TERBINAFINE HYDROCHLORIDE 1% CREAM
PL 19611/0085

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TABLE OF CONTENTS

TERBINAFINE HYDROCHLORIDE 1% CREAM
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LAY SUMMARY

The MHRA granted Niche Generics Ltd a Marketing Authorisation (licence) for the medicinal product Terbinafine Hydrochloride 1% cream (PL 19611/0085). This license was initially granted to PharmaSolve Consultancy Ltd on 30 March 2007 and the Change of Ownership was approved on 20 September 2007. This product is a prescription only medicine (POM) for the local treatment of fungal infections of the skin.

Terbinafine Hydrochloride 1% cream contains the active ingredient terbinafine which is an antifungal agent.

The test product was considered to be equivalent to the original product Lamisil Cream (Novartis Pharmaceuticals UK Ltd, trading as Sandoz Pharmaceuticals) based on the data submitted.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of using Terbinafine Hydrochloride 1% cream outweigh the risks, hence a Marketing Authorisation has been granted.

TERBINAFINE HYDROCHLORIDE 1% CREAM
PL 19611/0085

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a Marketing Authorisation for the medicinal product Terbinafine Hydrochloride 1% cream to Niche Generics Ltd on 20 September 2007. This license was granted to PharmaSolve Consultancy Ltd on 30 March 2007 prior to the Change of Ownership. The product is a prescription only medicine.

This application for terbinafine was submitted according to Article 10.1 of Directive 2001/83/EC as amended, claiming to be a generic product of Lamisil Cream (Novartis Pharmaceuticals UK Ltd, trading as Sandoz Pharmaceuticals). The reference product has been authorised in the UK since October 1990 and so the 10-year period of data exclusivity has expired.

The product contains the active ingredient terbinifine and is indicated for Fungal infections of the skin caused by *Trichophyton* (e.g. *T. Rubrum*, *T.Mentagrophytes, T. Verrucosum, T. Violaceum), Microsporum canis* and *Epidermophyton floccosum*; yeast infections of the skin, principally those caused by the genus *Candida* (eg. *C.albicans*); and Pityriasis (tinea) versicolor due to *Pityrosporum orbiculare* (also known as *Malassezia furfur*).

Terbinafine is an antifungal for topical use. It is used to inhibit squalene epoxidase in the fungal cell membrane which leads to an intracellular accumulation of squalene which results in fungal cell death.

PHARMACEUTICAL ASSESSMENT

COMPOSITION

The product is formulated as a cream containing 1% w/w of the active pharmaceutical ingredient terbinafine hydrochloride. The excipients present are sodium hydroxide, benzyl alcohol, sorbitan stearate, cetyl palmitate, cetyl alcohol, cetostearyl alcohol, polysorbate 60, isopropyl myristate and purified water.

Terbinafine Hydrochloride 1% cream is presented in aluminium tubes with polyethylene caps in packs of 7.5g, 15g or 30g.

DRUG SUBSTANCE

Terbinafine Hydrochloride

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification based on the European Pharmacopoeia monograph is provided for terbinafine hydrochloride.

Analytical methods have been validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided for five batches and comply with the proposed specification.

Terbinafine hydrochloride is stored in appropriate packaging.

Stability data have been generated which support a retest period of 3 years when the drug substance is stored at 15-30°C in the proposed packaging, protected from light.

DRUG PRODUCT

Other ingredients

All excipients used in the manufacture of the cream are routinely tested for compliance with current relevant international standards.

Satisfactory certificates of analysis have been provided for all excipients.

No excipients used contain material of animal or human origin.

Impurity Profiles

The impurity profiles of the drug product (Terbinafine Hydrochloride 1% cream) and reference product (Lamisil Cream, Novartis Farma SpA, Italy) were comparable. The

applicant has confirmed that the composition of the reference product has the identical composition to Lamisil Cream from Novartis Pharmaceuticals UK Ltd.

Manufacture
A full description and a detailed flow-chart of the manufacturing method including in-process control steps has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out and the results are satisfactory.

Finished product specification
The proposed finished product specification is acceptable and the analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed release specification. Suitable reference standards were used.

Container Closure System
Satisfactory specifications and certificates of analysis have been provided for the packaging components. All primary product packaging complies with FDA regulations regarding contact with food.

Stability
Finished product stability data support the proposed shelf-life of 4 years with storage conditions “Store in original package.”

Bioequivalence/bioavailability
Refer to the clinical assessment report.

SPC, PIL and Labels
The SPC and labels are pharmaceutically acceptable.

A patient information leaflet (PIL) has been submitted to the MHRA along with a bridging report which refers to the results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC performed on the PIL of a similar product. The results indicate that the applicant’s PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act on the information that it contains.

CONCLUSION

The proposed product has been shown to be a generic product of the reference product and has met the requirements with respect to qualitative and quantitative content of the active substance. Similar impurity profiles have been demonstrated for the proposed and reference product.

It is recommended that a Marketing Authorisation should be granted for this application.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

INTRODUCTION AND BACKGROUND

This is a generic abridged application for a cream containing 1% terbinafine hydrochloride.

The application is submitted under the provisions of Directive 2001/83/EC Article 10.1, claiming that Terbinafine Hydrochloride 1% cream is a generic product of Lamisil Cream (Novartis Pharmaceuticals UK Ltd, trading as Sandoz Pharmaceuticals) which was authorised in the UK in October 1990.

Terbinafine is a well established antifungal agent used both orally and as a topical application for cutaneous mycoses, depending on the severity and specific nature of the mycoses. The current applications are for treatment of skin infections caused by trichophyton (including trichophyton verrucosum), micropsporum canis, Candida (princilally caused by C. albicans) and pityrosporum orbiculare (tinea), applied locally for 1-2 weeks.

INDICATIONS

The following indications have been approved:

> Fungal infections of the skin caused by *Trichophyton* (e.g. *T. Rubrum, T.Mentagrophytes, T. Verrucosum, T. Violaceum), Microsporum canis* and *Epidermophyton floccosum.*
>
> Yeast infections of the skin, principally those caused by the genus *Candida* (eg. *C. albicans*).
>
> Pityriasis (tinea) versicolor due to *Pityrosporum orbiculare* (also known as *Malassezia furfur*).

DOSE AND DOSE SCHEDULE

The proposed dose and dose schedule for this product to be used for the above indications are similar to the reference product.

CLINICAL PHARMACOLOGY

Pharmacokinetics

This is a locally acting locally applied preparation with minimal systemic absorption (<5%). Therefore, systemic pharmacokinetics are not relevant and will not be discussed here.

Pharmacodynamics

The pharmacodynamic effects of terbinafine have been well established both as a topical agent and for systemic administration in the indications sought. The applicant

has provided sufficient published literature to support the claims. These are considered to be acceptable. As bioequivalence is not applicable to this formulation, refer to the sections below for a review of the efficacy studies provided to demonstrate the therapeutic equivalence with the brand leader.

Bioavailability and Bioequivalence
No bioavailability or bioequivalence data were submitted and none are required for formulations of this type.

CLINICAL EFFICACY

Introduction
The applicant has provided a review of clinical efficacy for terbinafine (Lamisil) in the indications sought.

Overview of efficacy:
The applicant has discussed each study in some detail justifying the applicability of data obtained using Lamisil (innovator product) to the current formulation. Whilst the studies do demonstrate the effectiveness of Lamisil in infections caused by trichophyton species, no references relating to Candida infections were included. However, yeast was present in the number of subjects (n=76/447, 17%) that were part of the therapeutic equivalence study (see below for details of study) and there was a proportional reduction of yeast isolation at visit 3 (n=19 /421, 4.5%) as per full population count based on mycological cultures. This could be considered as evidence of some efficacy of terbinafine in yeast infections, but has not been specifically presented as efficacy data by the applicant.

In addition to the above overview, the applicant has provided a therapeutic equivalence study in tinea pedis that is detailed and discussed below. This is considered to be satisfactory as the generic product is considered to be therapeutically equivalent to the innovator product, and therefore the data for the innovator product may also apply to the generic product.

Therapeutic Equivalence study:
This was a randomised, prospective, comparative, double-blind, active controlled, parallel group, multi-centre (n=36) study.

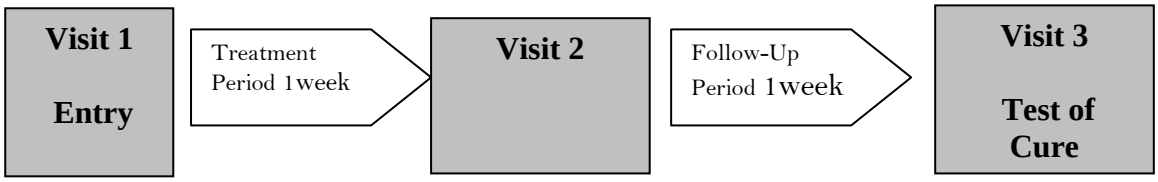
Male and female patients aged from 18 to 80 years old with a clinical diagnosis of interdigital tinea pedis (confirmed by mycological cultures) were included. There were 3 clinic visits and evaluation of all cultures was performed at the same location.

The sample sizes were as follows:

	Terbinafine	Lamisil (Novartis)	
Randomised	733	366	356
Efficacy Population	718	362	356 (Visit 2)
Clinical PP population	538	270	268
Mycology Full Population	447	214	233
Complete per-protocol	296	144	152

The complete per protocol population formed the population for primary efficacy criterion.

Study Flow Chart:



End points:

Primary Efficacy Variable

- Mycological cure at Visit 3

Secondary efficacy variables

- Mycological cure at Visit 2
- Clinical Cure (Visit 2 & 3)
- Complete Cure (Visit 2 & 3)
- Score of Clinical signs and Symptoms
  The applicant employed the following scale:

0:	None	Complete absence of any signs
2:	mild	Obvious but minimal involvement
3:	moderate	Something that is easily noted
4:	Severe	Quite marked.

- Sum of scores of Clinical signs and Symptoms
  The sum of scores was calculated from scores of signs- fissuring, erythema, maceration, vesiculation, exudation, desquamation and from the symptoms; pruritus, burning/stinging.
- Investigator's Rating
  The investigator's rating based on 75%, 50% or less improvement. These however appear to have been arbitrary assessment.
- Patient's assessment of efficacy.

Statistical methods

The confidence interval approach to assess the therapeutic equivalence of efficacy was used. Equivalence was concluded if the centre-weighted two-sided 95% CI for the difference between the two treatments lay entirely within the equivalence range (±10%). The clinical signs and symptom scores were analysed with relevant statistical software. All tests were two tailed.

Results

Efficacy evaluation

Mycological cure was achieved in 231 patients (112 terbinafine, 119 Lamisil) in the mycological PP population with cure rates of 77.8 % and 78.3% respectively. The calculated CI was -9.9% - 8.9% which was entirely within the equivalence range (±10%). Therapeutic equivalence was concluded.

Analysis of the full mycological population appear to confirm the above results. Cure rates were 70.6% and 71.2 % for generic terbinafine and Lamisil respectively, with a difference of 0.7% (CI -9.1 to +7.7%).

Secondary efficacy parameters;

- Mycological cure at Visit 2 showed wider confidence intervals with the cure rates being lower than at Visit 3 and difference between cure rates (for terbinafine and Lamisil) being higher.

- Clinical cure (no residual signs/symptoms) rates at Visit 2 and 3 were as follows:

	Terbinafine	Lamisil
Visit 2	10%	10%
Visit 3	33.7%	28.7%

- Cure rates in clinical population were similar in the clinical full population.

- Complete Cure at Visit 2 & 3
  The rates were higher in the terbinafine group but not statistically significant. The other secondary efficacy parameters were not statistically significant between treatment groups as per the clinical study report.

Predominant organisms:
The study primarily included interdigital tinea pedis (majority of patients). Yeast infections were not studied specifically but there were a small proportion of patients wherein yeast was demonstrated from scrapings and cultures. The cure rates in these subjects were in the same range as those for other organisms.

Conclusion
The rates of cure between Test terbinafine and Lamisil appear to be similar without significant differences, for mycological full or mycological per protocol populations. For the secondary efficacy parameters, the upper confidence interval value has been higher than 10% for clinical cure and complete cure. The expert however, disregards this as the difference between treatment groups was small.

Statistical Assessment

This assessment considers the EQUATE study, which compared generic terbinafine with a licensed formulation (Lamisil).

The study was randomised, double-blind, parallel-group and multicentre (36 centres). The aim was to demonstrate therapeutic equivalence between the two formulations (terbinafine, n= 366, Lamisil, n=367) following 1-week of treatment (Visit 2) and a further two weeks of follow-up (Visit 3).

The primary endpoint was the mycological cure rate at Visit 3 assessed in the mycological per-protocol (PP) population. Supportive analyses on the mycological full analysis set (FAS) and at Visit 2 were also presented. Secondary endpoints considered complete cure and clinical cure in the complete PP/FAS and clinical PP/FAS populations respectively. Definitions of the analysis populations were as follows:

- The mycological FAS consisted of all patients with positive mycological culture and KOH test for fungi at baseline (Visit 1) plus one further mycological examination (terbinafine, n= 214, Lamisil, n=233).
- The clinical FAS consisted of all patients with a diagnosis of tinea pedis, a sum of clinical signs and symptoms ≥ 6 at Visit 1, plus one further clinical evaluation terbinafine, n= 362, Lamisil, n=356).
- The complete FAS comprised patients included in both of the above populations (terbinafine, n= 214, Lamisil, n=233).
- The mycological PP was a subset of the respective FAS, including patients satisfying certain additional aspects of the protocol (terbinafine, n= 144, Lamisil, n=152).
- The clinical PP was a subset of the respective FAS, including patients satisfying certain additional aspects of the protocol (terbinafine, n= 270, Lamisil, n=268).
- The complete PP comprised patients included in both of the above populations (terbinafine, n= 144, Lamisil, n=152).

It appears that all mycologically evaluable patients were also clinically symptomatic at baseline.

There are two sources of excluded data in this trial. First, patients are excluded from the analysis populations based on the above-described eligibility criteria. It is noted that the clinical FAS comprises almost all of the randomised patients (except for 15 randomised patients who provided no further efficacy data). Just under two thirds of those patients were mycologically evaluable. Approximately 25-30% of patients deviated from an important aspect of the protocol and were excluded from the PP populations. This is not unusual in this type of study. That so many patients were excluded, in particular from the primary analysis, is not a major concern on its own, given that the reasons for exclusion were pre-specified and that the data are robust to these exclusions when results across the different endpoints, patient populations and visits were considered.

The second source of missing data is from patients who discontinued during the course of the trial or who completed the trial but didn't provide a particular assessment. This type of absent data is relatively small in this study.

Although there were several amendments to the trial protocol, the Statistical Analysis Plan confirms that the criteria for determining the analysis populations were pre-specified. The final protocol amended the equivalence margin to delta=10%, which is usually acceptable from a regulatory point of view, providing that the proportion of responders is not extreme (e.g. greater than 85-90% or less than 10-15%). The primary endpoint was also ammended, from complete cure at Visit 3 to mycological cure at Visit 3. The rationale for this was the number of patients mycologically negative at baseline, which, the sponsor presumed, was likely to decrease statistical power to the extent that equivalence would not be demonstrated on the endpoint of 'complete cure'.

The following table summarises the efficacy data:

Endpoint and analysis population	terbinafine	Lamisil	Difference and 95% CI
Mycological cure Visit 3 – PP	77.8	78.3	-0.5 (-9.9, 8.9)
Mycological cure Visit 3 – FAS	70.6	71.2	-0.7 (-9.1, 7.7)
Mycological cure Visit 2 - PP	75.7	68.4	7.3 (-2.9, 17.5)
Mycological cure Visit 2 – FAS	64.5	69.5	-5.0 (-13.8, 3.7)
Clinical cure Visit 3 – PP	33.7	28.7	5.0 (-2.8, 12.8)
Clinical cure Visit 3 – FAS	27.3	25.8	1.5 (-5.0, 8.0)
Clinical cure Visit 2 - PP	10.0	10.1	-0.1 (-5.2, 5.0)
Clinical cure Visit 2 – FAS	9.1	8.1	1.0 (-3.1, 5.1)
Complete cure Visit 3 – PP	29.9	23.7	6.2 (-3.9, 16.3)
Complete cure Visit 3 – FAS	26.6	21.5	5.2 (-2.8, 13.1)
Complete cure Visit 2 - PP	11.1	5.9	5.2 (-1.2, 11.5)
Complete cure Visit 2 – FAS	8.9	5.2	3.7 (-1.0, 8.5)

Conclusion

This was a large, well designed study. The primary endpoint offers evidence of equivalence between terbinafine and Lamisil.

CLINICAL SAFETY

Introduction

The applicant has provided a review of the literature reports on the well established safety of terbinafine (as Lamisil) that has been in clinical use since 1990. This is applicable to the topical formulation and simultaneously, the orally administered form.

The applicant has submitted a therapeutic equivalence study as a substitute for a bioequivalence study and claims that Terbinafine Hydrochloride 1% cream is a generic product of Lamisil Cream. No specific safety studies were conducted by the applicant.

In the therapeutic equivalence study, 733 subjects (patients with tinea pedis) were exposed to terbinafine (Generic formulation n=366) or Lamisil (n=367) during the 3 week study. A total of 10.1% (74) patients experienced adverse events and only 0.4% (n=3) had an adverse event of severe intensity.

The most frequent adverse events (study medication related or not) were, application site burning (15.6%), flu like symptoms (8.4%), increased hepatic transaminases (6.0%), pruritus at application site (4.8) and pharyngeal pain (4.8%). A total of 2.6% (n=19) were determined to have experienced study medication related adverse events (9 in the generic terbinafine group and 10 in the Lamisil group). Burning at the application site (n=13), pruritus (n=3), warmth (n=2) and erythema with application site pain (n=1) were the most common. There were no obvious differences between the two formulations in terms of adverse events in this study. The table below provides a frequency distribution of study medication related events.

Adverse event	Terbinafine		Lamisil	
	N=	**%**	N=	**%**
Burning at application site	5	6 %	8	9.6%
Erythema	1	1.2%	0	0
Pain	1	1.2%	0	0
Pruritus (site)	2	2.4%	1	1.2%
Warmth	0	0	2	2.4%
Total	9	10.85	11	13.2%

Conclusion

There were no differences demonstrated in the reasonably sized therapeutic equivalence study, and therefore no new safety concerns relating to the generic formulation of terbinafine arose. This is supported by the published literature relating to Lamisil; no major safety issues exist.

CLINICAL EXPERT REPORT

The clinical expert report has been written by an appropriately qualified pharmaceutical physician. It is an adequate summary of the clinical data provided in the dossier.

SPC, PIL and LABELS

The SPC, PIL and labels are acceptable.

CONCLUSIONS

The clinical efficacy and safety of terbinafine have been demonstrated by the data submitted in these applications. No bioequivalence data was presented as systemic absorption of the product is considered minimal due to the nature of the formulation. Marketing Authorisations should be granted for these applications.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Terbinafine Hydrochloride 1% cream are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The data submitted support the claim that the applicant's product and the reference product are interchangeable. The risk benefit is, therefore, considered to be positive.

TERBINAFINE HYDROCHLORIDE 1% CREAM
PL 19611/0085

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation application on 19 July 2004.

2 Following standard checks and communication with the applicant, the MHRA considered the application valid on 12 August 2004.

3 Following assessment of the application, the MHRA requested further information relating to the quality dossier on 27 January 2005, 03 August 2005 and 02 February 2006 and further information relating to the clinical dossier on 28 September 2005.

4 The applicant responded to the MHRA's requests, providing further information on 12 May 2005, 17 January 2006, 17 July 2006 and 28 September 2006 for the quality sections, and again on 17 October 2005 for the clinical sections.

5 The application was determined on 30 March 2007.

TERBINAFINE HYDROCHLORIDE 1% CREAM
PL 19611/0085

STEPS TAKEN AFTER AUTHORISATION – SUMMARY

Date submitted	Application type	Scope	Outcome
16 June 2007	Change of Ownership	To change the Marketing Authorisation Holder from PharmaSolve Consultancy Ltd to Niche Generics Limited	Granted 20 September 2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

TERBINAFINE HYDROCHLORIDE 1 % cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

10 mg terbinafine hydrochloride (equivalent to 8.89 mg terbinafine), 40 mg cetyl alcohol and 40 mg cetostearyl alcohol in 1 g cream.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cream.

White or almost white cream, with slight almond odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fungal infections of the skin caused by *Trichophyton* (e.g. *T. Rubrum, T.Mentagrophytes, T. Verrucosum, T. Violaceum), Microsporum canis* and *Epidermophyton floccosum.*

Yeast infections of the skin, principally those caused by the genus *Candida* (eg. *C. albicans*).

Pityriasis (tinea) versicolor due to *Pityrosporum orbiculare* (also known as *Malassezia furfur*).

4.2 Posology and method of administration

Terbinafine cream can be applied once or twice daily. Cleanse and dry the affected areas thoroughly before application of Terbinafine cream. Apply the cream to the affected skin and surrounding area in a thin layer and rub in lightly. In the case of intertriginous infections (submammary, interdigital, intergluteal, inguinal) the application may be covered with a gauze strip, especially at night.

The likely durations of treatment are as follows:

Tinea corporis, cruris: 1 to 2 weeks

Tinea pedis: 1 week

Cutaneous candidiasis: 2 weeks

Pityriasis versicolor: 2 weeks

Relief of clinical symptoms usually occurs within a few days. Irregular use or premature discontinuation of treatment carries the risk of recurrence. If there are no signs of improvement after two weeks, the diagnosis should be verified.

Children

The experience with topical Terbisil in children is still limited and its use cannot therefore be recommended.

Use in the elderly

There is no evidence to suggest that elderly patients require different dosages or experience side-effects different to those of younger patients.

Method of administration

Via the topical route.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Terbinafine cream is for external use only. Contact with the eyes should be avoided. If it gets into the eyes accidentally, the eyes should be washed with plenty of water and the patient should turn to an ophthalmologist if necessary. Terbinafine cream may cause local skin reactions (e.g. contact dermatitis).

4.5 Interaction with other medicinal products and other forms of interaction

There are no known drug interactions with Terbinafine cream.

4.6 Pregnancy and lactation

Foetal toxicity and fertility studies in animals suggest no adverse effects.

There is no clinical experience with Terbinafine cream in pregnant women, therefore, unless the potential benefits outweigh any potential risks, Terbinafine cream should not be administered during pregnancy.

Terbinafine is excreted in breast milk and therefore mothers should not receive Terbinafine cream whilst breast-feeding.

4.7 Effects on ability to drive and use machines

There are no data available that terbinafine would affect driving ability or any other activity requiring concentration.

4.8 Undesirable effects

Redness, itching or stinging occasionally occur at the site of application; however, treatment rarely has to be discontinued for this reason. This must be distinguished from allergic reactions which are rare but require discontinuation.

4.9 Overdose

Terbinafine cream is for external use only. If accidental ingestion of the cream occurs, appropriate method of gastric lavage can be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Antifungals for topical use

ATC code: D01A E15

Terbinafine is an antimycotic with a broad-spectrum of anti-fungal activity belonging to the allylamine group. At low concentrations terbinafine is fungicidal against dermatophytes, moulds and certain dimorphic fungi. The activity against yeasts, e.g. Candida species is fungicidal or fungistatic depending on the species.

Terbinafine interferes with fungal sterol biosynthesis by the inhibition of squalene epoxidase in the fungal cell membrane, which leads to an intracellular accumulation of squalene, resulting in fungal cell death.

Terbinafine does not influence the cytochrome P-450 enzyme system and the metabolism of hormones and other drugs depending on cytochrome P-450 system.

5.2 Pharmacokinetic properties

Less than 5% of the dose is absorbed after topical application; systemic exposure is therefore very slight.

5.3 Preclinical safety data

None stated

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide

Benzyl alcohol

Sorbitan stearate

Cetyl palmitate

Cetyl alcohol

Cetostearyl alcohol

Polysorbate 60

Isopropyl myristate

Water purified.

6.2 Incompatibilities

None known.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store in original package.

6.5 Nature and contents of container

Aluminium tube closed by polyethylene cap. The tubes are containing 7.5 g, 15 g or 30 g cream.

6.6 Special precautions for disposal

No special instructions.

7 MARKETING AUTHORISATION HOLDER

Niche Generics Limited

1 The Cam Centre

Wilbury Way, Hitchin

Hertfordshire SG4 OTW

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 19611/0085

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/03/2007

10 DATE OF REVISION OF THE TEXT

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Terbinafine Hydrochloride 1% Cream

Terbinafine hydrochloride

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

1. What Terbinafine is and what it is used for

Terbinafine is an anti-fungal preparation. It kills fungi, which cause skin infections.

Terbinafine is used for the local treatment of fungal infections of the skin.

Terbinafine should NOT be used for fungal infections of the nail.

For external use only.

2. Before you use Terbinafine

DO NOT USE Terbinafine:

- If you are allergic (hypersensitive) to terbinafine hydrochloride or any of the other ingredients of Terbinafine.
- The use of Terbinafine is not recommended for children.

TAKE SPECIAL CARE with Terbinafine:

- For external use only.
- Avoid contact of the cream with your eyes. If it gets into the eyes accidentally, the eyes should be washed with plenty of water and the patient should consult an ophthamolgist if necessary.
- After application, you should always wash your hands.

Taking or using other medicines

Please tell your doctor or pharmacist if you are taking/using or have recently taken/used any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding

Pregnancy

Ask your doctor or pharmacist for advice before using Terbinafine.
If you do become pregnant whilst using Terbinafine, tell your doctor.

Breast-feeding

Ask your doctor or pharmacist for advice before using Terbinafine.

Driving and using machines

Terbinafine Cream does not affect your ability to drive or operate machinery when used as directed and only externally.

Important information about some of the ingredients of Terbinafine

Cetyl alcohol and cetostearyl alcohol, which are among the other ingredients of the cream, may cause local skin reactions (e.g. contact dermatitis).

3. How to use Terbinafine

Your doctor will decide the right amount of Terbinafine for you to use and will tell you how long to use your medicine. **Follow your doctor's instructions exactly.**

Usage of the cream
Unless otherwise instructed by your doctor, apply the cream **once** or **twice** daily. The cream is generally used for 1 to 2 weeks, but this will depend upon the type and area of infection. Make sure that you have cleaned and dried the affected skin and surrounding areas thoroughly before applying Terbinafine cream in a thin layer. The cream should be rubbed in gently and the affected areas may be covered with a gauze dressing, especially at night.

If there are no signs of improvement after two weeks of therapy, consult your doctor.

If you USE MORE Terbinafine than you should
If you or someone else, including a child, accidentally swallow the cream, contact your doctor immediately.

If you FORGET TO USE Terbinafine
If you forget to use your cream, apply the cream as soon as possible and then continue the rest of your treatment as usual.

4. Possible side effects

Like all medicines, Terbinafine can have side effects, although not everybody gets them.

Redness, itching or stinging occasionally occur at the site of application. If these side effects occur, contact your doctor.

Hypersensitivity reactions may develop with any medicine. Therefore, if you experience any of the following symptoms, such as swelling of the treated area, pain and redness, you should stop treatment and contact your doctor.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. How to store Terbinafine

Do not use after the expiry date stated on the pack. The expiry date refers to the last day of that month.

No special precautions for storage.

Store in original container.

Do not use Terbinafine if you notice visible signs of deterioration.

Keep out of the reach and sight of children.

If your doctor decides to stop your treatment, return any leftover medicine to the pharmacist. Only keep it if your doctor tells you to.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further Information

What Terbinafine contains
The active substance is terbinafine hydrochloride.
The other ingredients are sodium hydroxide, benzyl alcohol, sorbitan stearate, cetyl palmitate, cetyl alcohol, cetostearyl alcohol, polysorbate 60, isopropyl myristate, water purified.
Packs contain 1 tube of cream (7.5 g, 15 g or 30 g).

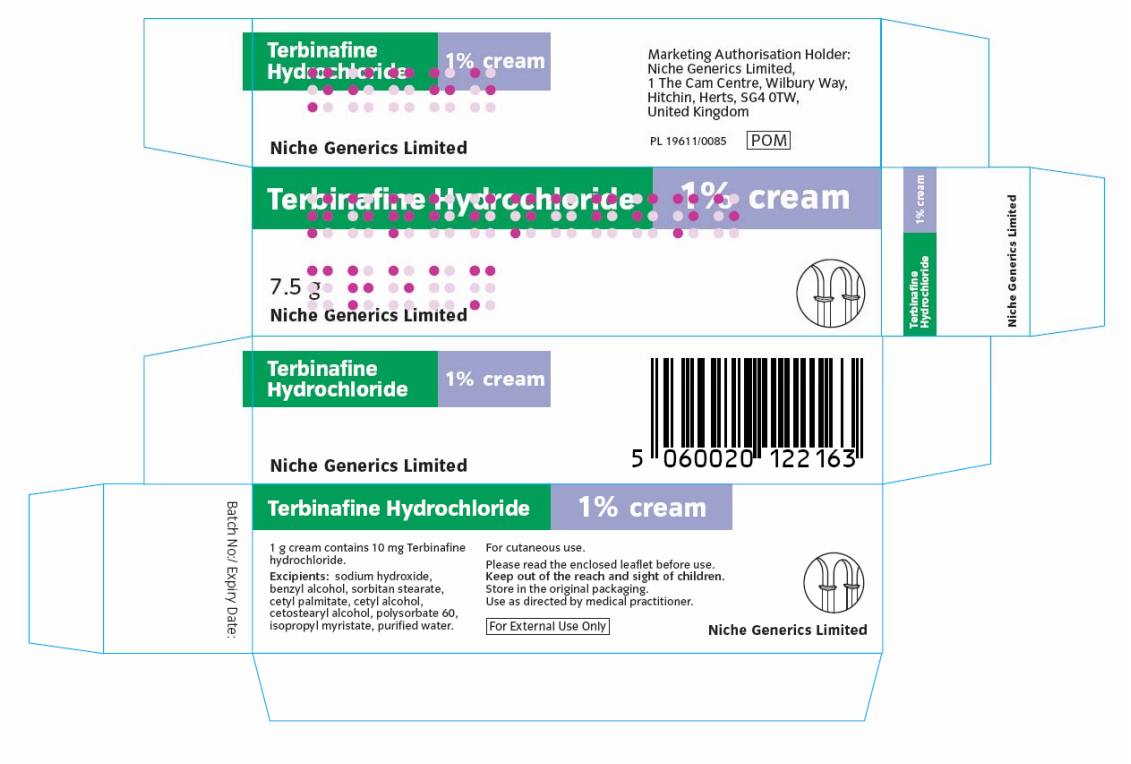
What Terbinafine looks like and contents of the pack
White or almost white cream, with slight almond odour.
Packs contain 1 tube of cream (7.5 g, 15 g or 30 g).

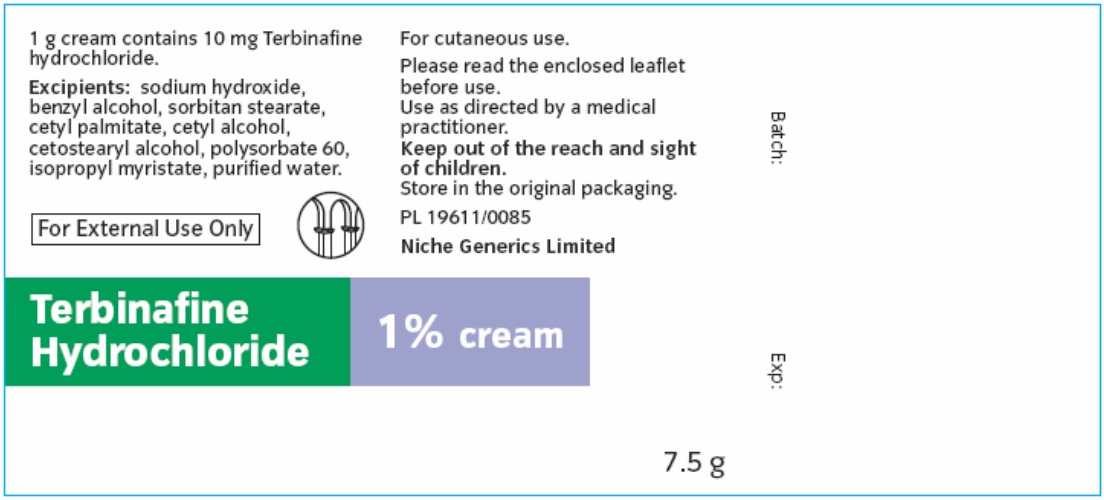
Marketing Authorisation Application held by:
Niche Generics Limited, 1 The Cam Centre, Wilbury Way, Hitchin, Herts, SG4 0TW, United Kingdom.

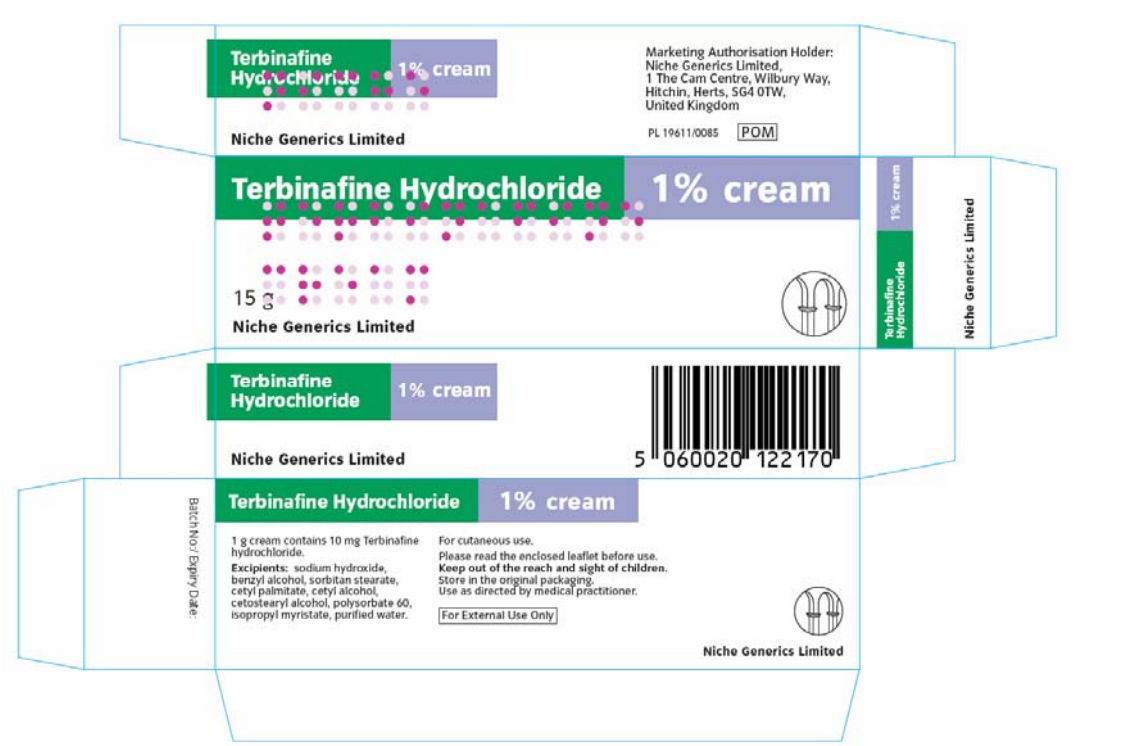
Manufactured by:
Gedeon Richter Ltd., 1103 Budapest, Gyömroi út 19-21, Hungary.

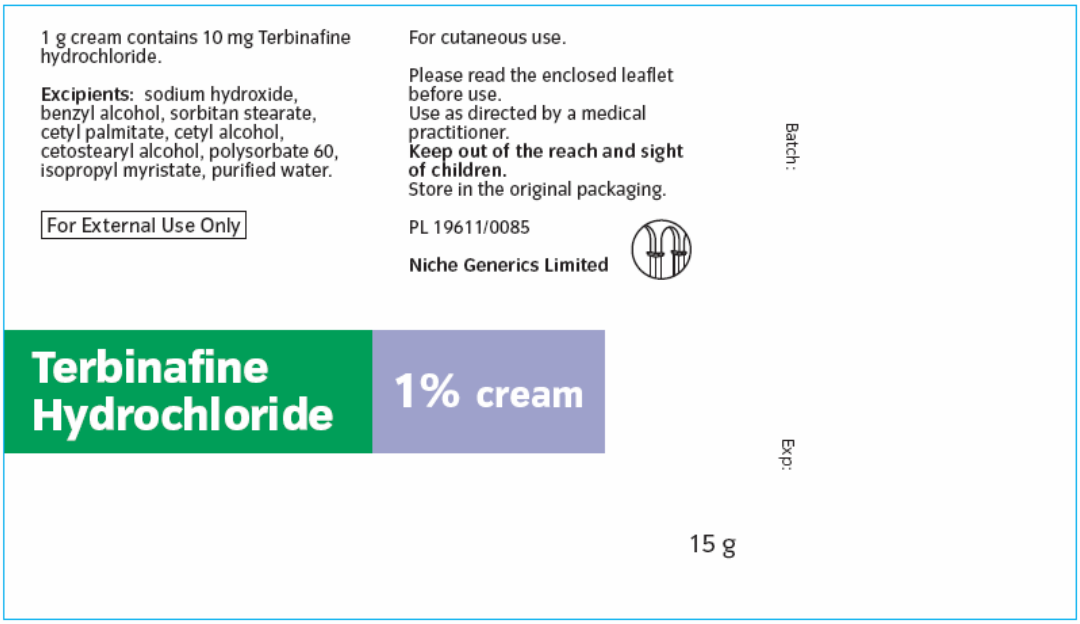
Leaflet revised in May 2007.

LABELLING

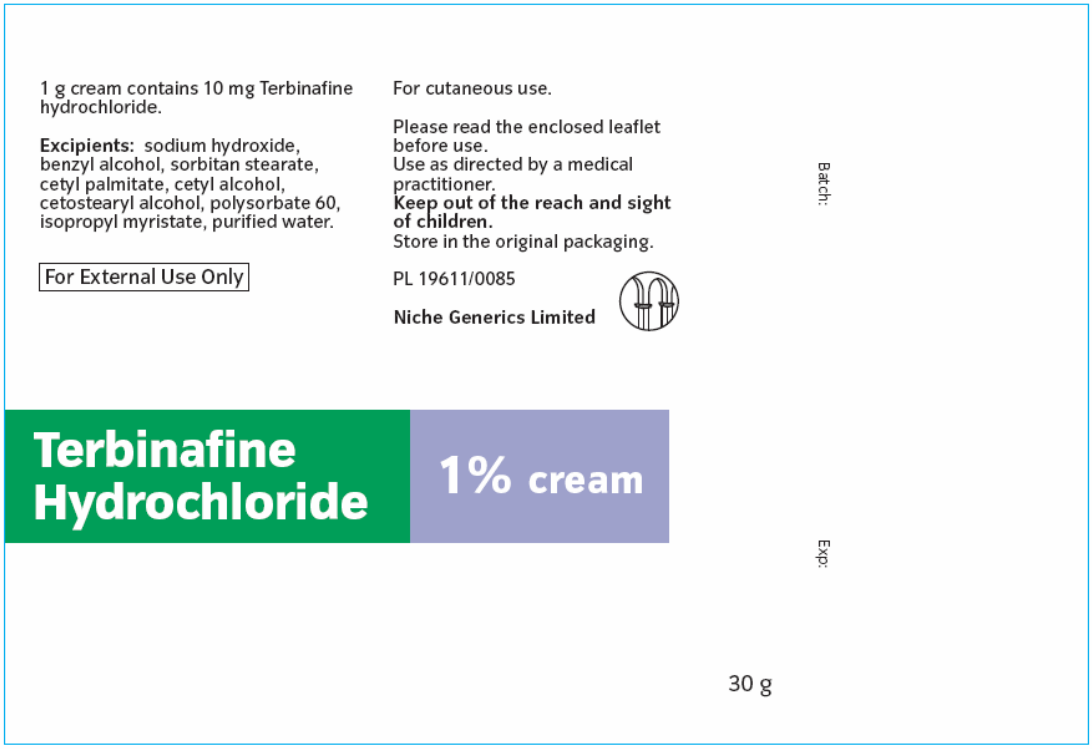

Terbinafine Hydrochloride
1% cream
Niche Generics Limited
Marketing Authorisation Holder:
Niche Generics Limited,
1 The Cam Centre, Wilbury Way,
Hitchin, Herts, SG4 0TW,
United Kingdom
PL 19611/0085
POM
7.5 g
5 060020 122163
Batch No./ Expiry Date:
1 g cream contains 10 mg Terbinafine hydrochloride.
Excipients: sodium hydroxide, benzyl alcohol, sorbitan stearate, cetyl palmitate, cetyl alcohol, cetostearyl alcohol, polysorbate 60, isopropyl myristate, purified water.
For cutaneous use.
Please read the enclosed leaflet before use.
Keep out of the reach and sight of children.
Store in the original packaging.
Use as directed by medical practitioner.
For External Use Only


1 g cream contains 10 mg Terbinafine hydrochloride.
Excipients: sodium hydroxide, benzyl alcohol, sorbitan stearate, cetyl palmitate, cetyl alcohol, cetostearyl alcohol, polysorbate 60, isopropyl myristate, purified water.
For External Use Only
For cutaneous use.
Please read the enclosed leaflet before use.
Use as directed by a medical practitioner.
Keep out of the reach and sight of children.
Store in the original packaging.
PL 19611/0085
Niche Generics Limited
Batch:
Exp:
Terbinafine Hydrochloride
1% cream
7.5 g


Terbinafine Hydrochloride 1% cream
Niche Generics Limited
Marketing Authorisation Holder:
Niche Generics Limited,
1 The Cam Centre, Wilbury Way,
Hitchin, Herts, SG4 0TW,
United Kingdom
PL 19611/0085
POM
Terbinafine Hydrochloride 1% cream
15 g
Niche Generics Limited
Terbinafine Hydrochloride 1% cream
Niche Generics Limited
5 060020 122170
Terbinafine Hydrochloride 1% cream
Batch No./ Expiry Date
1 g cream contains 10 mg Terbinafine hydrochloride.
Excipients: sodium hydroxide, benzyl alcohol, sorbitan stearate, cetyl palmitate, cetyl alcohol, cetostearyl alcohol, polysorbate 60, isopropyl myristate, purified water.
For cutaneous use.
Please read the enclosed leaflet before use.
Keep out of the reach and sight of children.
Store in the original packaging.
Use as directed by medical practitioner.
For External Use Only
Niche Generics Limited


1 g cream contains 10 mg Terbinafine hydrochloride.
Excipients: sodium hydroxide, benzyl alcohol, sorbitan stearate, cetyl palmitate, cetyl alcohol, cetostearyl alcohol, polysorbate 60, isopropyl myristate, purified water.
For External Use Only
For cutaneous use.
Please read the enclosed leaflet before use.
Use as directed by a medical practitioner.
Keep out of the reach and sight of children.
Store in the original packaging.
PL 19611/0085
Niche Generics Limited
Batch:
Terbinafine Hydrochloride 1% cream
Exp:
15 g


Terbinafine Hydrochloride
1% cream
Niche Generics Limited
Marketing Authorisation Holder:
Niche Generics Limited,
1 The Cam Centre, Wilbury Way,
Hitchin, Herts, SG4 0TW,
United Kingdom
PL 19611/0085
POM
Terbinafine Hydrochloride
1% cream
30 g
Niche Generics Limited
1% cream
Terbinafine Hydrochloride
Niche Generics Limited
Terbinafine Hydrochloride
1% cream
Niche Generics Limited
5 060020 122187
Terbinafine Hydrochloride
1% cream
Batch No/ Expiry Date
1 g cream contains 10 mg Terbinafine hydrochloride.
Excipients: sodium hydroxide, benzyl alcohol, sorbitan stearate, cetyl palmitate, cetyl alcohol, cetostearyl alcohol, polysorbate 60, isopropyl myristate, purified water.
For cutaneous use.
Please read the enclosed leaflet before use.
Keep out of the reach and sight of children.
Store in the original packaging.
Use as directed by medical practitioner.
For External Use Only
Niche Generics Limited


1 g cream contains 10 mg Terbinafine hydrochloride.
Excipients: sodium hydroxide, benzyl alcohol, sorbitan stearate, cetyl palmitate, cetyl alcohol, cetostearyl alcohol, polysorbate 60, isopropyl myristate, purified water.
For External Use Only
For cutaneous use.
Please read the enclosed leaflet before use.
Use as directed by a medical practitioner.
Keep out of the reach and sight of children.
Store in the original packaging.
PL 19611/0085
Niche Generics Limited
Batch:
Terbinafine Hydrochloride
1% cream
Exp:
30 g