SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BUTEFIN 1% Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 g of cream contains;

Active substance:

Butenafine hydrochloride	10 mg

Excipients:

Benzyl alcohol	10 mg/g
Cetyl alcohol	40 mg/g
Stearyl alcohol	66.7 mg/g
Sodium hydroxide	1.13 mg/g

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cream
Almost white cream

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

BUTEFIN is indicated for the topical treatment of the dermatologic infections as tinea (pityriasis) versicolor due to *M. furfur* (former name: P. *orbiculare*), interdigital tinea pedis, tinea corporis, and tinea cruris due to *E. floccosum, T. mentagrophytes, T. rubrum and T. tonsurans.*

4.2. Posology and method of administration

Posology/frequency of administration and duration

Adults:

In the treatment of interdigital tinea pedis, BUTEFIN should be applied twice daily for 7 days or once daily for 4 weeks. For the treatment of tinea (pityriasis) versicolor, tinea corporis or tinea cruris, BUTEFIN should be applied once daily for two weeks. Sufficient amount of BUTEFIN should be applied to cover affected areas and the surrounding skin of the patients.

If no clinical improvement is observed after the treatment period, the diagnosis and the therapy should be reviewed.

Additional information on special populations:

Pediatric population:

Safety and efficacy in patients under 12 years of age have not been studied since tinea versicolor is not common in patients under 12 years of age.

Geriatric population:
There is no special warning regarding use of BUTEFIN in the elderly.

4.3. Contraindications

BUTEFIN is contraindicated in patients who have known or suspected sensitivity to butenafine hydrochloride or any of its components.

It should not be used for children under 12 years of age.

4.4. Special warnings and precautions for use

If irritation or sensitivity develops with the use of cream, treatment should be discontinued and appropriate therapy should be started.

Diagnosis of the disease should be confirmed either by culture on an appropriate medium, [except *M. furfur* (former name: *P. orbiculare*)] or by direct microscopic examination of infected superficial epidermal tissue in a potassium hydroxide solution.

Patients who are known to be sensitive to allylamine antifungal agents should use BUTEFIN with caution since cross-reactivity may occur.

It should not be concurrently used with other topical creams.

Avoid contact of BUTEFIN with eyes or mucous membranes and in case of accidental contact; wash immediately with water.

The product is not for oral use. Wash hands after application.

BUTEFIN contains benzyl alcohol. But it is not required any warning with the reason for its route.

Since BUTEFIN contains cetyl alcohol and stearyl alcohol, it may cause local skin reactions (e.g., contact dermatitis).

BUTEFIN contains sodium. But it is not required any warning with the reason for its route.

4.5. Interaction with other medicinal products and other forms of interaction

There is not known or expected interaction of BUTEFIN with other medicinal products through topical administration.

4.6. Pregnancy and lactation

General recommendation:
Pregnancy category is: C

Women with potential for childbearing/Contraception
No data available.

It may be used by pregnant or lactating women under the supervision of a physician. It should be used in pregnant women only after a risk/benefit evaluation is made by the doctor.

Pregnancy
Animal studies are insufficient with respect to effects on pregnancy/ and-or/embryonic / fetal development/ and-or postnatal development (see section 5.3). The potential risk for humans is unknown.

BUTEFIN should not be used during pregnancy unless it is necessary.

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) are 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, 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 (primary generation) or their subsequent maturation and fertility 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.

Lactation

Since there are limited studies on excretion of Butenafin hydrochloride into breast milk and possible effects on lactating infants, it is not recommended in lactating women until sufficient data is obtained.

Fertility

No data available.

4.7. Effects on the ability to drive and use machines

There are no studies on the effects of BUTEFIN on the ability of driving or using machines.
For this reason, it does not know whether it is effect or not.

4.8. Undesirable effects

Reported adverse effects are classified as shown below:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1.000 to <1/100); rare (≥1/10.000 to <1/1.000); very rare (<1/10.000), unknown (cannot be estimated from available data).

Skin and subcutaneous tissue disorders:

Common: Burning/stinging, itching, worsening of the condition, contact dermatitis, erythema, irritation

4.9. Overdose and treatment

No overdosage is expected with the topical administration of BUTEFIN.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: Other Topical Antifungals
ATC Code: D01AE23

Butenafine HCl is a benzylamine derivative with 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 at 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 are unknown.

Butenafine HCl has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections:

Epidermophyton floccosum

Trichophyton rubrum

Malassezia furfur

Trichophyton tonsurans

Trichophyton mentagrophytes

5.2. Pharmacokinetic properties

Absorption:

In one study conducted in healthy subjects for 14 days, 6 grams of BUTEFIN 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, 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,

AUC0–24 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 AUC0–24 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).

In 11 patients with tinea pedis, butenafine HCl cream, 1%, was applied by the patients to cover the affected and immediately surrounding skin area once daily for 4 weeks. Asingle 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, butenafine HCl 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. 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.

Distribution:
Total amount (or dose percentage) of absorbed Butenafine HCl through the skin into the systemic circulation has not been quantitated.

Biotransformation:
It was determined that the primary metabolite in urine was formed through hydroxylation at the terminal *t*-butyl side-chain.

Elimination:
It was determined that the primary metabolite in urine was formed through hydroxylation at the terminal *t*-butyl side-chain.

5.3. Preclinical safety data

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 score of zero for erythema, scaling, and pruritus.

Two separate studies compared Butenafine hydrochloride 1% 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 (butenafine hydrochloride 1% cream 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) (butenafine hydrochloride 1% cream 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.

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 week 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* (former name: *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 immediately result in restoration of pigment of 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.

6. PHARMACEUTICAL PROPERTIES

6.1. List of excipients

Benzyl alcohol
Sorbitan monostearate
Cetyl palmitate 95
Zinc oxide
Sodium hydroxide
Cetyl alcohol
Stearyl alcohol
Polysorbate 60
Isopropyl myristate
Deionised water

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Keep at room temperature below 25ºC

6.5. Nature and contents of container

It is presented in 15g and 30g aluminum tubes closed with HDPE caps.

6.6. Special precautions for disposal and other handling

Any unused product or waste materials should be disposed according to the regulations on "Control of Medicinal Wastes" and "Control of Packaging and Packaging Wastes".

7. MARKETING AUTHORIZATION HOLDER

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241/27

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 08.03.2012
Date of latest renewal: 05.10.2018

10. DATE OF REVISION OF THE TEXT

18.07.2017