

Public Assessment Report
Decentralised Procedure

Terbinafine 1% Cream
(terbinafine hydrochloride)

UK/H/1497/001/DC

UK licence numbers: PL 04569/0889

Generics [UK] Limited

LAY SUMMARY

On 10th February 2010, the MHRA granted Generics [UK] Limited a Marketing Authorisation (licence) for the medicinal product, Terbinafine 1% cream (PL 04569/0889, UK/H/1497/001/DC). This is a prescription-only medicine (POM).

Terbinafine 1% cream is an antifungal preparation. It kills fungi, which cause skin infections. Terbinafine 1% cream is used for the local treatment of fungal infections of the skin only.

This application is based on a reference product with a valid UK licence. No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of using Terbinafine 1% cream outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Information about Initial Procedure

Product Name	Terbinafine 1% cream
Type of Application	Generic, Article 10.3
Active Substance	Terbinafine hydrochloride
Form	Cream
Strength	1% (10 mg/g)
MA Holder	Generics [UK] Limited, Potters Bar, Herts, EN6 1TL, United Kingdom
Reference Member State (RMS)	UK
Concerned Member State / s (CMS)	AT, BE, CZ, DE, FI, FR, NL, NO, PL, SE and SI
Procedure Number	UK/H/1497/001/DC
Timetable	Day 210; 12 th January 2010

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Terbinafine 1% cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g cream contains 10 mg Terbinafine hydrochloride equivalent to 8.89 mg of Terbinafine.

Excipients: 40 mg cetostearyl alcohol and 40 mg cetyl alcohol / gram cream.

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Cream

White or almost white cream

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of tinea pedis (athlete's foot) and tinea cruris (dhobie itch/jock itch)

Fungal infections of the skin caused by dermatophytes such as species of Trichophyton (e.g. *T. rubrum*, *T. mentagrophytes*, *T. verrucosum*, *T. violaceum*), *Microsporum canis* and *Epidermophyton floccosum*.

Infections of the skin caused by *Candida* (e.g. *Candida albicans*).

Pityriasis (tinea) versicolor caused by *Pityrosporum orbiculare* (*Malassezia furfur*).

4.2 Posology and method of administration

For topical use.

Adults and adolescents (>12 years of age)

Duration and frequency of treatment:

Tinea pedis: once daily for 1 week.

Tinea cruris and Tinea corporis: once daily for 1 week.

Cutaneous Candida: once daily for 1 week.

Pityriasis versicolor: once daily for 2 weeks.

For Pityriasis; cream may be applied 1-2 times daily and for cutaneous candidiasis; treatment duration may be increased to 2 weeks in more profound cases after medical assessment.

The skin should be clean and dry. The cream should be applied in a thin layer on and around the affected skin and rubbed in gently. In cases of reddened and weeping infection (under the breasts, between the fingers, buttocks or in the groin) the skin may be covered with a sterile compress after application of the cream, especially at night.

Relief of symptoms is usually obtained within a few days.

Irregular use or an inadequate treatment period increases the risk of the symptoms returning. If no improvement is obtained after 2 weeks, the diagnosis should be re-evaluated.

Elderly

There has been nothing to indicate that elderly patients require a different dosage or have a side effects profile different from younger patients.

Children

Terbinafine 1% cream is not recommended for children below 12 years of age due to insufficient data on safety. The experience in children is limited.

4.3 Contraindications

Hypersensitivity to terbinafine or to any of the excipients.

4.4 Special warnings and precautions for use

Terbinafine 1% cream is intended for topical use only. Contact with the eyes should be avoided. If the cream should come into contact with the eye, it should be rinsed carefully under running water.

Terbinafine 1% cream is not recommended to treat hyperkeratotic chronic plantar tinea pedis (moccasin type).

In the event of allergic reaction, the cream should be removed and the treatment interrupted.

The cream contains cetostearyl alcohol, which can cause local skin reactions (e.g. contact eczema).

Candidiasis: It is not recommended to use acid pH soap. (This provides favourable growth conditions for *Candida* spp.)

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. The co-administration of other products intended to treat the same areas is not recommended

4.6 Pregnancy and lactation

There is no clinical experience of use in pregnant women. Fetotoxicity- and fertility studies conducted in animals suggest no adverse effects. Terbinafine 1% cream should not be used during pregnancy unless clearly necessary.

Terbinafine is excreted into breast-milk. After topical use only a low systemic exposure is expected, see section 5.2. Terbinafine 1% cream should not be used during the lactation period unless clearly indicated.

4.7 Effects on ability to drive and use machines

Terbinafine 1% cream does not affect the ability to drive and use machines.

4.8 Undesirable effects

The undesirable effects are classified under organ headings and the frequency is indicated as follows: *Very common* ($\geq 1/10$), *common* ($\geq 1/100$ to $< 1/10$), *uncommon* ($\geq 1/1000$ to $< 1/100$), *rare* ($\geq 1/10,000$ to $< 1/1000$), *very rare* ($< 1/10,000$), not known (cannot be estimated from the available data).

The undesirable effects are presented within each frequency range according to decreasing severity.

Immune system disorders

Rare: Allergic reactions such as itching, rash, blisters and urticaria.

Skin and subcutaneous tissue disorders

Redness, rash and itching or a pricking sensation may occur on the treated area. However, these reactions rarely result in the treatment having to be discontinued. It is important to distinguish basically harmless symptoms from allergic reactions that may require discontinuation of the treatment.

4.9 Overdose

If terbinafine should accidentally be swallowed, undesirable effects similar to those observed in cases of overdose of terbinafine tablets may be expected, e.g. headache, nausea, abdominal pain and dizziness.

Gastric lavage may be performed if it is judged appropriate

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antifungal for topical use (ATC code D01A E15)

Terbinafine is an allylamine that has a broad spectrum of antimycotic activity. It has an antimycotic effect on 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*. At low concentrations terbinafine has a fungicidal effect against dermatophytes and moulds. Its activity against yeasts is fungicidal (e.g. *Pityrosporum orbiculare* or *Malassezia furfur*) or fungistatic, depending on the species.

Terbinafine interferes specifically with fungal sterol biosynthesis at an early step. This leads to a deficiency in ergosterol and to an intracellular accumulation of squalene, resulting in fungal cell death. Terbinafine acts by inhibition of squalene epoxidase in the fungal cell membrane.

The enzyme squalene epoxidase is not linked to the cytochrome P-450 system. Terbinafine does not influence the metabolism of hormones or other drugs

5.2 Pharmacokinetic properties

Less than 5% of the dose is absorbed after topical application to humans: systemic exposure is thus very low.

5.3 Preclinical safety data

In toxicological studies effects were seen only after considerably higher doses than those associated with clinical exposure. These effects are therefore considered to be of no clinical relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide
Benzyl alcohol
Sorbitan stearate
Cetyl palmitate
Cetyl alcohol
Cetostearyl alcohol
Polysorbate 60
Isopropyl myristate
Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

Shelf life after opening 28 days

6.4 Special precautions for storage

Store in original container after first opening

Do not freeze

Keep the tube tightly closed.

6.5 Nature and contents of container

Collapsible aluminium Tube with a polyethylene screw cap, in pack sizes of 7.5 g, 15g or 30 g. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable

- 7 MARKETING AUTHORISATION HOLDER**
Generics [UK] Limited, Potters Bar, Herts, EN6 1TL, United Kingdom
- 8 MARKETING AUTHORISATION NUMBER(S)**
PL 04569/0889
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
10/02/2010
- 10 DATE OF REVISION OF THE TEXT**
10/02/2010

Module 3

Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

TERBINAFINE 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 please 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 or pharmacist.

In this leaflet:

1. What Terbinafine 1% cream is and what it is used for.
2. Before you use Terbinafine 1% cream.
3. How to use Terbinafine 1% cream.
4. Possible side effects.
5. How to store Terbinafine 1% cream.
6. Further information.

1. WHAT TERBINAFINE 1% CREAM IS AND WHAT IT IS USED FOR

Terbinafine 1% cream is an antifungal preparation. It kills fungi, which cause skin infections. Terbinafine 1% cream is used for the local treatment of fungal infections of the skin only.

2. BEFORE YOU USE TERBINAFINE 1% CREAM

Do not use Terbinafine 1% cream if you are allergic (hypersensitive) to terbinafine hydrochloride or any of the other ingredients of Terbinafine 1% cream.

Take special care with Terbinafine 1% cream:

- This cream is for external use only. Avoid contact with the eyes.
- If the cream gets in your eyes, wash with clean water and tell your doctor immediately.
- Terbinafine 1% cream is not intended to treat hyperkeratotic chronic plantar tinea pedis (moccasin type).
- In the event of allergic reaction, the cream should be removed and the treatment interrupted.

Taking other medicines - Terbinafine 1% cream is not known to react with any other medicine.

Pregnancy and breast-feeding - If you are pregnant you should not use Terbinafine 1% cream unless it is clearly necessary.

Do not use this cream if you are breast-feeding as terbinafine hydrochloride can pass into breast milk. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines - Terbinafine 1% cream should not affect your ability to drive or operate machines.

Important information about some of the ingredients of Terbinafine 1% cream -

Terbinafine 1% cream contains cetyl and cetostearyl alcohol, which may cause local skin reactions (e.g. contact dermatitis). **Do not** use this cream if you know you are allergic to these ingredients.

3. HOW TO USE TERBINAFINE 1% CREAM

Dosage - Always use Terbinafine 1% cream exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Adults (including the elderly) - Apply the cream to the affected area and just around it, once or twice a day.

Clean and dry the area before applying the cream in a thin layer. Rub cream in gently.

In cases of reddened and weeping infection; if you are treating an area between the toes, fingers, buttocks or in the groin, the skin may be covered with a sterile compress, especially at night.

Duration and frequency of treatment - Tinea pedis (athlete's foot): once daily for 1 week.

Tinea cruris (dhobie itch/jock itch) and Tinea corporis: once daily for 1 week.

Cutaneous Candida: once daily for 1 week.

Pityriasis versicolor: once daily for 2 weeks.

Terbinafine 1% cream may be applied as your doctor has told you, usually 1-2 times daily. Treatment may be extended to 2 weeks.

It is important that you use the cream regularly even if the infection has improved. If you see no improvement in your skin condition after a week, go to your doctor.

Children - Terbinafine 1% cream is **not** recommended for children under 12 years.

If you use more Terbinafine 1% cream than you should - Remove some of the cream if you apply more than a thin layer.

If you or someone else swallows the cream, go to your doctor or nearest hospital emergency department for advice.

If the cream gets in your eyes, wash with clean water and tell your doctor **immediately**.

If you forget to use Terbinafine 1% cream - If you forget to use the cream, apply it as soon as you remember. If it is time for the next application, carry on as normal. It is important to try to remember to use the cream or you risk the infection returning.

If you stop using Terbinafine 1% cream - Do not stop using Terbinafine 1% cream before the recommended time, as the infection will be more likely to return.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Terbinafine 1% cream can cause side effects, although not everybody gets them.

Rare side effects (affecting fewer than 1 in 1,000 but more than 1 in 10,000 people):

- allergic reactions such as itching, rash, blisters, urticaria.

Redness, rash and itching or a pricking sensation may occur on the treated area. However, these reactions rarely result in the treatment having to be discontinued. It is important to distinguish basically harmless symptoms from allergic reactions that may require discontinuation of the treatment.

Sometimes you may suffer from mild redness, itching or stinging of the area where the cream is applied. These effects are harmless and usually you can continue with the treatment.

If any side effect gets serious, or if you notice any side effects not mentioned in the leaflet, please tell your pharmacist or doctor.

5. HOW TO STORE TERBINAFINE 1% CREAM

Keep out of the reach and sight of children.

Do not use Terbinafine 1% cream after the expiry date stated on the label or carton after 'EXP'. The expiry date refers to the last day of that month.

Store in the original container.

Do not freeze.

Keep the tube tightly closed.

You can use Terbinafine 1% cream 28 days after first opening of the tube. 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 1% cream contains - The active substance is terbinafine hydrochloride. One gram of cream contains 10 mg of terbinafine hydrochloride equivalent to 8.89 mg of terbinafine. The other ingredients are sodium hydroxide, benzyl alcohol, sorbitan stearate, cetyl palmitate, cetyl alcohol, cetostearyl alcohol, polysorbate, isopropyl myristate and purified water.

What Terbinafine 1% cream looks like and the contents of the pack - Terbinafine 1% cream comes as a cream in aluminium tubes of, 7.5 g, 15 g or 30 g. Not all pack sizes may be marketed.

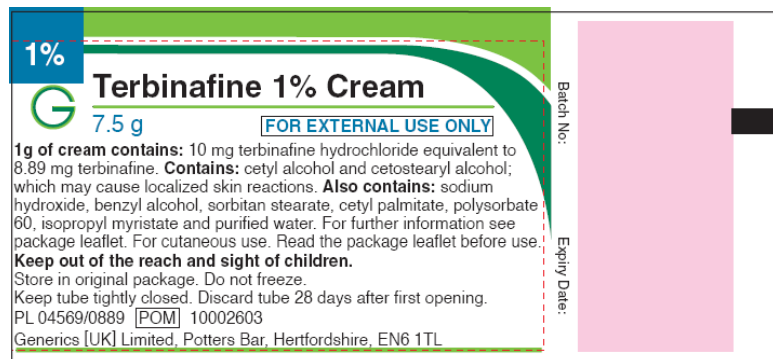
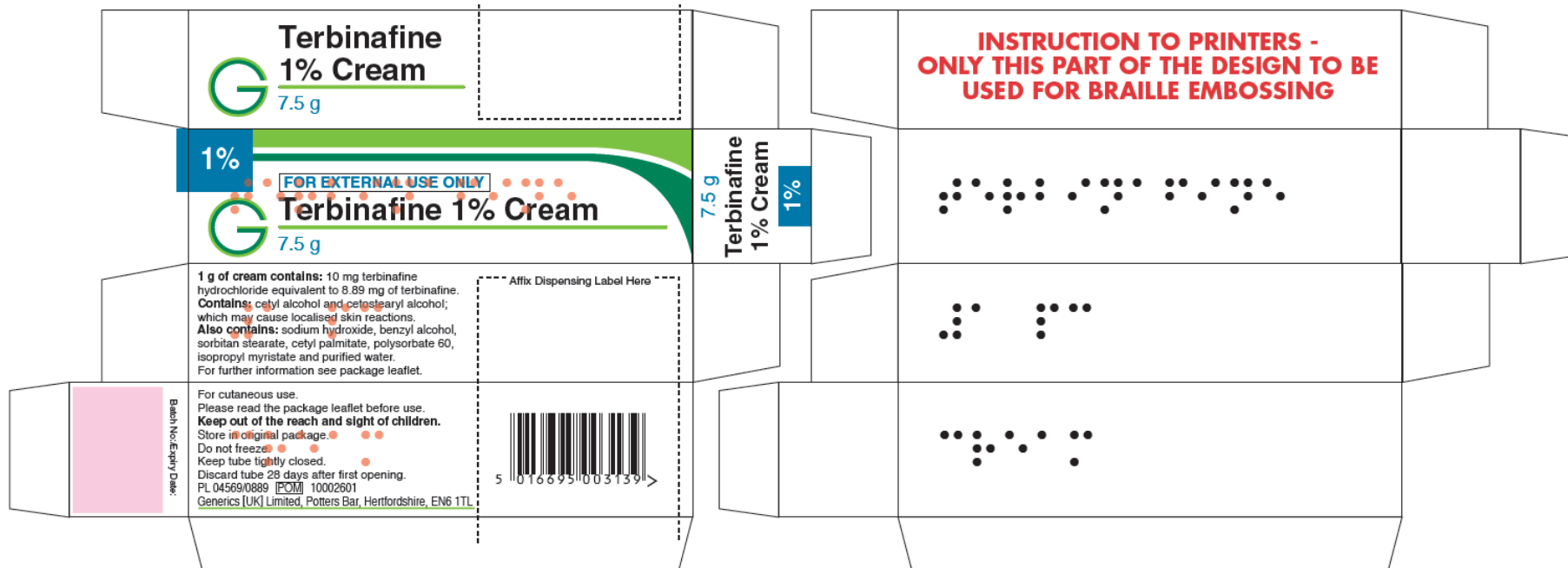
Marketing Authorisation Holder: Generics [UK] Limited, Potters Bar, Hertfordshire, EN6 1TL, UK.

Manufacturer:

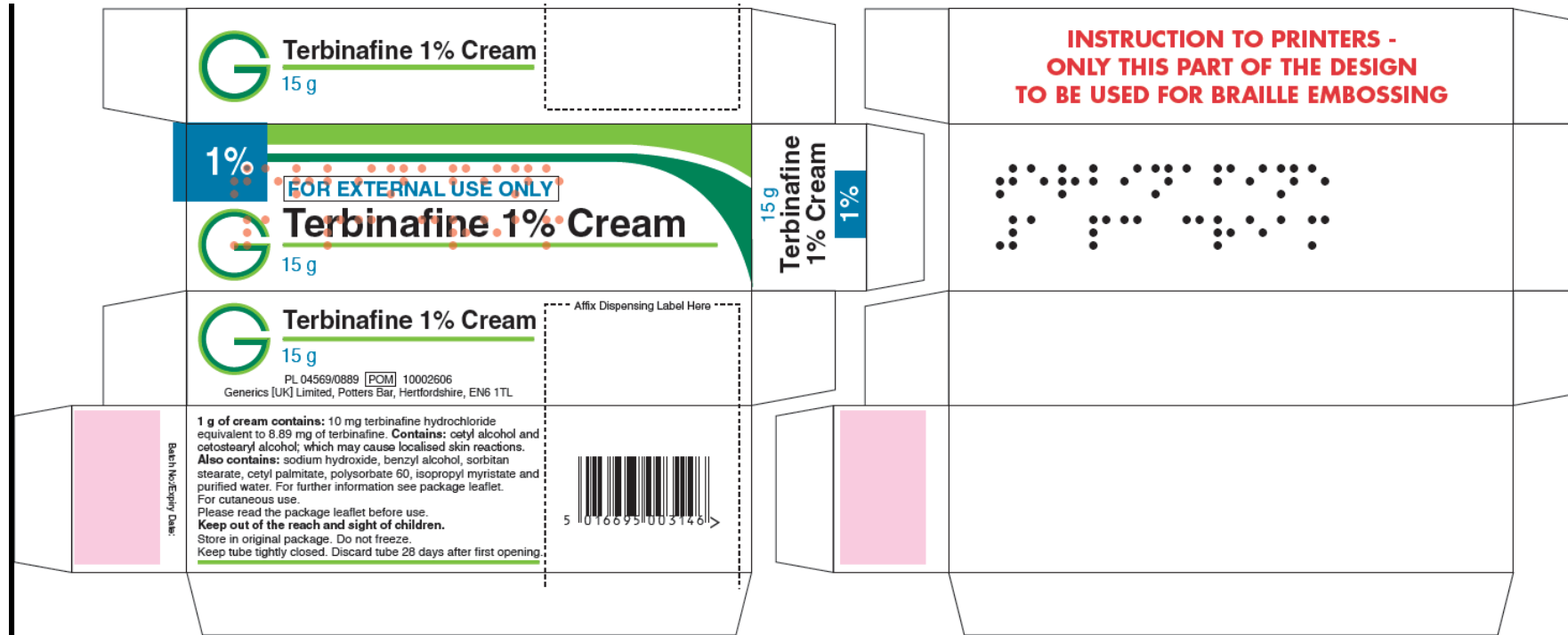
McDermott Laboratories trading as Gerard Laboratories, 35/36 Baldoyle Industrial Estate, Grange Road, Dublin 13, Ireland.

Module 4 - Labelling

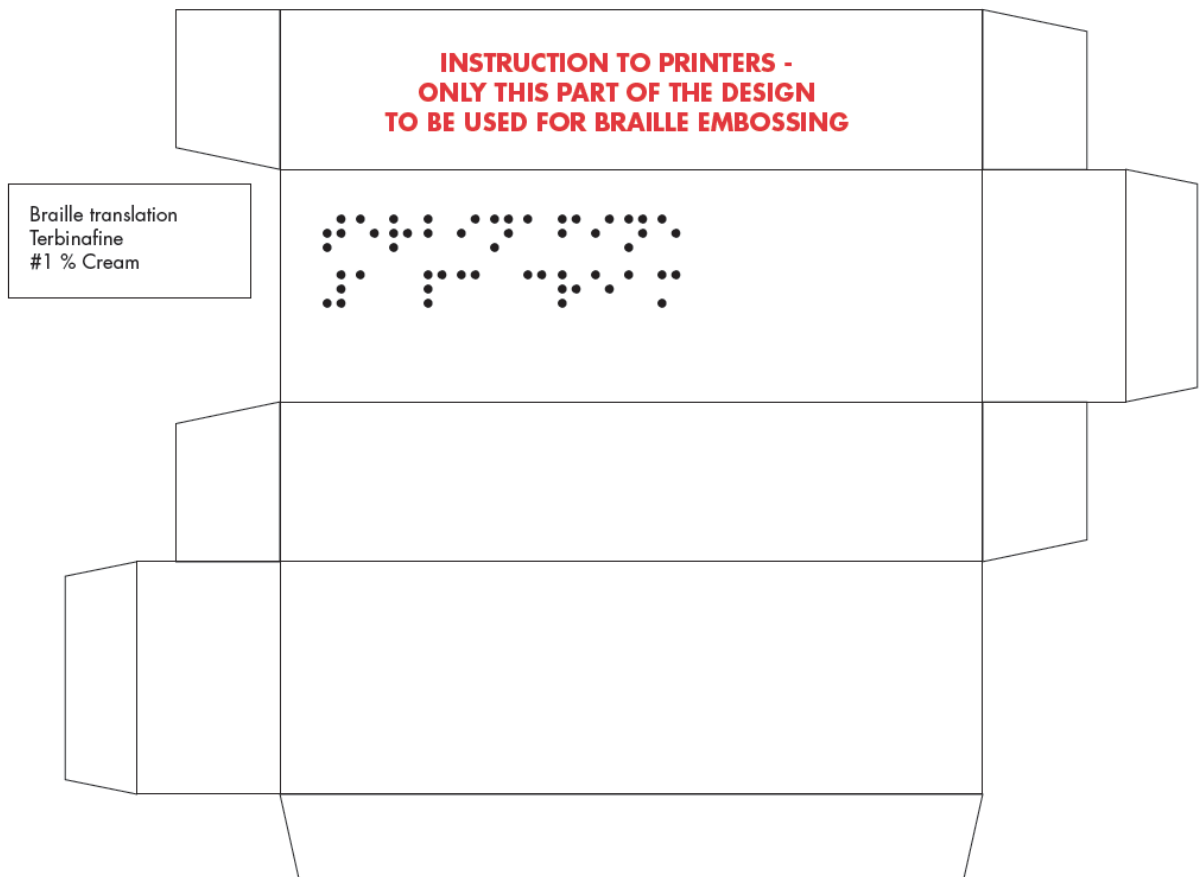
Tube carton and tube label – 7.5mg



Tube carton and tube label – 15mg



Tube carton and tube label – 30mg



1%

G **Terbinafine 1% Cream**
30 g **FOR EXTERNAL USE ONLY**

1 g of cream contains: 10 mg terbinafine hydrochloride equivalent to 8.89 mg terbinafine. **Contains:** cetyl alcohol and cetostearyl alcohol; which may cause localised skin reactions. **Also contains:** sodium hydroxide, benzyl alcohol, sorbitan stearate, cetyl palmitate, polysorbate 60, isopropyl myristate and purified water. For further information see package leaflet. For cutaneous use.

Read the package leaflet before use.
Keep out of the reach and sight of children.
Store in original package. Do not freeze.
Keep tube tightly closed. Discard tube 28 days after first opening.

PL 04569/0889 **POM** 10002605
Generics [UK] Limited, Potters Bar, Hertfordshire, EN6 1TL

Batch No:
Expiry Date:

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Generics [UK] Limited a Marketing Authorisation for the medicinal product, Terbinafine 1% cream (PL 04569/0889, UK/H/1497/001/DC) on 10th February 2010. The product is a prescription-only medicine.

This is an abridged application for Terbinafine 1% cream, submitted under Article 10.3 of Directive 2001/83 EC, as amended. The application refers to the reference medicinal product Lamisil 1% Cream (PL 00030/0421), authorised to Novartis Consumer Health UK Limited on 28th November 2006 through a Change of Ownership. The reference product was originally authorised to Novartis Pharmaceuticals UK Limited on 3rd October 1990. The reference product has been registered in the EEA for more than 10 years, hence the period of data exclusivity has expired. With the UK as the Reference Member State in this Decentralised Procedure, Generics [UK] Limited applied for a Marketing Authorisation for Terbinafine 1% cream in AT, BE, CZ, DE, FI, FR, NL, NO, PL, SE and SI.

Terbinafine 1% cream is indicated for:

- The treatment of tinea pedis (athlete's foot) and tinea cruris (dhotie itch/jock itch)
- Fungal infections of the skin caused by dermatophytes such as species of *Trichophyton* (e.g. *T. rubrum*, *T. mentagrophytes*, *T. verrucosum*, *T. violaceum*), *Microsporum canis* and *Epidermophyton floccosum*.
- Infections of the skin caused by *Candida* (e.g. *Candida albicans*).
- Pityriasis (tinea) versicolor caused by *Pityrosporum orbiculare* (*Malassezia furfur*).

Terbinafine is an allylamine that has a broad spectrum of antimycotic activity. It has an antimycotic effect on 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*. At low concentrations terbinafine has a fungicidal effect against dermatophytes and moulds. Its activity against yeasts is fungicidal (e.g. *Pityrosporum orbiculare* or *Malassezia furfur*) or fungistatic, depending on the species.

Terbinafine interferes specifically with fungal sterol biosynthesis at an early step. This leads to a deficiency in ergosterol and to an intracellular accumulation of squalene, resulting in fungal cell death. Terbinafine acts by inhibition of squalene epoxidase in the fungal cell membrane. Less than 5% of the dose is absorbed after topical application to humans: systemic exposure is thus very low.

Bioequivalence studies are not necessary to support this application. For products for local application intended to act without systemic absorption, the approach to determine bioequivalence based on systemic measurements is not applicable and pharmacodynamic or comparative clinical studies are required. The applicant has submitted a clinical therapeutic equivalence study comparing the test product to the reference. This study is described in the Clinical Aspects section.

A local tolerance study has also been conducted by the applicant, in which no differences in irritancy index or clinical signs were observed between the proposed product and the originator. This study is discussed in the Pre-Clinical Aspects section.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation holder (MAH) has provided adequate justification for not submitting a Risk Management Plan (RMP) and Environmental Risk Assessment (ERA). The lack of an Environmental Risk Assessment is justified since the application is for a generic version of an approved product and it is not likely to change the total market of terbinafine.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Terbinafine 1% cream
Name(s) of the active substance(s) (INN)	Terbinafine hydrochloride
Pharmacotherapeutic classification (ATC code)	Antifungal for topical use (D01A E15)
Pharmaceutical form and strength(s)	Cream 1% (10 mg/g)
Reference numbers for the Mutual Recognition Procedure	UK/H/1497/001/DC
Reference Member State	United Kingdom
Member States concerned	AT, BE, CZ, DE, FI, FR, NL, NO, PL, SE and SI
Marketing Authorisation Number(s)	PL 04569/0889
Name and address of the authorisation holder	Generics [UK] Limited, Potters Bar, Herts, EN6 1TL, United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

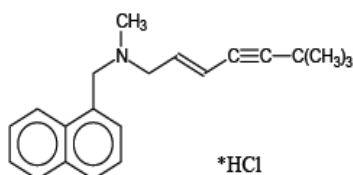
Terbinafine hydrochloride

Nomenclature:

INN: Terbinafine hydrochloride

Chemical name: (2*E*)-*N*,6,6-Trimethyl-*N*-(naphthalen-1-ylmethyl)hept-2-en-4-yn-1-amine hydrochloride

Structure:



Molecular formula: C₂₁H₂₅N.HCl

Molecular weight: 327.9 g/mol

CAS No: 78628-80-5

Physical form: Almost white or pale cream coloured crystalline powder

Solubility: Soluble in absolute ethanol, in ethanol 96%, methanol and chloroform, slightly soluble in water, acetone, 2-propanol, insoluble in toluene and ethyl-acetate

The active substance, oxaliplatin, is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

Synthesis of the active substance from the designated starting materials 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. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

An appropriate specification has been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided for 3 commercial batches and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. It is packed in double polyethylene bags which are closed and sealed separately and placed into sealed drums. Specifications and Certificates of Analysis have been provided for the packaging materials used. The polyethylene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended).

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and support the retest period of 3 years, when stored protected from light.

DRUG PRODUCT

Description & Composition

The drug product is presented as a white or almost white cream with slight almond odour. Each 1g of cream contains 10mg of the active ingredient terbinafine hydrochloride.

Other ingredients consist of the pharmaceutical excipients, sodium hydroxide, benzyl alcohol, sorbitan stearate, cetyl palmitate, cetyl alcohol, cetostearyl alcohol, polysorbate 60, isopropyl myristate, and purified water. Appropriate justification for the inclusion of each excipient has been provided. All excipients have previously been approved for cutaneous use. All excipients used comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The MAH has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product.

There were no novel excipients used and no overages.

Impurity profiles

Comparative impurity profiles were provided for test and reference products. The impurity profiles were found to be similar, with all impurities within the specification limits.

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Satisfactory data were provided for three commercial-scale validation batches. All data were within specification.

Finished product specification

The finished product specifications are provided for both release and shelf life and are satisfactory; they provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory Certificates of Analysis have been provided for three production scale batches of each of the product presentations (7.5mg, 15mg, and 30mg tubes). All parameters are well within specification and comparable. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The drug product is presented in collapsible aluminium tubes with polyethylene screw caps, in pack sizes of 7.5 g, 15g or 30 g. The tubes are packaged individually with the Product Information Leaflet (PIL) into cardboard outer cartons. The MA Holder has stated that not all pack sizes may be marketed. The tubes satisfy the requirements of Directive 2002/72/EC (as amended). Specifications and Certificates of Analysis for all packaging components used have been provided, and are satisfactory.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 4 years has been set, which is satisfactory. The shelf-life after first opening a tube is 28 days. Storage instructions are “Store in original container after first opening. Do not freeze. Keep the tube tightly closed.”.

Bioequivalence Study

Bioequivalence studies are not necessary to support this application. For products for local application intended to act without systemic absorption, the approach to determine bioequivalence based on systemic measurements is not applicable and pharmacodynamic or comparative clinical studies are required. The applicant has submitted a therapeutic equivalence study comparing the test product to the reference. The study is evaluated in the Clinical Aspects section.

Expert Report

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Product Information

The approved SmPC, leaflet, and labelling are satisfactory. Colour mock-ups of the labelling and PIL have been provided. The labelling fulfils the statutory requirements for Braille.

Conclusion

The proposed product, Terbinafine 1% cream, has been shown to be a generic version of the reference product, Lamisil 1% Cream (PL 00030/0421, Novartis Consumer Health UK Limited), with respect to qualitative and quantitative content of the active substance, and the pharmaceutical form. The test product is pharmaceutically equivalent to the reference product, which has been licensed in the UK for over 10 years. Given the route of administration and pharmaceutical form, it is not necessary to demonstrate bioequivalence of the proposed product to the reference product.

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. A Marketing Authorisation was therefore granted.

III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable for this application for a generic version of a product that has been licensed for over 10 years. The non-clinical overview refers to 20 publications up to year 2000 and provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of terbinafine hydrochloride. The CV of the pre-clinical expert has been supplied.

The applicant has conducted a local tolerance study in rabbits to compare the proposed product with the originator which is described below. However, as terbinafine hydrochloride is a widely used, well-known active substance, the applicant has not provided any further studies and an overview largely based on literature review is, thus, appropriate.

Comparative repeated dose dermal tolerance of Terbinafine 1% and Lamisil 1% creams in rabbits (GLP).

Seven-day local tolerance studies were conducted on intact and abraded skin of New-Zealand White Rabbits (6 per group) using 0.5 g of either 1% Lamisil cream, 1% Terbisil cream or respective vehicle controls for 4 hours per day. Following daily exposure the test article was removed and irritancy potential assessed. The test, reference and control creams were all found to be slightly irritant and no differences were observed in clinical signs or irritation index between treatment and control groups. All effects were fully reversible within 8 days.

There were no objections to approval of Terbinafine 1% Cream from a non-clinical point of view.

III.3 CLINICAL ASPECTS

INDICATIONS

The indications are detailed fully in the SmPC and are consistent with those for the reference product.

POSODOLOGY AND METHOD OF ADMINISTRATION

Full details concerning the posology are provided in the SmPC. The posology is consistent with that for the reference product and is satisfactory.

TOXICOLOGY

A local tolerance study has been conducted by the applicant, in which no differences in irritancy index or clinical signs were observed between the proposed product and the originator.

CLINICAL PHARMACOLOGY

The clinical pharmacology of terbinafine hydrochloride is well known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for this application.

Clinical efficacy

To support the application, the applicant has submitted a therapeutic equivalence study.

Assessor's comment: Given the nature of the product, bioequivalence studies are not suitable to show equivalence; the therapeutic equivalence study submitted by the applicant is considered appropriate and therapeutic efficacy will need to be demonstrated.

Therapeutic Equivalence Study

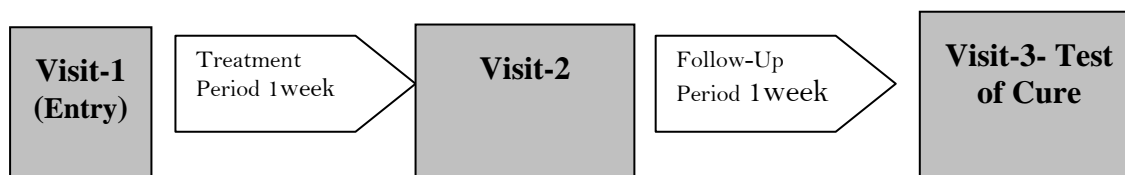
This was a randomised, prospective, comparative, double-blind, active controlled, parallel group, multi-centre (n=36) study. Patients (male and females, 18-80 years) with a clinical diagnosis of interdigital tinea pedis (confirmed by mycological cultures) were included.

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 and 3)
- Score of Clinical signs & 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 assessed.

- Patient's assessment of efficacy.

Statistical methods:

The confidence interval approach to assess 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% \pm). The clinical signs and symptom scores were analysed with the GEE option of Proc GENMOD of SAS system. All tests were two tailed.

Results;

Efficacy evaluation: Mycological cure was achieved in 231 patients (112 terbinafine, 119 lamisil) in the mycological PP population; cure rates of 77.8 % and 78.3% respectively. Calculated CI was -9.9%; 8.9% which was entirely within the equivalence range (-10%; +10%), therapeutic equivalence was concluded.

Analysis of the full mycological population appear to confirm the above results; Cure rates of 70.6% and 71.2 % for generic terbinafine and lamisil respectively, 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 rates at visit 2 and 3; Clinical cure (no residual sign /symptoms) were as follows;

	Terbinafine	Lamisil
V-2	10%	10%
V-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 test product group but not statistically significant. The other secondary efficacy parameters were not statistically significant between treatment groups.

Predominant organisms:

The study primarily included interdigital tinea pedis - majority of patients. Yeast infections were not studied specifically. There was a small proportion of patients where in yeast was demonstrated from scrapings and cultures. The cure rates in these subjects are in the same range as other organisms. However, it is unclear whether the yeast was the primary organism isolated in the culture or as mixture and possibly a contaminant.

Assessor's Comments

It should be noted that mycological cure was assessed in a population that was a fraction of the overall included population (296 of 715; 41%). 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. The expert argues that "non-inferiority criteria" have been satisfied.

There are certain points of issue; Firstly, the protocol was amended on 6 occasions within the 18 month study. The size of the population assessed for primary efficacy was much smaller than the number of subjects enrolled. This could affect the results. It is unclear if this was predetermined sample size. Moreover, there were nearly 5% treatment failures in mycological cure at visit 3. This issue has not been addressed although the table shows this difference. In the statistical analysis, it is stated that assumptions of normality were not fulfilled. These should be detailed.

The clinical expert discusses the choice of the condition to demonstrate therapeutic equivalence. Tinea pedis is notorious for showing a placebo effect of simple improvement in hygiene such as washing feet regularly and possibly a more reliable condition could have been chosen. The expert argues that this indication was chosen because of the great number of patients required by a therapeutic equivalence study. The chosen indication of this study was interdigital tinea pedis based on well-characterised clinical appearance (localisation, consistent size and common occurrence) to gain homogenous study population. These arguments are accepted.

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.

Statistical Assessor's Comments:

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. Clinical consideration is required to determine whether this is usual or whether this gives rise to concerns over the internal and external validities of the study. Approximately 25-30% of patients deviated from an important aspect of the protocol and were hence excluded from the PP populations. Again this is not unusual in this type of study. Nevertheless, the nature of the deviations causing exclusion should be considered. That so many patients are excluded, in particular from the primary analysis, is not a major concern on its own, providing 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 are considered.

The second source of missing data is patients who discontinue during the course of the trial or complete the trial but don't provide a particular assessment. This type of missing data are relatively few in this study.

There were 7 amendments to the trial protocol, all implemented prior to the last patient being recruited and the data being unblinded. 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%). Also amended was the primary endpoint, 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'.

Assessor's Comment:

A primary endpoint should be selected on the basis of clinical relevance rather than statistical power. The sponsor argues that equivalence on mycological cure is sufficient given that the efficacy of both preparations comes from their anti-fungal activity. The choice of primary endpoint should be considered from a clinical perspective. The protocol amendment which implemented the change to the endpoint was introduced without knowledge of accumulating trial data (i.e. interim data) or treatment allocations and is, hence, considered not to introduce worrisome bias. Notwithstanding, it is reassuring that the trial results appear robust to the choice of endpoint – see below. [Note also that the original primary endpoint was not inferior on Terbinafine 1% cream].

The following table summarises the efficacy data:

Endpoint and analysis population	Terbisil	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)

Assessor's Comments:

It is noted that:

- Whilst the estimates of treatment effect vary from -5.0 to 7.3, the majority of analyses support a conclusion of non-inferiority based on $\delta=10\%$. The exception is the mycological cure rates at Visit 2. The rationale for differences between the PP and FAS populations should be further elucidated.*
- A number of the analyses fail to demonstrate equivalence according to the protocol led margin of $\delta=10\%$. This generally happens because the test agent is estimated to be marginally more efficacious than the reference agent. Intuitively it is difficult to consider that any additional efficacy worrisome, unless, of course, it is an indication of additional concerns over safety or tolerability (e.g. is an effect of, for example, greater potency).*
- The lower confidence limit for the primary endpoint is -9.9. Thus, on the primary endpoint selected, the evidence for equivalence is borderline. Such a conclusion is, however, supported by the other analyses performed.*
- There is no placebo arm to put into context the results on the active treatments. It is stated in the trial report that mycological cure rates with placebo would be expected to be less than 30%, based on previous clinical trial data. If the arguments are adequate*

that a placebo rate could not conceivably reach 60-70% then the assay sensitivity of the trial with regards mycological outcome might be verified. A similar argument has not been made with regards clinical outcome or complete cure and this should be provided.

Statistical Assessor's Overall Conclusions

The trial design appears appropriate. The clinical FAS excludes few randomised patients and is hence acceptable (the limited number of exclusions would not be expected to bias in favour of Terbinafine). The remaining analysis populations do exclude a number of patients. It should be considered whether the proportion of patients in the trial found to be mycologically negative at baseline is similar to that expected in this patient population, also whether the exclusions from the per-protocol population were both reasonable and pre-specified.

The contradiction between the FAS and the PP in the analysis of mycological cure at Visit 2 should be investigated, otherwise the primary endpoint provides borderline evidence that Terbinafine is equivalent to Lamisil and a conclusion of non-inferiority is generally supported by the numerous secondary and supportive analyses. The trends toward increased efficacy on some endpoints are only worrisome inasmuch as the formulation may be more potent and, hence, be associated with additional adverse events or problems with local tolerability. One further analysis which would be of value is an assessment of the clinical response in the mycological FAS and PP populations.

As in all applications, two pivotal studies would be preferable. There is borderline evidence of equivalence on the primary endpoint in this study. Whether or not these data can be extrapolated to all indications for Lamisil requires clinical consideration.

Assessor's overall conclusions on clinical efficacy

In a therapeutic equivalence study of a disease subject to large placebo effect, a placebo arm would normally be required.

The clinical expert has provided a justification for the absence of a placebo arm in the study; the design was mirrored to the design of an earlier successful trial to provide external validation. In a double-blind, multicentre, placebo-controlled trial 159 patients were involved with interdigital tinea pedis. Patients were treated with terbinafine 1% cream (Lamisil) twice daily compared with placebo cream twice daily for one week. Mycologic examination and clinical symptoms were assessed at baseline, after one week of treatment and 1, 3 and 5 weeks after cessation of therapy. Authors (Berman, B et al, 1992) found that both terbinafine and placebo cream provided early relief of symptoms. However, only terbinafine gave progressive mycologic improvement. 5 weeks after treatment negative mycology was observed in 88% of the patients, treated with terbinafine cream, compared with 23% of the patients treated with placebo cream. The study was similar regarding indication, treatment schedule, treatment duration and exclusion and inclusion criteria. The clinical expert states that a "mirror" design has been employed. This essentially equates to using previous placebo data as historical control. Providing that the trial designs and patient populations are sufficiently similar, this approach is reasonable, though inferior to a randomised, concurrent control group. The data quoted are "negative mycology" at 5 weeks after treatment (88% for terbinafine, 23% for placebo). This compares to mycological cure of 70-80% in the equivalence trial being considered here. It is not entirely clear that like is being compared to like. The time of the assessment appears to be different, the analysis population quoted is unclear, the precise design and conduct of the study are unclear and, importantly, there is no discussion of the similarity of the two trial populations. Furthermore, only mycological cure rates are reported. Clinical cure rates are not reported. The applicant discusses this below.

a) The active comparator is usually a licensed medicine, which has been evaluated in controlled trials against placebo, perhaps during the phase III studies used to support its marketing application. If the equivalence trial mirrors as closely as possible the methods used in these earlier placebo controlled trials then confidence in its results will be increased, since the methods have been positively validated in a similar context.

b) The **Primary efficacy parameter** was complete cure, as proposed in “Note for Guidance on evaluation of a new anti-bacterial medicinal Product”. The primary target parameter has been changed from Complete cure to Mycological cure. Too many patients need to be included in the trial to prove equivalence with complete cure due to the high drop out rate, which is caused by the negative baseline mycological culture. It is considered to be unreasonable to involve and treat such a large number of patients with a local antimycotic in this trial, without mycological proof of the disease. Therefore an acceptable and reliable primary parameter was selected. The new primary parameter supported the original aim of the study of proving the equivalence between the test and the reference product at a reasonable size of patient population and within an acceptable time frame. Furthermore, therapeutic equivalence can be claimed based on the mycological cure, since the mechanism of action of the two preparations is related to their antifungal activity (referring to the indications from the SmPCs: “fungal infection of the skin caused by Trichophyton, Microsporum canis and Epidermophyton floccosum, yeast infections of the skin”). According to recent literature data the Mycological cure is widely used to establish the effectiveness of topical treatments used for fungal infections of the skin.

c) The equivalence criterion defined in the protocol is related exclusively to the primary parameter.

Mycological cure is a precondition of the clinical cure; it was the reason why antifungal activity was measured as primary parameter.

Mycological cure at Visit 2: according to “Note for Guidance on evaluation of a new anti-bacterial medicinal products (CPMP/EWP /558/95)” microbiological outcomes should be presented and analysed at Test of cure visit (in our study Visit 3) since the results at the End of the treatment visit (Visit 2) are influenced adversely by the presence of antimicrobial agent. In the original protocol there was similar primary endpoint i.e. Complete cure, but the primary target parameter was later changed from Complete cure to Mycological cure because of the high dropout rate requiring the involvement of large number of patients. The selected primary parameter was considered acceptable and reliable. The change of the primary parameter was agreed with the MHRA on the use of a non clinical endpoint as the primary parameter.

Clinical cure was chosen as secondary parameter. Therefore clinical cure rates are not reported in details. However, the fact that equivalence was not demonstrated on some of the secondary parameters does not have any relevance with regard to efficacy, safety or local tolerability.

Assessor’s comments

Ideally this type of trial would have included a placebo arm in order to establish assay sensitivity. However, it may be considered that the mycological response rates evident in the trial are adequate demonstration of assay sensitivity and therefore the absence of a placebo control may be considered less important.

The justification that “mirroring a previously conducted study” supports placebo arm could be criticised as the studies have inherent differences. It is however possible to extend the placebo cure rates to provide some reassurance that the cure rates in the current study were far superior to placebo rates and this could be considered to partially address the point raised.

The efficacy data were collected 2 weeks after the end of the treatment period in the EQUATE study. The efficacy data were collected 5 weeks after the end of the treatment period in the study comparing the originator with placebo (Berman, B et al., 1992). The applicant compares the efficacy of the originator and placebo 2 weeks after the end of the treatment period, below:

The placebo arm is necessary to avoid stating equivalence between non effective treatments and the placebo arm provides internal validity of the trial. Another possibility to ascertain internal validity is through an external validity i.e. to mirror the design of an earlier successful trial of the active comparator with placebo arm as closely as possible. We have chosen the external validation using a mirror study, in which Lamisil proved to be effective regarding clinical and complete cure rates compared to placebo arm. In this double-blind, multicenter, placebo-controlled trial 159 patients were involved with interdigital tinea pedis. Patients were treated with terbinafine 1 % cream twice daily compared with placebo cream twice daily for one week. Mycologic examination and clinical symptoms were assessed at baseline, after one week of treatment and 1, 3 and 5 weeks after cessation of therapy. Authors (Berman, B et al., 1992) found that both terbinafine and placebo cream provided early relief of symptoms. However, only terbinafine gave progressive mycologic improvement. 5 weeks after treatment negative mycology was observed in 88% of the patients, treated with terbinafine cream, compared with 23 % of the patients treated with placebo cream. The post treatment results were reported in the article in the following table:

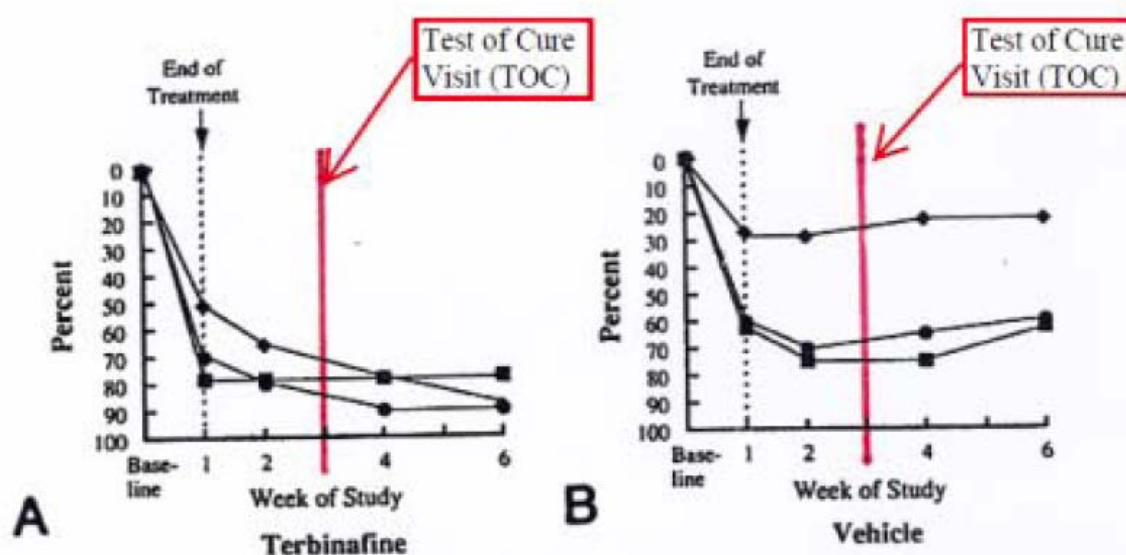


Fig. 1. Relation of symptomatic and mycologic response to terbinafine (A) and vehicle (B) at end of 1 week of treatment and during subsequent 5 weeks of follow-up. Patients considered to have negative mycology are *both* KOH and culture negative. Symptoms evaluated are pruritus and burning/stinging. ●, Percent reduction in pruritus severity score; ■, percent reduction in burning/stinging severity score; ◆, percent of patients with normal mycology.

The differences in treatment groups in rate of conversion from positive to negative mycology were statistically significant in all post treatment observations. Our study was similar

regarding indication, treatment schedule, treatment duration and exclusion and inclusion criteria. The difference in duration of the study was based on valid guidelines. According to CPMP Guideline CPMP/EWP/558/95 (Evaluation of New Anti-Bacterial Medicinal Products), which was valid during the trial, the assessment of outcome of microbiological parameter should be done at the test of cure visit (TOC). This time-point should be the focus of the primary analysis and should be determined based on the assumption that no active drug remains in the treatment site to the sought indication. In case of EQUATE study 2 weeks were chosen for TOC visit. The purpose of 14 days was based on the pharmacokinetics of Lamisil 1% cream (t_{1/2} for Lamisil 1% cream is 35.2 h).

Assessor's comments

From the graphs presented above, the percentage of patients with normal mycology was much higher in the terbinafine arm even at time points earlier than 5 weeks. Lamisil is a licensed product with proven efficacy.

The clinical expert discusses the point made above by the statistical assessor on the contradiction between the FAS and the PP in the analysis of mycological cure at Visit 2. The argument is that the difference was due to the fact that the cure rate among patients who were excluded from the PP population was different from that of the FAS population (in case of both arms). More specifically, in the Terbinafine arm the mycological cure rate among the excluded patients was 41.4%, thus the original FAS cure rate of 64.5% increased to 75.4%. Similarly, in the Lamisil arm the cure rate among the excluded patients was 71.6%, thus the original FAS cure rate of 69.5% decreased slightly (to 68.9%). This explanation is limited to the obvious algebraic facts. The applicant addresses why this might have occurred below.

The calculations of the required sample sizes for equivalence margins of 10% and 15%, with 80% of power, using “mycological cure” and “complete cure” as primary efficacy variables are as follows:

Primary parameter - mycological cure:

for equivalence margins of 10%, power 80%: 370 subjects per group

for equivalence margins of 15%, power 80%: 155 subjects per group

Primary parameter - complete cure:

for equivalence margins of 10%, power 80%: 2100 subjects per group

for equivalence margins of 15%, power 80%: 400 subjects per group

The sample size of 240 subjects per group allowed detecting 10% difference between treatments at power 70%.

Based on the study, therapeutic equivalence was verified. This sample size resulted in a low power. For truly equivalent treatments, there is a higher (45%) probability of not having enough evidence to demonstrate equivalence. The confidence in therapeutic equivalence has been guaranteed by choosing the significance level as 0.05. This means that there is at most 5% chance that the Terbinafine and the Lamisil are not equivalent. On the other hand, this number of patients (296=144+152) would be enough to detect 10% or more difference between the treatment arms.

In case of secondary efficacy parameters the Shapiro-Wilk test showed a significant deviation from the normal distribution thus the non-parametric method was used. This is not unusual statistical behaviour for these type of parameters.

Assessor's comments

The explanation provided by the applicant is accepted. Although there are some issues with the clinical study, the results of the study showed therapeutic equivalence.

The observation period was just two weeks (three visits, one week interval): Considering the chronic-relapsing entity of tinea pedis a follow-up period of at least eight weeks, i. e. an observation period for about twelve weeks for the evaluation of actual mycological and clinical cure rates is more appropriate. The applicant has commented on this below.

The primary analysis focused on post-treatment assessment which was 2 weeks after the last dose has been administered, based on the assumption that no active drug remains on the treatment area; as proposed in "Note for Guidance on evaluation of a new anti-bacterial medicinal product". The late follow-up was not planned; because results could be influenced by relapses, or re-infections which would show a false bias against efficacy.

According to CPMP Guideline CPMP/EWP/558/95 (Evaluation of New Anti-Bacterial Medicinal Products), which was valid during the trial, response to therapy must be based on clinical and microbiological criteria whenever possible. We selected acceptable and reliable microbiological criteria to assess the efficacy based on the mechanism of action of the two preparations being related to their antifungal activity.

The CPMP/EWP/558/95 stated that the assessment of outcome of microbiological parameter should be done at the test of cure visit (TOC). This time-point should be the focus of the primary analysis and should be determined based on the assumption that no active drug remains in the treatment site to the sought indication. In case of EQUATE study 2 weeks were chosen for the TOC visit. The proposal of 14 days was based on the pharmacokinetics of Lamisil 1% cream (t_{1/2} for Lamisil 1% cream is 35.2 h). According to CPMP Guideline CPMP/EWP/558/95 to ascertain eradication of the etiologic agents causing infection, long-term follow-up is mandatory in most infections (endocarditis, osteomyelitis, meningitis); however, this may not be necessary for topically administered medicinal products. Since we had to assess the microbiological efficacy at the test of cure visit we did not include the late follow up visit to assess the late relapses or re-infections.

Assessor's comments

The explanation provided above by the applicant on why the follow-up period was not eight weeks is acceptable. It is accepted that results could be influenced by relapses and re-infections. Furthermore, it appears that for this type of product the observation period applied in this study is commonly used in similar studies.

The applicant chose a valid endpoint based on current guidelines. The main aim of a therapeutic equivalence study for what is essentially a generic product, is to provide a surrogate for bioequivalence – as a typical bioequivalence study cannot be conducted for a topical product. The applicant has proven essential similarity to the reference product. As the reference product is a licensed product with a known efficacy and safety profile, nothing further should be required.

A number of secondary end points did not demonstrate equivalence; with terbinafine showing improved efficacy in certain endpoints. A concern would be that this is due to increased potency and thus affecting the safety profile of the drug. The clinical expert has discussed this issue and concludes that there were no differences between the two groups regarding the incidence of adverse events and the assessment of the tolerability by the patient.

Clinical safety

Terbinafine hydrochloride has an acceptable adverse events profile. 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 AE of severe intensity.

The most frequent adverse event (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 adjudged 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%

As no differences were demonstrated in this reasonably sized study, the expert concludes that there are no safety concerns related to this generic formulation and claims this is supported by the published literature relating to Lamisil.

Assessor's overall conclusions on clinical safety

There are no new safety concerns arising out of the "therapeutic equivalence study" submitted by the applicant. The assessor concurs with the expert that based on the published data relating to Lamisil, no major safety issues exist.

Post-marketing experience

Terbinafine has a well-recognised efficacy and an acceptable level of safety in the indications approved for Lamisil 1% Cream, and corresponding products have been widely used in many countries. Therefore, the submission of PSUR at the renewal of the marketing authorisation is supported. The RMS considers the submission of 6-monthly PSURs not necessary.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPC is consistent with that for the reference product and is acceptable.

Product Information Leaflet (PIL)

The final PIL is in line with the approved SmPC and is satisfactory.

Labelling

The labelling is satisfactory.

Expert report

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

CONCLUSIONS

The grounds for establishing the proposed product, Terbinafine 1% cream, as a generic version of the reference product, Lamisil 1% Cream (PL 00030/0421, Novartis Consumer Health UK Limited), are considered adequate. The product literature is approved.

Sufficient clinical information has been submitted to support this application. All issues have been adequately addressed by the MAH. When used as indicated, Terbinafine 1% cream has a favourable benefit-to-risk ratio. The granting of a Marketing Authorisation was therefore recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Terbinafine 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.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY

The applicant's Terbinafine 1% cream has been demonstrated to be a generic version of the reference product Lamisil 1% Cream (Novartis Consumer Health UK Limited). For products for local application intended to act without systemic absorption the approach to determine bioequivalence based on systemic measurements is not applicable and pharmacodynamic or comparative clinical studies are required. The applicant has submitted a therapeutic equivalence study comparing the test product to the reference. This was accepted.

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The text of the approved SmPCs is satisfactory and consistent with that of the reference product.

A mock-up PIL has been submitted. A user consultation with target patient groups on the package information leaflet (PIL) text has been performed on the basis of a bridging report making reference to Terbinafine Hydrochloride 1 % cream [PL 21300/0002, MPX International Limited], for non-prescription use. The bridging report submitted by the applicant has been found acceptable.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant's Terbinafine 1% cream is a generic version of the reference product, Lamisil 1% Cream (PL 00030/0421, Novartis Consumer Health UK Limited). Extensive clinical experience with terbinafine is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit ratio is considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

There have been no variation applications submitted after approval of the initial procedure.

Date submitted	Application type	Scope	Outcome