524

Supplement #006/5

Mentax (butenafine HCl cream) Cream 1%

Final Printed Labeling

PN 339.01D: Carton, 30-gram tube



30g

Rx only

30g

Usual Dosage: See accompanying package insert for full prescribing information.
Distributed by:
BERTEK PHARMACEUTICALS INC.
Morgantown, WV 26505

Exp:
LOT:
804320200
Topex
g
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