CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Crème bij schimmelinfecties van de huid terbinafine HCl 10 mg/g, cream
Healthypharm B.V., the Netherlands

terbinafine (as hydrochloride)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/0744/001/MR
Registration number in the Netherlands: RVG 33309

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Pharmacotherapeutic group:	Other antifungals for topical use
ATC code:	D01AE15
Route of administration:	cutaneous
Therapeutic indication:	fungal infections of the skin, yeast infections of the skin and pityriasis (tinea) versicolor.
Prescription status:	non prescription
Date of first authorisation in NL:	13 December 2005
Concerned Member States:	Mutual recognition procedure with DE
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member state has granted a marketing authorisation for Crème bij schimmelinfecties van de huid terbinafine HCl 10 mg/g, cream from Healthypharm B.V., the Netherlands. The date of authorisation was on 13 December 2005 in the Netherlands.

The product is indicated for the treatment of:

- Fungal infections of the skin, caused by dermatophytes, such as 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 (e.g. Candida albicans).
- Pityriasis (tinea) versicolor, caused by Pityrosporum orbiculare (Malassezia furfur).

A comprehensive description of the indications and posology is given in the SPC.

Terbinafine, an allylamine, is an antimycotic with a broad spectrum of activity. At low concentrations terbinafine is fungicidal against mycelium moulds forming fungi (dermatophytes and others) and some dimorph fungi. Its activity against yeasts is fungicidal or fungistatic, depending on the species.
Terbinafine specifically inhibits fungal sterol synthesis at an early stage. This leads to a deficiency in ergosterol and intracellular accumulation of squalene, which leads to fungal cell death.
Terbinafine acts by inhibition of the enzyme squalene epoxidase in the fungal cell membrane. This enzyme does not have any relationship with the cytochrome P450-system. As far as known, terbinafine does not influence the metabolism of other medicinal products or hormones.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Lamisil® 1% cream (NL License RVG 14843). The innovator product has been registered in the Netherlands by Novartis Consumer Health B.V. since 5 December 1991. In addition, reference is made to Lamisil authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. Since less than 5% of the terbinafine dose is absorbed when Lamisil® is applied on intact skin, no pharmacokinetic bioequivalence studies were performed. For this application, the applicant submitted data of a randomised, double-blind, therapeutic equivalence study on 733 patients, diagnosed with interdigital tinea pedis. The test product Crème bij schimmelinfecties van de huid terbinafine HCl 10 mg/g cream was compared to the reference product Lamisil 1% cream, registered in the United Kingdom. This generic product can be used instead of its reference product.

There was no paediatric development programme.

No scientific advice has been given to the MAH with respect to this product.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Drug substance
The drug substance is an almost white or pale creamy coloured crystalline powder. Terbinafine hydrochloride has no asymmetric carbon atoms, therefore it does not have enantiomers. Two geometrical isomers exist: cis-terbinafine hydrochloride and trans-terbinafine hydrochloride (the pharmaceutically active form). The cis-isomer is limited as impurity to 0.1%.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.
A new Certificate of Suitability of the active substance terbinafine hydrochloride was submitted and approved via a type IA variation (NL/H/0744/001/IA/001) on 13 November 2008.

Specification
The active substance specification includes tests for appearance, colour and clarity of solution, pH, melting range, identification, loss on drying, sulphated ash, heavy metals, related substances, residual solvents, microbiological test, assay and partile size distribution. A Ph.Eur.* monograph on terbinafine hydrochloride was adopted in November 2004 and came into force on 1 January 2006. In this monograph the limit for sulphated ash is 0.1%, which is already applied.
The specification for individual impurities is in accordance with the Note for Guidance on Impurities in new drug substances and the Ph.Eur. monograph for Substances for pharmaceutical use. It is not considered necessary to identify and toxicologically qualify the individual impurities. The limit for total impurities is in accordance with the results of 5 batches and the new Ph.Eur. monograph.
The limit for methyl isobutylketone impiruty is tighter than the ICH limit in the Guideline on Impurities. The remainder of the specifications are usual for active substances provided by chemical synthesis. Batch analytical data demonstrating compliance with this specification have been provided for 5 batches.

Stability
Stability data have been obtained during storage at 25°C/60% RH (3 pilot-scale and 8 full-scale batches) and 40°C/75% RH (3 pilot-scale and 6 full-scale batches). The stability data show that no changes occur in the tested parameters when the batches are stored under both storage conditions. Based on the submitted stability data, the claimed retest period of 3 years, when stored at 15-30ºC, in double PE bag in fibre drum, protected from light, has been granted.

***** *Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Drug product
Crème bij schimmelinfecties van de huid terbinafine HCl 10 mg/g is a white or almost white cream with slight almond odour, washable with water. The cream is packed in aluminium tube with a polyethylene screw cap. One gram of cream contains 10 mg of terbinafine hydrochloride.

The excipients are: sodium hydroxide (E524), benzyl alcohol, sorbitan stearate, cetyl palmitate, cetyl alcohol, cetostearyl alcohol, polysorbate 60, ispropyl myristate and purifed water.

The excipients are common and well known. All excipients comply with the requirements laid down in their respective Ph.Eur. monographs.

Pharmaceutical development
Different manufacturing procedures were tested, during which optimisation of temperatures of aqueous and fatty phase were done and the shear ratio of the two surfactant types were reached. The up-scaling from laboratory/pilot scale to production scale is described. It was shown that the terbinafine is instable with Al^{3+} molecules; therefore, the aluminium tubes are coated on the inside. The development of the product is satisfactorily performed and explained. The objective was to develop a product that would be bioequivalent with the innovator product Lamisil.

Manufacture of the product
The manufacturing process is described in sufficient detail, mixing times and temperatures are given. Process validation data on the product have been presented for three consecutive batches in accordance with the relevant European guidelines. The process is sufficiently validated.

Product specification
The finished product specifications are adequate to control the relevant parameters for the dosage form. The product specification for the cream includes physical tests (characters, filling weight, homogeneity, pH, viscosity), identifications (active substance, preservative, chloride ions), tests for purity (related substances, microbiological purity) and assays (active substance content, preservative content). Limits in the specifications have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data for 13 batches have been provided, demonstrating compliance with the specifications.

Packaging
Aluminium tube, inside double lacquered with epoxide resin. The tubes are closed by a PE cap with cutting drift. Specifications are agreed. It is accepted that the epoxide resin is suitable for packaging cosmetics (or food). For the sealing lacquer (gray) of the tube and the inside lacquer compatibility is shown.

In-vitro equivalence studies
For local acting o/w type semi solid dosage form, where the active is in the external phase, the comparison of physical characteristics of the product and reference product show the *in vitro* equivalency. As the preservative is similar between the product and reference product, microbiological stability and equivalency has been shown. The most important physical parameters regarding stability were compared (pH and viscosity) with Lamisil after 12 months storage at 25ºC/60%RH and 30ºC/60%RH, and 6 months 40ºC/75%RH. Moreover, the impurity profiles are compared by HPLC. The only impurity found is secondary amine (slightly higher levels in Lamisil). The MEB concluded that the most important chemical and physical parameters on different storage conditions are similar of Lamisil and Crème bij schimmelinfecties van de huid terbinafine HCl 10 mg/g.

Stability of the product
The cream has been stored at 25°C/60% RH (16 batches), 30°C/60% RH (8 batches) and 40°C/75% RH (14 batches). The results show that the product is rather stable. Assay and content of the preservative show some fluctuations but no trends. The pH shows a slight decrease but within specification. Based on the stability data submitted, a shelf life of 4 years in the original packaging can be granted. The storage conditions are: *"Store in the original package", "Do not freeze"* and *"Keep the tube tightly closed"*.
After finalisation of the MRP, additional data were submitted, justifying an extension of the shelf life to 5 years (NL/H/0744/001/IB/002).

For in-use stability one batch was tested over 3 months. Testing of microbial stability on one batch is not in line with the Note for Guidance on in-use stability testing. However, the main problem area for creams in a tube is the microbial contamination, as the majority of cream does not come in contact with air or light. It is shown that the cream can maintain its microbial stability for 3 months. Moreover, this is supported by the preservative efficacy testing that has been performed. Therefore, no objection is raised to the fact that only one batch was used. The in-use stability of 3 months has been granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non clinical aspects

This product is a generic formulation of Lamisil, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for identical products on the market. The approval of this product will not result in an increase in the total quantity of terbinafine released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Terbinafine is a well-known active substance with established efficacy and tolerability.

Pharmacodynamics
Terbinafine interferes with fungal sterol biosynthesis at an early step by inhibiting squalence epoxidase in the fungal cell membrane. This leads to a deficiency in ergosterol and to an intracellular accumulation of squalence resulting in fungal death.

Clinical efficacy
As for products for local application intended to act without systemic absorption the approach to determine bioequivalence based on systemic measurements is not applicable, pharmacodynamic or comparative clinical studies are required. For this generic application, the MAH submitted a multicenter, randomised, double-blind, comparative parallel phase IV study in which Crème bij schimmelinfecties van de huid terbinafine HCl 10 mg/g was compared to the British reference product, Lamisil 1% cream (Novartis UK), in the treatment of interdigital tinea pedis. The choice of the British reference product has been justified by comparison of the quantitative compositon of the Dutch and the British reference product. The formula and preparation of the Crème bij schimmelinfecties van de huid terbinafine HCl 10 mg/g batch was identical to the formula proposed for marketing.

The test and reference products were applied twice daily, for one week, followed by a 2 week follow-up period. The study took place in 36 sites in Hungary. 733 patients with clinical diagnosis tinea pedis, aged 18-80 years, were included. Diabetes patients were excluded. Clinical and mycological evaluations were performed at baseline, end of therapy (visit 2, week 1) and during follow-up visit (visit 3; 2 weeks after finishing therapy). Patients were treated at home. The primary parameter for the evaluation of efficacy was defined posterior by the MAH as the proportion of patients with mycological cure at visit 3 (follow-up visit). Secondary parameters were amongst others clinical cure, safety and tolerance.

The MAH chose a two-armed study design with the test and reference product, without a placebo-arm. In other studies from literature, treatment with terbinafine 1% cream clearly showed superiority over placebo treatment regarding mycological eradiciation rate (mycological eradication 88% versus 23%; Berman et al.

1992, J Am Acad Dermatol;26;956-60). It is therefore acceptable, that a placebo group was not included in the study.
In this study, a treatment period of 1 week was chosen for the treatment of tinea pedis. It was confirmed in the literature that a 1 week treatment period is equally effective as longer periods (Berman et al. 1992, J Am Acad Dermatol; 26:956-60 and Evans 1994, Br J Dermatol; 130:12-4).
At the end of the study, mycological cure data instead of clinical cure data were used as primary outcome (according to protocol amendment number 07). This is acceptable according to NfG on Evaluation of Medicinal Product indicated for treatment of bacterial infections (CPMP/EWP/558/95 rev1). As can be concluded from literature, mycological cure rate is commonly used in clinical studies to establish the effectiveness of topical treatments of fungal infections of the skin.

733 patients were randomised and received at least one dose of study medication (safety population). 538 patients completed the study per protocol (Clinical PP population). Only 296 of the Clinical PP population had actually a positive mycological culture for dermatophytes at baseline (mycological PP population, n=144 in Test group, n=152 in Reference group).
The mycological cure rate (primary endpoint) was 77.8% (112/144) in the Test group and 78.3%(119/152) in the reference group (95% CI Test/Reference -9.9%; 8.9%), see also table below. The clinical cure rate was 33.7% (91/270) and 28.7% (7/268) in the Test and Reference group respectively (95% CI -2.8%; 12.8%). There were no statistical significant differences in mycological or clinical cure rates between the group that was treated with Test product (Crème bij schimmelinfecties van de huid terbinafine HCl 10 mg/g) and the group treated with Reference product (Lamisil 1% cream) (zero was included in the 95% interval). The lowest limits of the 95% CI for mycological and clinical cure rates were above the acceptance criterion of -10.0%. Therefore, essential similarity between Crème bij schimmelinfecties van de huid terbinafine HCl 10 mg/g and innovator product Lamisil 1% cream was demonstrated.

	population	**Test-group**	**Reference-group**	**95% CI Test/Reference**	
Mycological cure rate Visit 3	Mycological PP	77.8% (112/144)	78.3% (119/152)	**-9.9%; 8.9%**	**Primary parameter**
Clinical cure rates Visit 3	Clinical PP	33.7% (91/270)	28.7% (77/268)	-2.8%;12.8%	Secondary parameter
Mycological cure rate Visit 3	Mycological ITT	70.6% 151/214	71.2% 166/233	-9.1%; 7.7%	Secondary parameter
Clinical cure rates Visit 3	Clinical ITT	27.3% 99/362	25.8% 92/268	-5.0%; 8.0%	Secondary parameter

PP=per protocol; ITT=intention to treat

The number of patients available for evaluation of mycological cure rate is much lower than planned beforehand (240 available subjects in each study arm). This is mainly due to the fact that dermatophytes were only cultured in 52% of the samples.
However, the power of the study is considered to be sufficient by the MEB. Inclusion of more patients would probably result in even smaller 95% confidence intervals. In other words, inclusion of a larger population would not lead up to another conclusion. This is supported by data of the ITT population (mycological cure rate 70.6% (151/214) and 71.2% (166/233) in the Test and Reference group; 95% CI Test/Reference -9.1% - 7.7%)

2.6% (19/733) of the safety population reported one or more adverse events that were related to the study medication. There were no obvious differences between the two treatment groups regarding the incidence of drug related adverse events.

In conclusion, essential similarity between Crème bij schimmelinfecties van de huid terbinafine HCl 10 mg/g and innovator product Lamisil 1% cream was demonstrated regarding mycological eradication rate, clinical efficacy and safety profile.

Clinical experience
The efficacy and safety of terbinafine for the treatment of superficial dermatophyte infections are sufficiently known. An overview was provided by the MAH in the clinical expert report.

GCP and GLP
The MEB has been assured that the clinical/therapeutic equivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk Management Plan
Terbinafine was first approved in 1990, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of terbinafine can be considered to be well-established and no product-specific pharmacovigilance issues were identified pre- or post-authorisation, which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The applicant has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the mutual recognition procedure is in accordance with the most recent Dutch SPC text of the reference product Lamisil.
With respect to SPC section 4.2 (posology and method of administration) regarding the posology for children: The MAH committed to apply for the respective Type II Variation as soon as the ongoing evaluation of the Paediatric Worksharing Project of the HMA is finalised.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. A pilot test was performed with 3 participants, subsequently a second and third round was performed with 10 participants each. After the second test, the MAH has made some improvements, this led to an increase in readability index of 88% (second round) to 96% (third round). The readability test has been adequately performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Crème bij schimmelinfecties van de huid terbinafine HCl 10 mg/g, cream has a proven chemical-pharmaceutical quality and is a generic form of Lamisil® 1% cream. Lamisil is a well-known medicinal product with an established favourable efficacy and safety profile.

Essential similarity has been shown to be in compliance with the requirements of European guidance documents as the equivalence has been demonstrated by a clinical comparative study with a relevant clinical endpoint. The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the reference product Lamisil.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates. Braille conditions are met by the MAH.

The Board followed the advice of the assessors. Crème bij schimmelinfecties van de huid terbinafine HCl 10 mg/g was authorised in the Netherlands on 13 December 2005.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The mutual recognition procedure was finished on 16 August 2006. The concerned member state, on the basis of the data submitted, considered that essential similarity has been demonstrated for Crème bij schimmelinfecties van de huid terbinafine HCl 10 mg/g with the reference product, and has therefore granted a marketing authorisation.

The first PSUR will cover the period from December 2005 till October 2008, after which the PSUR submission cycle is 3 years. Further PSURs will be submitted in accordance with the EU PSUR Synchronisation Scheme.

The date for the first renewal will be: 14 October 2010.

The following post-approval commitments were made during the procedure:

Product information – SPC

- The MAH committed to apply for the respective Type II Variation as soon as the ongoing evaluation of the Paediatric Worksharing Project of the HMA is finalised (with respect to SPC section 4.2 regarding the posology for children).

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Submission of a new Certificate of Suitability for the active substance terbinafine hydrochloride.	NL/H/0744/001 /IA/001	IA	30-10-2008	13-11-2008	Approval	N
Extension of shelf life to 60 months.	NL/H/0744/001 /IB/002	IB	6-3-2009	6-4-2009	Approval	N