Package Insert

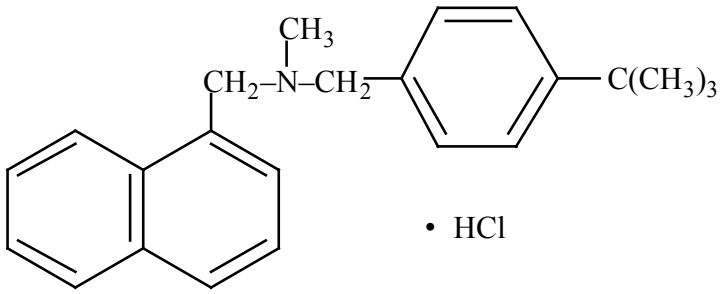
MENTAX®-TC (butenafine HCl) Cream, 1%

Rx Only

DESCRIPTION

MENTAX®-TC 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. It has the empirical formula $C_{23}H_{27}N$•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®-TC Cream, 1%, contains 10 mg of butenafine HCl in a white cream base of purified water USP, propylene glycol dicaprylate, propylene glycol USP, glycerin USP, glyceryl monostearate SE, cetyl alcohol NF, white petrolatum USP, stearic acid NF, polyoxyethylene (23) cetyl ether, polyolprepolymer-2, benzyl alcohol NF, trolamine NF, and sodium benzoate NF.

CLINICAL PHARMACOLOGY

The contribution to efficacy of individual components of the vehicle has not been established.

Pharmacokinetics

In a pharmacokinetic study of 12 patients with extensive tinea versicolor, a range of 14 to 49 grams of MENTAX®-TC Cream, 1%, was applied at 5 mg/cm^2 to cover each lesion and a 10.2 centimeter margin of surrounding clear skin (mean total area of application:

5,000.3 ± 2,221.9 cm^2) once daily for 7 days. On the 7th day of application, the mean peak plasma butenafine concentration (Cmax) was 4.1 ± 1.9 ng/mL. The mean time to peak plasma concentration (Tmax) was12.3 ± 8.5 hours. The mean area under the plasma-concentration-time curve (AUC_{0-24}) was 62.7 ± 28.9 ng-hr/mL.

Microbiology

It is hypothesized that butenafine HCl inhibits the growth of fungi by inhibiting the epoxidation of squalene, thus blocking the biosynthesis of ergosterol, an essential component of the fungal cell membrane. Lack of or diminished quantities of ergosterol in the fungal cell membrane injures the cell causing inhibition of growth. Results of nonstandardized *in vitro* susceptibility tests suggest that butenafine HCl has activity against *Malassezia furfur* (formerly *Pityrosporum orbiculare*).

CLINICAL STUDIES

Tinea (pityriasis) versicolor is a superficial, chronically recurring infection of the 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 scaly, hyperpigmented or hypopigmented patches on the trunk which may extend to the neck, arms and upper thighs. Diagnosis of the disease may be confirmed by direct microscopic examination for blastospores and hyphae in superficial epidermal tissue in a solution of potassium hydroxide; culture methods are not routinely available.

Treatment may not result in restoration of pigment to the affected sites. Normalization of pigment following control of redness and scaling is variable and may take months. The rate of recurrence of infection is variable.

Two controlled studies of patients with tinea (pityriasis) versicolor demonstrated the statistically significant superiority of MENTAX®-TC Cream, 1%, over vehicle in Effective Treatment, 43% versus 23% and 54% versus 34%, respectively. The definitions below were applied in six-week post-treatment efficacy assessment of MENTAX®-TC Cream, 1%, in the treatment of tinea versicolor once daily for seven days:

Negative Mycology: Absence of hyphae in a KOH preparation of skin scrapings, i.e., no fungal forms seen or the presence of yeast cells (blastospores) only in KOH

Effective Treatment: Negative Mycology + Total Signs and Symptoms score ≤ 1 six weeks post-treatment, where the score for scaling must be zero

Complete Cure: Negative Mycology + Total Signs and Symptoms score of zero at Day 49 (six weeks post-treatment)

Primary efficacy was assessed by Effective Treatment six weeks post-treatment. The results of the intent-to-treat analysis are presented in the table below.

Efficacy Results at 6 Weeks Post Treatment*

	Study 1			Study 2		
Criterion	Butenafine	Vehicle	p-value**	Butenafine	Vehicle	p-value**
Negative Mycology	44/86 (51%)	10/43 (23%)	0.0010	87/143 (61%)	25/74 (34%)	0.0001
Effective Treatment	37/86 (43%)	10/43 (23%)	0.0176	77/143 (54%)	25/74 (34%)	0.0033
Complete Cure	34/86 (40%)	8/43 (19%)	0.0110	74/143 (52%)	23/74 (31%)	0.0021

* Intent To Treat Population
** p-value from Cochran-Mantel-Haenszel test adjusted for centers

INDICATIONS AND USAGE

MENTAX®-TC Cream, 1%, is indicated for the topical treatment of tinea (pityriasis) versicolor due to *Malassezia furfur* (formerly *Pityrosporum orbiculare)*.

MENTAX®-TC Cream, 1%, was not studied in immunocompromised patients. (See DOSAGE AND ADMINISTRATION Section).

CONTRAINDICATIONS

MENTAX®-TC Cream, 1%, is contraindicated in individuals who have known or suspected sensitivity to MENTAX®TC Cream, 1%, or any of its components.

WARNINGS

MENTAX®-TC Cream, 1%, is not for ophthalmic, oral, or intravaginal use.

PRECAUTIONS

General

MENTAX®-TC Cream, 1%, is for external use only. If irritation or sensitivity develops with the use of MENTAX®-TC Cream, 1%, treatment should be discontinued and appropriate therapy instituted.

Caution should be exercised to prevent accidental exposure with topically applied MENTAX®-TC Cream, 1% to infants and children less than 12 years of age as no testing has been conducted with MENTAX®-TC Cream in this population.

Physicians should also exercise caution in prescribing MENTAX®-TC Cream, 1%, to patients known to be sensitive to allylamine antifungals, since cross-reactivity may occur.

Information for Patients

The patient should be instructed to:

1. Use MENTAX®-TC Cream, 1%, as directed by the physician. Wash your hands after applying the medication to the affected area(s). Avoid contact with the eyes, nose, mouth, and other mucous membranes. MENTAX®-TC Cream, 1%, is for external use only.

2. If you wish to apply MENTAX®-TC Cream, 1%, after bathing, then dry the affected area(s) thoroughly before application.

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 in the scaling or redness 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®-TC 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®-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 development 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.

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®-TC Cream, 1%, to a nursing woman.

Pediatric Use

Safety and efficacy in pediatric patients below the age of 12 years have not been studied, since tinea versicolor is uncommon in patients below the age of 12 years of age.

ADVERSE REACTIONS

In controlled clinical trials, five of 223 (2%) subjects treated with MENTAX®-TC Cream, 1%, reported a total of six adverse events characterized by the investigators as being at least possibly related to treatment. All but one of the treatment-related adverse events were application site reactions. The exception was a report of taste disturbance of mild severity that began on Day 4 and was one day in duration. The remaining four subjects (1.8%) experienced application site reactions. These reactions included burning/stinging, itching, and one report of contact dermatitis, which was not further characterized. The investigator considered that the contact dermatitis would compromise the ability to conduct study evaluations, and the subject was withdrawn from the study prematurely. The subject had completed dosing “several” days prior to being discontinued.

One of 114 (<1%) subjects in the vehicle group experienced an adverse event considered to be possibly related to treatment. This reaction was reported as itching.

In provocative testing in 215 subjects, there was no evidence of allergic contact sensitization for either the cream or vehicle base for MENTAX®-TC Cream, 1%. In 26 subjects in a phototoxicity study and 31 subjects in a cumulative irritation study, there was no evidence of phototoxicity or cumulative irritation, respectively. Of 26 subjects in a photoallergy study, one subject had a response suggestive of photoallergy.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

Patients with tinea (pityriasis) versicolor should apply MENTAX®-TC Cream, 1%, once daily for seven days.

Sufficient MENTAX®-TC Cream, 1%, should be applied to cover affected areas and extending 4 inches (10.2 cm) onto normal skin immediately surrounding the affected area. Efficacy at greater than 12 g /day has not been established. If a patient shows no improvement in scaling or erythema after the treatment period, the diagnosis and therapy should be reviewed.

HOW SUPPLIED

MENTAX®-TC Cream, 1%, is supplied in tubes in the following sizes:

15-gram tube (NDC 62794-161-02)

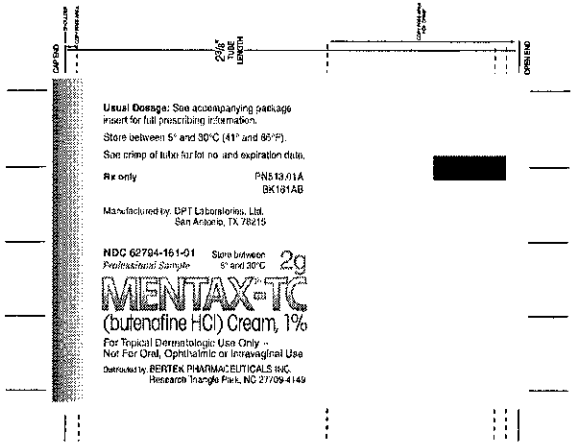
30-gram tube (NDC 62794-161-03)

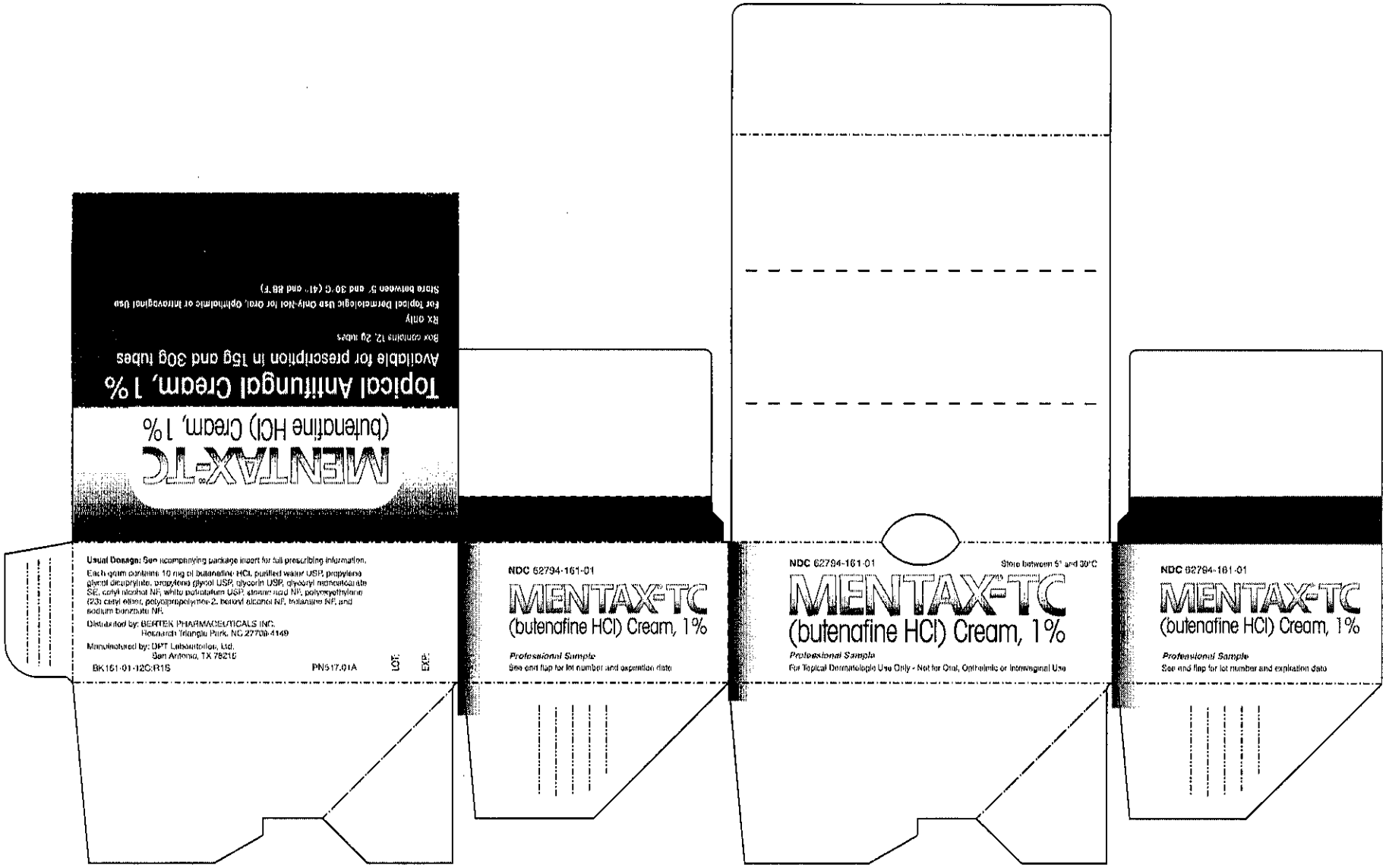
STORE BETWEEN 5°C and 30°C (41° and 86°F).

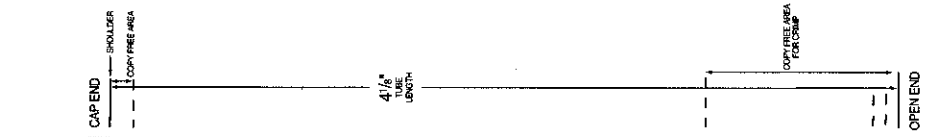
Manufactured By: DPT Laboratories
San Antonio, TX 78215

Distributed By: BERTEK PHARMACEUTICALS INC.
Research Triangle Park, NC 27709-4149

October 11, 2002
PN516.01A


CAP END
2⅝"
TUBE
LENGTH
CRIMP END
Usual Dosage: See accompanying package insert for full prescribing information.
Store between 5° and 30°C (41° and 86°F).
See crimp of tube for lot no. and expiration date.
Rx only
PN513.01A
BK161AB
Manufactured by: DPT Laboratories, Ltd.
San Antonio, TX 78215
NDC 62794-161-01
Professional Sample
Store between 5° and 30°C
2g
MENTAX-TC
(butenafine HCl) Cream, 1%
For Topical Dermatologic Use Only –
Not For Oral, Ophthalmic or Intravaginal Use
Distributed by: BERTEK PHARMACEUTICALS INC.
Research Triangle Park, NC 27709-4149


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)
MENTAX-TC
(butenafine HCl) Cream, 1%
Usual Dosage: See accompanying package insert for full prescribing information.
Each gram contains 10 mg of butenafine HCl, purified water USP, propylene glycol dicaprylate, propylene glycol USP, glycerin USP, glyceryl monostearate SE, cetyl alcohol NF, white petrolatum USP, stearic acid NF, polyoxyethylene (23) cetyl ether, polyoxypropylene-2- hexyl alcohol NF, tolaniaine NF, and sodium benzoate NF.
Distributed by: BERTEK PHARMACEUTICALS INC.
Research Triangle Park, NC 27709-4149
Manufactured by: DPT Laboratories, Ltd.
San Antonio, TX 78215
BK161-01-12C/R1S
PN517.01A
LOT:
EXP:
NDC 62794-161-01
MENTAX-TC
(butenafine HCl) Cream, 1%
Professional Sample
See end flap for lot number and expiration date
NDC 62794-161-01
Store between 5° and 30°C
MENTAX-TC
(butenafine HCl) Cream, 1%
Professional Sample
For Topical Dermatologic Use Only - Not for Oral, Ophthalmic or Intravaginal Use
NDC 62794-161-01
MENTAX-TC
(butenafine HCl) Cream, 1%
Professional Sample
See end flap for lot number and expiration date



Usual Dosage: See accompanying package insert for full prescribing information.

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

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BK161AG

See crimp of tube for lot no. and expiration date.

Manufactured by: DPT Laboratories, Ltd.
San Antonio, TX 78215

NDC 62794-161-02

Store between 5° and 30°C

MENTAX®-TC 15g

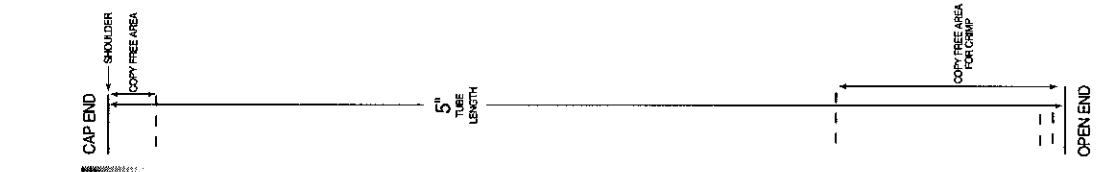
(butenafine HCl) Cream, 1%

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

Distributed by: BERTEK PHARMACEUTICALS INC.
Research Triangle Park, NC 27709-4149

Rx only


MENTAX®-TC
(butenafine HCl) Cream, 1%
See end flap for lot number and expiration date
15g
Each gram contains 10 mg of butenafine HCl, purified water USP, propylene glycol dicaprylate, propylene glycol USP, glycerin USP, glyceryl monostearate SE, cetyl alcohol NF, white petrolatum USP, stearic acid NF, polyoxyethylene (23) cetyl ether, polyolpolyether-2, benzyl alcohol NF, trolamine NF, and sodium benzoate NF.
NDC 62794-161-02
MENTAX®-TC
(butenafine HCl) Cream, 1%
15g
Store between 5° and 30°C (41° and 86°F)
For Topical Dermatologic Use Only – Not For Oral, Ophthalmic or Intravaginal Use
Rx only
LOT:
EXP:
MENTAX®-TC
(butenafine HCl) Cream, 1%
15g
Distributed by:
BERTEK PHARMACEUTICALS INC.
Research Triangle Park, NC 27709-4149
15g
Usual Dosage: See accompanying package insert for full prescribing information.
Manufactured by:
DPT Laboratories, Ltd.
San Antonio, TX 78215
PN518.01A
BK161-02-1C:R1
N 3 62794-161-02 3
MENTAX®-TC
(butenafine HCl) Cream, 1%
15g



Usual Dosage: See accompanying package insert for full prescribing information.

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

PN515.01A
BK161AH

See crimp of tube for lot no. and expiration date.

Manufactured by: DPT Laboratories, Ltd.
San Antonio, TX 78215

NDC 62794-161-03

Store between 5° and 30°C

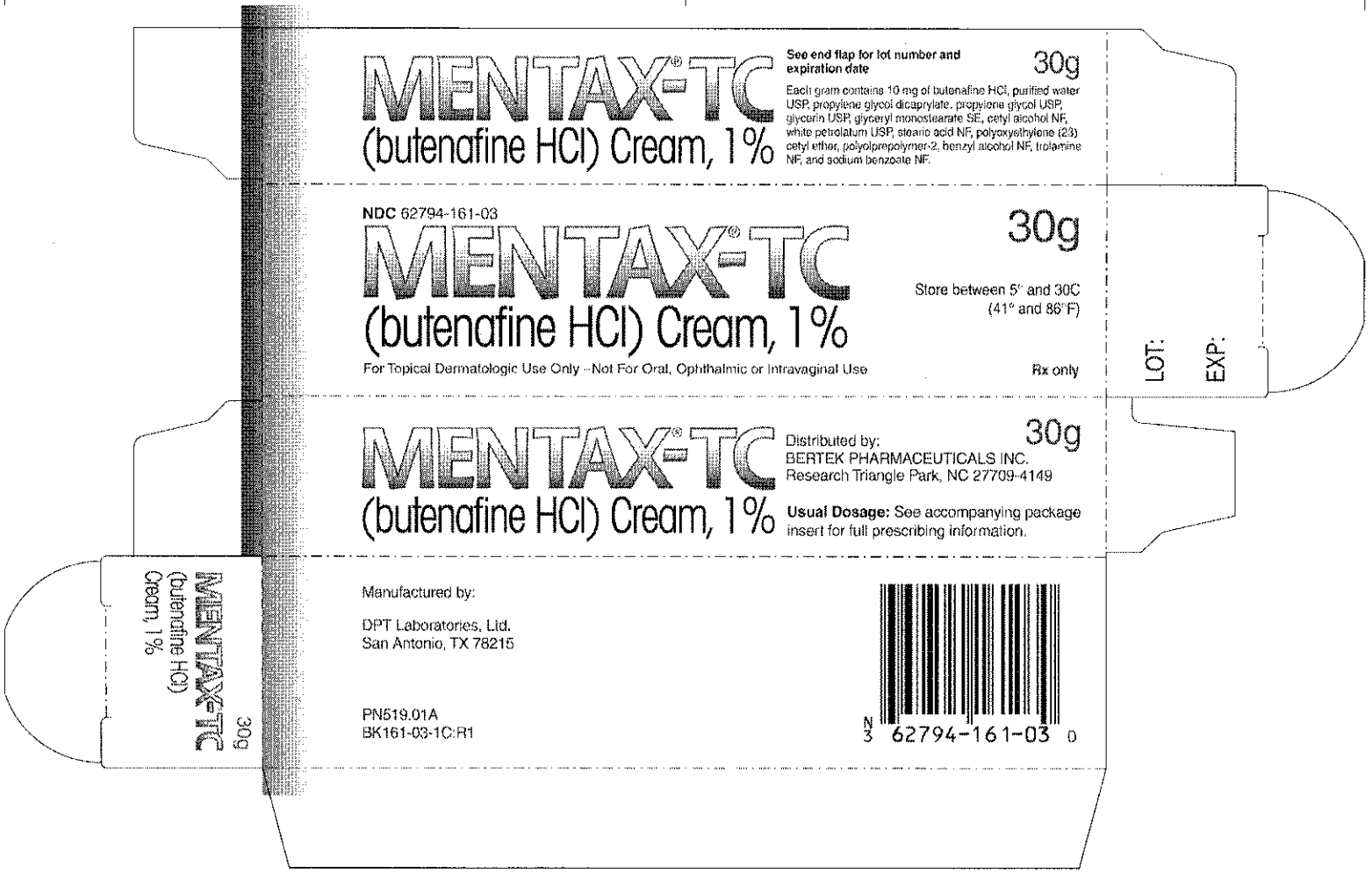
MENTAX®-TC 30g

(butenafine HCl) Cream, 1%

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

Distributed by: BERTEK PHARMACEUTICALS INC.
Research Triangle Park, NC 27709-4149

Rx only


MENTAX®-TC
(butenafine HCl) Cream, 1%
See end flap for lot number and expiration date
30g
Each gram contains 10 mg of butenafine HCl, purified water USP, propylene glycol dicaprylate, propylene glycol USP, glycerin USP, glyceryl monostearate SE, cetyl alcohol NF, white petrolatum USP, stearic acid NF, polyoxyethylene (23) cetyl ether, polyolprepolymer-2, benzyl alcohol NF, trolamine NF, and sodium benzoate NF.
NDC 62794-161-03
MENTAX®-TC
(butenafine HCl) Cream, 1%
30g
Store between 5° and 30C (41° and 86°F)
For Topical Dermatologic Use Only – Not For Oral, Ophthalmic or Intravaginal Use
Rx only
LOT:
EXP:
MENTAX®-TC
(butenafine HCl) Cream, 1%
30g
Distributed by:
BERTEK PHARMACEUTICALS INC.
Research Triangle Park, NC 27709-4149
Usual Dosage: See accompanying package insert for full prescribing information.
Manufactured by:
DPT Laboratories, Ltd.
San Antonio, TX 78215
PN519.01A
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/s/

Jonathan Wilkin

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