Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Mentax® Cream
Butenafine hydrochloride 1% w/w
Rx Only

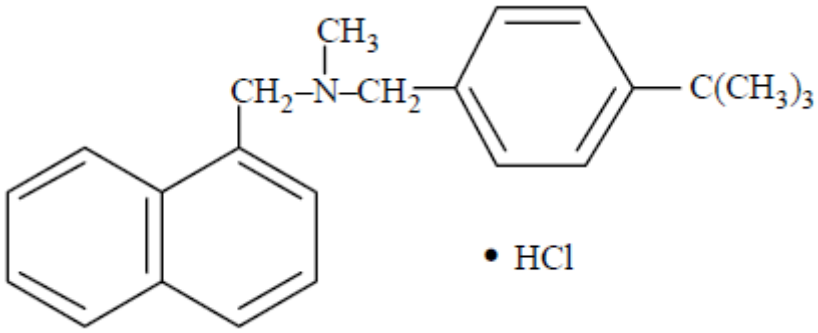
2.THERAPUETIC INDICATIONS

Interdigital tinea pedis, tinea corporis, tinea cruris . (Treatment in tinea corporis and tinea cruris is limited to up to 4 weeks).

3.DESCRIPTION

Mentax Cream, contains the synthetic antifungal agent, butenafine hydrochloride 1%. 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 $C_{23}H_{27}N$•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 Cream, contains 10 mg of butenafine HCl in a white cream base of purified water, propylene glycol dicaprilate, glycerin, cetyl alcohol, glyceryl monostearate, white soft parafin, stearic acid, polyoxyethylene cetyl ether, diethanolamine, and sodium benzoate.

4. CLINICAL PHARMACOLOGY

Pharmacokinetics

In one study conducted in healthy subjects for 14 days, 6 grams of Mentax Cream, was applied once daily to the dorsal skin (3,000 cm^2) of 7 subjects, and 20 grams of the cream was applied once daily to the arms, trunk and groin areas (10,000 cm^2) of another 12 subjects. After 14 days of topical applications, the 6-gram dose group yielded a mean peak plasma butenafine HCl concentration, Cmax, of 1.4 ± 0.8 ng/mL, occurring at a mean time to the peak plasma concentration, Tmax, of 15 ± 8 hours, and a mean area under the plasma concentration-time curve, $AUC_{0\text{-}24\ hrs}$ of 23.9 ± 11.3 ng-hr/mL. For the 20-gram dose group, the mean Cmax was 5.0 ± 2.0 ng/mL,

occurring at a mean Tmax of 6 ± 6 hours, and the mean $AUC_{0\text{-}24\ hrs}$ 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, 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, 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 ± 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.

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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 section 5. INDICATIONS AND USAGE:

Epidermophyton floccosum
Malassezia furfur
Trichophyton mentagrophytes
Trichophyton rubrum
Trichophyton tonsurans

5. 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, 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, 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)

Butenafine HCl cream was not studied in immunocompromised patients.

6. CONTRAINDICATIONS

Known or suspected hypersensitivity to active substance or any of the excipients listed.

7. WARNINGS
Mentax Cream, is not for ophthalmic, oral, or intravaginal use.

8. PRECAUTIONS

General
Mentax Cream, is for external use only. If irritation or sensitivity develops with the use of Mentax Cream, treatment should be discontinued and appropriate therapy instituted. Diagnosis of the disease should be confirmed either by culture on an appropriate medium, 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 Cream with caution, since cross-reactivity may occur.

Use Mentax Cream, 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, 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, is for external use only.
2. Dry the affected area(s) thoroughly before application, if you wish to apply Mentax Cream, 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 Cream, and other drugs have not been systematically evaluated.

Carcinogenesis, Mutagenesis, Impairment of Fertlity

Long-term studies to evaluate the carcinogenic potential of Mentax Cream 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/m^2 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/m ^{2} 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/m^2 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, to a nursing woman. Nursing mothers should avoid application of Mentax Cream, 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, in pediatric patients 12 to 16 years of age is supported by evidence from adequate and well-controlled studies of Mentax Cream, in adults.

9. ADVERSE REACTIONS

In controlled clinical trials, 9 (approximately 1%) of 815 patients treated with Mentax Cream, reported adverse events related to the skin. These included burning/stinging, itching, and worsening of the condition. No patient treated with Mentax Cream, 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, 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il
In additionally, you can report to Padagis via the following address: padagis.co.il

10. OVERDOSAGE

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

11. DOSAGE AND ADMINISTRATION

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 section CLINICAL STUDIES). 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 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.

12. PHARMACEUTICAL PARTICULARS

Nature and contents of container
Mentax Cream is supplied in tubes in the following size:
10, 15, 20-gram aluminum tube.

List of excipients:
Purified water, propylene glycol dicaprilate, cetyl alcohol, glyceryl monostearate, glycerine, white soft paraffin, stearic acid, polyoxylethylene cetyl ether, diethanolamine, sodium benzoate.

Special precautions for storage
STORE in a cool place, below 25°C.

Shelf life
The expiry date of the product is indicated on the packaging materials.
Shelf life after opening: 3 months .

Manufactured by: Padagis Israel Pharmaceuticals, Ltd. 1 Rkefet St., Shoham, Israel
Registration authorization holder: : Padagis Israel Pharmaceuticals, Ltd. 1 Rkefet St., Shoham, Israel
Registration authorization number: 110-63-28947

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