LAMISIL ONCE 1 % CUTANEOUS SOLUTION

PL 00030/0213

UKPAR

TABLE OF CONTENTS

LAMISIL ONCE 1 % CUTANEOUS SOLUTION and

PL 00030/0213

LAY SUMMARY

The MHRA today granted Novartis Consumer Health Ltd Marketing Authorisations (licences) for the medicinal products Lamisil Once 1 % Cutaneous Solution and Lamisil NCH 1 % Cutaneous Solution (PL 00030/0213-4). This medicine may be sold to the general public without prescription for the treatment of athlete's foot.

Athlete's foot is a common, persistent infection of the foot, usually caused by a fungus called a dermatophyte. The fungus lives on dead skin, hair and toenails and thrives in warm, moist environments. A variety of treatments for this condition already exist. Lamisil contains the active ingredient Terbinafine, which kills fungus.

The clinical data presented to the MHRA, pre licensing, demonstrated that Lamisil Once 1 % Cutaneous Solution and Lamisil NCH 1 % Cutaneous Solution eradicate the fungal infection and relieve the symptoms of Athlete's foot. There were no clinically significant safety concerns and it was therefore judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.

LAMISIL ONCE 1 % CUTANEOUS SOLUTION

PL 00030/0213

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Lamisil Once 1 % Cutaneous Solution and Lamisil NCH 1 % Cutaneous Solution (PL 00030/0213-4) to Novartis Consumer Health Ltd on 4 November 2005. The products can be obtained without prescription.

These are duplicate, stand-alone, national applications for Lamisil Once 1 % Cutaneous Solution and Lamisil NCH 1 % Cutaneous Solution, containing terbinafine hydrochloride, submitted under Article 8.3 (i) (known active substance) of Directive 2001/83/EC. They are line extensions to the marketing authorisations for Lamisil 125 mg and 250 mg Tablets held by Novartis Pharmaceuticals (UK) Ltd (PL 00101/0303-0304). The applicant states that a subsequent Mutual Recognition Procedure is considered for PL 00030/0214, but not for PL 00030/0213.

Lamisil Once 1 % Cutaneous Solution and Lamisil NCH 1 % Cutaneous Solution contain the active ingredient Terbinafine and are indicated for the treatment of Athlete's foot. Terbinafine inhibits fungal sterol biosynthesis by inhibiting squalene oxidase, causing an increase in intracellular squalene concentrations and subsequent cytotoxicity. Selectivity for fungal cells over mammalian cells is attributed to the presence of ergosterol in fungal cytoplasmic cell membranes, which becomes deficient with squalene oxidase inhibition.

It is recommended that Lamisil be applied once on both feet, even if lesions are visible on one foot only.

This application is the first for a single-dose, cutaneous solution of terbinafine hydrochloride seen in the UK.

PHARMACEUTICAL ASSESSMENT

GMP Statement

Batch release is performed under the control of a qualified person at eight batch release sites for PL 00030/0214 (Lamisil NCH 1 % Cutaneous Solution) and one for PL 00030/0213 (Lamisil Once 1 % Cutaneous Solution). Copies of the relevant manufacturing authorisations have been provided and are satisfactory. The sites for batch release are stated below. Only the first site (1) is proposed for PL 00030/0213.

(1) Novartis Consumer Health, West Sussex, UK
(2) Novartis Consumer Health – Gebro GmbH, Fieberbrunn, Austria
(3) Novartis Healthcare A/S, København Ø, Denmark
(4) Novartis Finland Oy, Espoo, Finland
(5) Novartis Consumer Health GmbH, München, Germany
(6) Novartis (Hellas) S.A.C.I., Athens, Greece
(7) Novartis Norge AS, Oslo, Norway
(8) Novartis Sverige AB, TÄBY, Sweden

Introduction

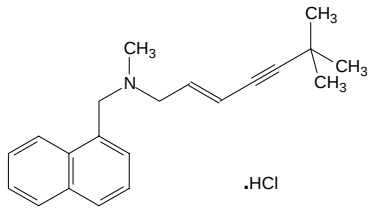
These are duplicate, stand-alone, national applications for Lamisil Once 1 % Cutaneous Solution and Lamisil NCH 1 % Cutaneous Solution, containing terbinafine hydrochloride, submitted under Article 8.3 (i) (known active substance) of Directive 2001/83/EC. These are applications for line extensions to the marketing authorisations for Lamisil 125 mg and 250 mg Tablets held by Novartis Pharmaceuticals (UK) Ltd (PL 00101/0303-0304). The CTD dossiers provided are dated May 2004.

This application is the first single-dose, cutaneous solution of terbinafine hydrochloride seen in the UK.

Terbinafine is an allylamine antifungal agent which, when used topically, is indicated for the treatment of fungal skin infections such as tinea pedis, tinea cruris and tinea corporis. A cream, gel or spray of terbinafine may be sold to the general public from pharmacies in formulations of 1 % maximum concentration, and the cream and spray may be sold elsewhere as they are on the General Sales List. The largest pack size currently available as a P medicine contains 300 mg terbinafine hydrochloride.

ACTIVE SUBSTANCE

The active substance has been assessed in relation to other approved products on the UK market.



INN: Terbinafine
Molecular formula: $C_{21}H_{26}N.HCl$

Mr: 327.89

Terbinafine hydrochloride is a white to off-white finely crystalline powder, which is freely soluble in methanol, soluble in ethanol, sparingly soluble in acetonitrile and slightly soluble in water.

The manufacturing process and controls have been adequately described and appropriate in-process controls and specifications are applied. Appropriate proof of structure has been supplied for the active substance.

There is no monograph for terbinafine hydrochloride in the British Pharmacopoeia, European Pharmacopoeia or United States Pharmacopoeia, but an appropriate specification for terbinafine hydrochloride has been proposed. Known impurities have been identified and characterised and the proposed limits for these are acceptable. Individual unknown and total impurities are controlled to acceptable levels.

The analytical procedures used by the active substance manufacturer were assessed in relation to other approved products with the exception of one method for the determination of an impurity for which satisfactory analytical methodology and validation data are provided. Reference standards are adequately described.

The routine tests performed by the finished product manufacturer on receipt of each batch of terbinafine hydrochloride are provided and are described satisfactorily.

Batch analyses have been supplied for six batches of the active substance. All batches demonstrated compliance to the proposed drug substance specification.

Stability trials were performed in the packaging proposed for marketing and stability data support a retest period of 5 years in the proposed packaging, protected from light.

DRUG PRODUCT

Description and composition of the drug product

The product is presented as a clear to slightly opaque, colourless to slightly yellow viscous solution, having an odour of ethanol. Each gram of the solution contains 10 mg terbinafine as terbinafine hydrochloride (11.25 mg). Other ingredients are acrylates/octylacrylamide copolymer, medium chain triglycerides, hydroxypropylcellulose and ethyl alcohol 96 % v/v.

The proposed container for the product is an aluminium laminated tube (polyethylene-aluminium-polyethylene) with a screw cap in polyethylene. The proposed pack size is 4g.

Novel excipient

The novel excipient, Acrylates/octylacrylamide copolymer (Acrylates/t-octylpropenamide copolymer, CAS no. 129702-02-9) has never been used in a pharmaceutical product in the UK but is listed on the Inventory of Cosmetic

Ingredients (INCI) compiled by the European Commission. The manufacturer's technical information and the Material Safety Data Sheet for the excipient have been provided. The copolymer is a white to off-white free flowing powder that is insoluble in water and soluble in ethanol and acetone. Satisfactory details of the proposed container closure system have been provided.

The manufacturing process for the novel excipient has been adequately described and process controls are documented. Evidence that starting materials are adequately controlled is provided, along with satisfactory confirmation of the proposed structure of the polymer.

The potential impurities in the Acrylates/octylacrylamide copolymer have been discussed and limits for the known impurities have been justified. The proposed specifications for the novel excipient have been provided, which are considered satisfactory for its control. Details of the analytical methods employed to test the Acrylates/octylacrylamide copolymer are provided, with appropriate validation data.

Acceptable batch analysis data have been provided for the Acrylates/octylacrylamide copolymer along with stability data for two batches of the excipient stored in the proposed packaging. Until such time as further long term stability data are provided to demonstrate the satisfactory stability of the excipient, the finished product manufacturer has agreed to retest the excipient prior to use.

Other excipients

All excipients apart from the novel excipient, acrylates/octylacrylamide copolymer (see below), are controlled to the relevant monographs in the European Pharmacopoeia and are tested using pharmacopoeial methods. Satisfactory Certificates of Analysis for the excipients were provided.

A statement is provided from the finished product manufacturer confirming that the product does not contain any material of animal origin, as defined in Guideline EMEA/410/01 rev. 03.

Pharmaceutical development

The aim of formulation development work was to design a single dose topical terbinafine product having greater rub- and water-resistance than conventional topical dosage forms and enhanced properties of dosing frequency and patient compliance.
The choice and function of each excipient has been described and the quantities justified. Stability data were considered adequate to demonstrate the compatibility of the components of the formulation. The formulation was optimised during development studies during which critical parameters for product quality were identified.

Comprehensive studies were performed to determine the compatibility of the product with the proposed container closure system, which is further substantiated by acceptable stability data.

The absence of an applicator with which to apply the product was justified with reference to the mode of application used in product trials. Given that the patient is

instructed to wash their hands following application and that statements are included in the SPC and PIL to this effect, the absence of an applicator in the pack is considered acceptable.

Product manufacture

A satisfactory batch formula has been provided for the manufacture of the product along with an appropriate account of the manufacturing process. No critical steps were identified in the process during development studies. The in process controls are described, with adequate specifications.

The manufacturing process has been validated appropriately at greater than 10 % of the maximum proposed commercial batch size. Results of the validation are acceptable and indicate that the manufacturing process is well controlled. A process validation scheme is provided for commercial scale process validation and a commitment is provided that process validation will be performed on the first three commercial scale production batches.

Control of drug product

The proposed finished product specification is based on the critical parameters identified for product quality in development studies and is in line with ICH guidelines and the Ph.Eur. monograph for liquid preparations for cutaneous application. The tests and limits included in the finished product specification are considered appropriate for the control of the product. Analytical methods used have been suitably validated and batch analysis data demonstrate compliance of the product with the proposed specification. Certificates of Analysis were provided for all of the working reference standards, which are adequately controlled.

Container closure system

The primary packaging material is an aluminium laminated tube (LDPE-Al-HDPE) with a shoulder and screw cap made of HDPE. Specifications for the aluminium-laminated tube with plastic cap are provided, indicating the tests performed upon receipt. Confirmation that the plastic primary packaging material complies with EC guidelines on primary packaging materials and EU food contact regulations has been provided, along with Certificates of Analysis for the packaging components. The packaging is appropriate for the type of product and is satisfactory.

Drug product stability

Stability trials were performed on the drug product stored in the primary packaging as proposed for market. Stability data are acceptable and indicate the long-term stability of the product. No trends were observed in the data, which support a shelf life of 36 months for the product, with no specific temperature requirements. Photostability testing indicated that the primary packaging is adequate to protect the product from light; therefore the statement ‘Store in the original container’ in order to protect from light will be stated on the labelling.

Commitments to continue long-term stability studies up to 60 months and to put the first three production scale batches onto long term and accelerated stability trials according to ICH guidelines have been provided.

Clinical Studies

As the product allows direct delivery of terbinafine hydrochloride to the stratum corneum, clinical studies were performed to support the safety and efficacy of the finished product. Full details of the dosage forms and batches involved in the clinical trials were provided and these were considered acceptable for the purpose. The product used in the Phase III study is considered equivalent to the product intended for the European market. Bioanalytical methods were adequately described and validated.

Legal classification

The proposed legal classification of the products is Pharmacy only, with an age restriction to patients aged 18 years or over.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and labelling

The SPC, PIL and labelling for these products are acceptable pharmaceutically.

ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

The acceptable quality of the proposed products has been demonstrated and it is recommended that Marketing Authorisations are granted for these applications.

PRECLINICAL ASSESSMENT

Introduction

Lamisil Once 1% Cutaneous Solution and Lamisil NCH 1% Cutaneous Solution are topical antifungal agents for the treatment of tinea pedis (athlete's foot) by single dose application. The active substance, terbinafine hydrochloride, is a potent and specific antimycotic, which is fungicidal to the dermatophytes that cause tinea pedis. It works by inhibiting squalene epoxidase, an enzyme essential for fungal ergosterol biosynthesis, thus producing a deficiency in ergosterol and an intracellular accumulation of squalene and cell death.

Terbinafine -containing products have been marketed by the applicant since the 1990s in oral and topical (1% cream, 1% solution/spray and 1% gel) formulations. The topical forms are approved world-wide for the treatment of fungal skin infections caused by dermatophytes (tinea pedis, tinea cruris and tinea corporis, with once daily application for one week) and for pityriasis versicolor. The cream formulation is also approved for the treatment of skin candidiasis.

Lamisil Once 1% Cutaneous Solution and Lamisil NCH 1% Cutaneous Solution use a new and innovative pharmaceutical formulation containing the active substance terbinafine hydrochloride, triglyceride and ethanol and the film-forming agents acrylates/octylacrylamide copolymer in combination with hydroxypropylcellulose. The acrylates/octylacrylamide copolymer is considered as a novel pharmaceutical excipient since it has not been used in medicinal products in Europe until now, although it is used commonly in cosmetic products such as water-resistant sunscreens. Upon application to the skin, the ethanol solvent in the formulation evaporates, leaving a water-resistant, smooth and almost invisible film containing active substance. This film maintains a high concentration of active substance at the surface of the stratum corneum, longer than previous topical formulations.

The nonclinical summaries presented in this dossier included all key data on the pharmacodynamics, pharmacokinetics and toxicology of terbinafine. These studies have already been submitted in previous applications for topical terbinafine products. In addition, this application included a number of new toxicology studies which have been conducted with the formulated terbinafine cutaneous solution product, including repeat dose toxicity, toxicokinetics, and tolerability studies. Furthermore, an extensive program of toxicology studies conducted with the film-forming excipient acrylates/octylacrylamide copolymer was presented, including single and repeat dose toxicity, genotoxicity and local tolerability studies.

Type of application

These are National Applications for Lamisil Once 1% Cutaneous Solution and Lamisil NCH 1% Cutaneous Solution. The applications are considered to be a change of pharmaceutical form for the approved product.

GLP aspects

Most of the nonclinical pharmacology and pharmacodynamic studies were conducted during the 1980s. With some exceptions, these studies were not conducted under GLP. Nonetheless, the quality of the studies in terms of study design and completeness and adequacy of reporting is considered satisfactory.

The toxicology testing program for terbinafine was conducted in compliance with GLP. The toxicology of terbinafine hydrochloride was characterised in a full program of nonclinical toxicology studies, including repeat-dose toxicity in mouse, rat, dog, monkey and minipig; bacterial and in vitro and in vivo mammalian cell genotoxicity; carcinogenicity in mouse and rat; reproductive toxicity in rat and rabbit; with additional studies on the toxicity of impurities and metabolites.

A number of new state-of-the-art toxicology studies with the 1% Cutaneous Solution have been conducted in support of the current application, including single- and repeat-dose dermal toxicology, toxicokinetics and local tolerability studies in rats, rabbits and minipigs; ocular irritation in rabbits; and dermal sensitisation and photosensitisation in guinea pigs. With the exception of the dermal exploratory tolerability study in the minipig, all new studies with this terbinafine cutaneous solution were performed in compliance with GLP.

Key preclinical safety tests with the novel pharmaceutical excipient acrylates/octylacrylamide copolymer were conducted under GLP conditions.

Pharmacology

Assessor's comment

No new studies were performed, which is considered to be acceptable.

Pharmacokinetics

Pharmacokinetic studies

In albino rabbits dosed with non-radiolabeled terbinafine dermally (intact or abraded skin), absorption in terms of plasma concentrations of the major terbinafine metabolite, carboxyterbinafine (CA) was slow after dermal administration (T_{max} 10 to 19 h) and was comparable between sexes. Based on dose-normalized oral/iv AUC ratios of this plasma metabolite, dermal bioavailability was 5 to 9 %, independent of skin condition (intact or abraded). After 14 days repeated dosing, AUC was minimally increased (average 33%) by the dermal routes in both sexes.

Based on total excreted radioactivity in urine and faeces 0 to 240 h after dermal application of a cream formulation to 240 $cm^2$of shaven skin at 10, 20 or 40 $mg \cdot kg^{-1}$, it was reported that the dermal systemic bioavailability of terbinafine in albino rabbits was 37 to 47%.

Based on total excreted radioactivity in urine and faeces 0 to 240 h after dermal application of a cream formulation to 123 cm^2 of shaven skin at 45 $mg \cdot kg^{-1}$, it was reported that the dermal systemic bioavailability of terbinafine in pigmented rabbits was 14%, about one third that reported in the albino rabbit study. Skin pigmentation could be a contributory factor, but the major factor is probably the area of dermal exposure, since systemic bioavailability after dermal application is normally linearly proportional to the area of skin exposed.

Repeat-dose studies in rats and minipigs show that absorption of terbinafine after dermal application of the Terbinafine 1% Cutaneous Solution is negligible (mean C_{max} 13 to 21 nM).

In rats, repeated application of a 1, 5 or 10% terbinafine cutaneous solution to a 30 cm^2 skin area (every other day for 2 weeks) produced plasma terbinafine $C_{max's}$ of 6.0, 21.5 and 122 $ng \cdot mL^{-1}$, respectively. In minipigs (skin area 600 cm^2), the corresponding $C_{max's}$ were 3.7, 2.8 and 4.6 $ng \cdot mL^{-1}$.

There were no consistent sex differences or repeat dose accumulation effects. Absorption of terbinafine was linearly related to cutaneous solution concentration in the rat and under proportional at higher concentrations in the minipig.

In both albino and pigmented rabbits treated dermally with terbinafine cream, excretion was predominantly renal (81 to 88%). This proportion of renal excretion is much higher than after oral dosing in mice and rats, which excrete about 50% of dose renally; whether this is due to species or the route of exposure cannot be decided with these data.

Assessor's comment

The new pharmacokinetic data presented are considered acceptable.

Toxicology

This section covers only the new studies with the Terbinafine Cutaneous Solution, specifically repeat dose dermal toxicity studies in rat and minipig with 1, 5 or 10% terbinafine and local tolerability studies in rabbit (skin and eye) and guinea pig (dermal irritation and photoirritation) using the 10% terbinafine FFS formulation.

Single dose toxicity

One female rabbit died following dermal administration of 1500 $mg \cdot kg^{-1}$.

Assessor's comment

There is insufficient data to say whether or not the dermal route has a different acute toxicity profile to the oral route.

Repeat-dose toxicity

In the 2-week repeat-dose dermal studies with terbinafine 1, 5 or 10% FFS in rat and minipig, there were no systemic effects or pathological changes at any dose. Systemic exposure of treated animals to terbinafine was minimal with this formulation: plasma terbinafine concentration with terbinafine 1% FFS was 3.7 $ng \cdot mL^{-1}$ in rats, 6 $ng \cdot mL^{-1}$ in minipigs.

Genotoxicity and Carcinogenicity

No new studies performed.

Assessor's comment

This is acceptable given the nature of the application.

Reproductive and developmental toxicity

Pigmented Chinchilla rabbits dosed dermally with 3% terbinafine gel revealed no embryotoxicity, fetotoxicity or teratogenicity.

Local tolerance

The local tolerability of a terbinafine 10% Cutaneous Solution was investigated in rabbit (skin and eye) and guinea pig (dermal irritation and photoirritation). In these standard rabbit and guinea pig tolerability studies, only the highest terbinafine FFS formulation concentration (*i.e.* 10% terbinafine) was tested, with the intention of providing "worst-case" conservative hazard estimates for lower concentrations, since any effects at lower concentrations are expected to be smaller. In addition, local dermal tolerability data were obtained in repeat dose dermal toxicity studies in rats and minipigs treated with 1, 5 or 10% terbinafine Cutaneous Solution.

In a rabbit dermal tolerability study with the terbinafine 10% Cutaneous Solution, erythema (also on untreated control sites) and histopathological inflammation (interface dermatitis, including superficial epidermal detachment and scab formation) on terbinafine FFS-treated skin was reported. This suggests skin irritation potential, unlike the good local tolerability reported in rat, minipig, and guinea pig (next paragraphs). However, in this rabbit study, dermal inflammation, epithelial hyperplasia, and hyperaemia were seen on both treated and on untreated control skin sites, *i.e.* also in the absence of terbinafine, strongly suggesting that the occlusion (by gauze bandage) was probably relatively complete in this study.

Addition of the terbinafine 10% Cutaneous Solution to the gauze bandage produced additional dermal effects, namely minimal to moderate subcutis oedema, subepidermal clefts, haemorrhage and necrosis at the dermal-epidermal junction ("interface dermatitis"). A likely cause of the observed effects with the terbinafine Cutaneous Solution in this study was the continued presence of unevaporated solvent (95% ethanol) on the skin due to the occlusive bandaging. Moreover, the product was applied daily for 7 days, whereas this is a single application product.

In an exploratory minipig 2-week dermal tolerability study, 0 and 10% terbinafine Cutaneous Solution and 76% ethanol solvent control applied to different non-

occluded sites resulted in minimal non-dose-related transient focal erythema, more pronounced at 0 and 10% Cutaneous Solution than at the ethanol treatment sites, with minimal focal epidermal necrosis in the female. It was concluded that ethanol has a potential for slight irritation, slightly more pronounced with the 0 or 10% terbinafine Cutaneous Solution, possibly due to greater retention of ethanol on the skin with the formulation. There was a trend to delayed onset and reduced severity of erythema with application every 2 days versus every day.

In the 2-week dermal toxicity studies in rats and minipigs, terbinafine 1, 5 and 10% Cutaneous Solution produced only minimal transient focal erythema in all groups, including controls. Terbinafine FFS was well tolerated in both species and displayed no dermal irritation potential.

In a rabbit ocular tolerability study 10% terbinafine Cutaneous Solution produced moderate reddening of conjunctivae and sclerae, discharge and swelling, and slight to moderate corneal opacities (due to the formulation film), all reversible within 21 days, showing that terbinafine Cutaneous Solution is not irritating to the rabbit eye.

In a guinea pig dermal photo-irritation study, the Cutaneous Solution was well tolerated (no erythema or oedema or any other changes) with or without post-administration exposure to UV light; showing that the terbinafine Cutaneous Solution is not a skin irritant or photo-irritant.

Excipients

No dermal absorption studies could be performed with acrylates/octylacrylamide copolymer because apparently there is no analytical technique that is sensitive enough. Therefore, in lieu, a 4-week oral toxicity test was performed as a worst case scenario, assuming that all of the product could be absorbed.

The excipient acrylates/octylacrylamide copolymer is a novel pharmaceutical excipient, although it is in widespread use as a human dermal cosmetic. Because it is a novel pharmaceutical excipient, an extensive program of single dose (oral, dermal and inhalation) and repeat dose (oral and dermal) toxicity studies have been conducted in rat and rabbit, in addition to the standard set of genotoxicity tests in bacteria, mammalian cells *in vitro* and *in vivo*, to the dermal and ocular tolerability and to the skin sensitisation and photosensitisation.

The single dose oral, inhalation and dermal toxicity studies with the acrylates/octylacrylamide copolymer were conducted by the producer in the 1980s with batches that were not precisely identified. All other tests were recently conducted under GLP conditions and in accordance with modern international guidelines with a defined batch that met manufacturing specifications and stability criteria during its testing period.

The specifications for residual monomer levels will be isobutylmethacrylate: <65 ppm, acrylic acid: <220 ppm and t-octylacrylamide; <375 ppm.

Acrylates/octylacrylamide copolymer has very low oral, dermal and inhalation toxicity.

It was reported that the oral LD_{50} of acrylates/octylacrylamide copolymer in the rat is >5000 $mg \cdot kg^{-1}$. Acrylates/octylacrylamide copolymer produced no systemic or local toxicity in rabbits by single dose dermal administration at 2000 $mg \cdot kg^{-1}$.

Acrylates/octylacrylamide copolymer is not toxic by repeat dose dermal or oral administration to rats.

In a dermal study in rats treated for 4 weeks at up to 500 $mg \cdot kg^{-1} \cdot day^{-1}$, an oral range-finding study in rats treated for 5 days at up to 1000 $mg \cdot kg^{-1} \cdot day^{-1}$, and an oral toxicity study in rats treated for 4 weeks at up to 1000 $mg \cdot kg^{-1} \cdot day^{-1}$ no adverse effects or pathology at any dose were found.

Acrylates/octylacrylamide copolymer displayed no genotoxic potential in the standard battery of genotoxicity tests.

Acrylates/octylacrylamide copolymer is not an eye irritant.

Assessor's comment

It is considered that the acrylates/octylacrylamide copolymer has been sufficiently tested and that no toxicological hazards have been identified.

Ecotoxicity/environmental risk assessment

No risk to the environment is anticipated with this product.

Assessor's overall conclusions on toxicology

There are no new nonclinical concerns identified with the Terbinafine 1% Cutaneous Solution (as the hydrochloride).

The inclusion of the novel excipient acrylates/octylacrylamide copolymer does not raise any nonclinical concerns.

Conclusion

There are no preclinical reasons why a marketing Authorisation should not be granted.

CLINICAL ASSESSMENT

1. INTRODUCTION

1.1 Therapeutic Class

Terbinafine is an allylamine anti-fungal agent.

1.2 Background

This is an abridged application, line extention, for an anti-fungal film forming solution for the treatment of athlete's foot. This is the first UK application for a single-dose, film-forming solution of terbinafine hydrochloride. Terbinafine cream, gel or spray may be sold to the general public from pharmacies in formulations of 1 % maximum concentration, and the cream and spray may be sold elsewhere as they are on the General Sales List.

The company obtained advice from the MCA, August 2002, and from the BfArM, April 2002, and again in February 2003. The MCA agreed with the proposal for a placebo-controlled Phase III trial, but noted that some European member states may request comparative data. It was recommended to include clear usage instructions, including the course of action in cases of relapse. The question of safety in patients with psoriasis of the soles was raised and what to do in case of an allergic reaction. It was noted that POM Exemption Statutory Instrument permits terbinafine 1% external use preparations under 15 g as Pharmacy only (P). The MCA recommended that the new formulation should still be assessed for P status, involving the Post-Licensing Division.

The BfArM recommended that to establish non-inferiority to an approved active comparator, such as Lamisil cream or clotrimazole, Phase III trials should be carried out, even though it would be an open trial, as a double dummy trial would not be possible. It was recommended that the response assessor remained blind to the treatment.

1.3 Regulatory status

These are duplicate, stand-alone, national applications for Lamisil 10mg/g Film Forming Solution, containing terbinafine hydrochloride, submitted under Article 8.3 (i) (known active substance) of Directive 2001/83/EC. They are line extensions to the marketing authorisations for Lamisil 125 mg and 250 mg Tablets held by Novartis Pharmaceuticals (UK) Ltd (PL 00101/0303-0304). The applicant states that a subsequent Mutual Recognition Procedure is considered for PL 00030/0214, but not for PL 00030/0213.

1.4 Indication

From the SPC:

4.1. Therapeutic indications

Treatment for tinea pedis (athlete's foot)

1.5 Dose and dose regimen

On submission, the SPC stated the following:

4.2. Posology and method of administration

Adults and adolescents 15 years of age and over: single administration.

Lamisil FFS film forming solution should be applied once on both feet, even if lesions are visible on one foot only. This ensures elimination of the fungi (dermatophytes) that might be found in areas of the foot where no lesions are visible.

Patients should wash and dry both feet and hands before applying the product. They should treat one foot, then the other.

Starting between the toes, patients should apply a thin layer evenly between and all around the toes, as well as cover the sole and sides of the foot for up to 1.5 cm. The product should be applied in the same way to the other foot, even if the skin looks healthy. The product should be left to dry to a film for 1-2 minutes. Patients should then wash their hands. Lamisil FFS film forming solution should not be massaged into skin.

For the best results, the treated area should not be washed for 24 hours after application. It is therefore recommended to apply Lamisil FFS film forming solution after a shower or bath and wait until the same time the following day before washing the feet again.

Patients should use the quantity they need to cover both feet as instructed above. Any unused medication is to be discarded.

Relief of clinical symptoms usually occurs within a few days. If there are no signs of improvement after one week, patients should see a doctor.

Children:
On submission, the SPC stated that Lamisil FFS film forming solution had not been studied in the paediatric population. Its use is therefore not recommended in children below 15 years of age.

The elderly:
There is no evidence to suggest that elderly patients require different dosages or experience side effects different from those in younger patients.

1.6 Clinical Assessor's Comment

There are insufficient data to recommend treatment for 15-18 year old, therefore the lower age limit should be 18.

Section 4.2 should state that there are no data on repeated treatment and therefore a second treatment cannot be recommended.

2. PHARMACODYNAMICS

2.1 Primary pharmacodynamics

Terbinafine inhibits fungal sterol biosynthesis by inhibiting squalene oxidase, intracellular squalene concentrations increase, causing cytotoxicity. Selectivity for fungal over mammalian cells is attributed to the presence of ergosterol in fungal cytoplasmic cell membranes, which becomes deficient with squalene oxidase inhibition.

There were three efficacy trials: a proof of concept trial using terbinafine 100 mg/g FFS, a phase II trial and a phase III trial (see Efficacy, below).

2.2 Secondary pharmacodynamics

2.2.1 Excipients

The excipients include ethanol as a solvent, medium chain triglycerides and hydroxypropylcellulose. An acrylate - octylacrylamide copolymer (5%) is used as a waterproofing film. This is a novel use for a pharmaceutical formulation, but it has been used in cosmetics, such mascara and sunscreens.

On application, the ethanol evaporates to leave a water resistant film containing the active.

2.2.2 Irritation and sensitisation

There were three studies in healthy volunteers, LANT-DE-113,114 & 115, to evaluate skin irritation, photo-toxic potential, and sensitisation.

LANT-DE-113 (Module 5, vol 8) - irritation

This double-blind, randomised, placebo controlled cumulative irritation study was carried out in Germany in 2003 and enrolled 37 healthy volunteers, of whom 36 completed. The test agent, vehicle or sodium lauryl sulphate was applied to the skin of the back under Finn chambers. There were 10 consecutive patch applications of approximately 5 mg/cm^2 each, total dose 127 mg of terbinafine. Each was left on for 24 h, except for 72 h when over a weekend. The primary analysis was the evaluation of the cumulative Irritation score/10 subjects for a 14 day irritation test with six classes of irritation. The cumulative irritation effect was minimal, with a CIS score of 0.6, compared to the positive control sodium lauryl sulphate score of 58.1, a negative control score of 4.2, or vehicle score of 1.4.

LANT-DE-114 (Module 5, vol 9) - phototoxicity

The primary objective was to study phototoxic potential. This was a single centre, single application, open label, vehicle controlled, German study which enrolled 35 healthy subjects, all of whom completed. Three areas of skin on the back of approximately 2.5 cm^2 were given the test agent or vehicle, or left untreated. After 15 min to allow drying, Finn chambers were applied for 24 h. The Finn chambers were then removed and the two of the three sets were irradiated with UVA or UVA&B. Erythema was assessed by independent blinded observers.

Of the 35 subjects, six subjects showed barely perceptible erythema on nine sites, and two subjects showed mild erythema in two sites compatible with phototoxicity. Most were observed at 24 h. Barely visible erythema was seen 55 times in 21 subjects and mild erythema was seen 22 times in 18 subjects in treated alone, non-treated-non-irradiated, or irradiated alone areas.

The study provides no evidence of phototoxicity attributable to terbinafine, but there was no positive control to confirm that the dose of irradiation was adequate.

LANT-DE-115 (Module 5, vol 8) - sensitisation to Sodium lauryl sulphate

This double-blind, randomised, vehicle controlled study was carried out in Germany in 2003 and enrolled 32 healthy volunteers, of whom 31 completed. The test agent or vehicle were applied to the skin of the back under Finn chambers. There were 11 consecutive patch applications of approximately 5 mg/cm^2 each, total dose 140 mg of terbinafine. There was a one week patch test, induction phase, repeat occlusive applications and evaluations over three weeks, a rest phase of 10 days, a patch challenge test at one week, and a re-challenge test if required. Sodium lauryl sulphate 2.5% (SLS) given at baseline, at the induction phase, in the challenge phase, and, if necessary, in the re-challenge phase. There was an eight point irritation scale and sensitisation was assessed 48-72 h after each induction application at 2,3,4,5 & 7 days after challenge test application. The Cumulative Irritation score/10 subjects was 32.8, 37.8 and 40.6 for SLS+terbinafine, SLS+vehicle, or SLS alone.

The results show no sensitisation by terbinafine or vehicle to the irritant response to sodium lauryl sulphate.

2.3 Pharmacodynamics - Clinical Assessor's comments

The irritation and sensitisation studies appear well designed and data are reassuring.

There was no evidence of phototoxicity attributable to terbinafine, but there was no positive control to confirm the dose of irradiation was adequate. This is considered to be satisfactory as no photo safety issue has been identified with other forms of topical terbinafine.

3. PHARMACOKINETICS

3.1 Systemic absorption

Systemic absorption was measured in two studies, LANT-DE-111 and LANT-DE-112.

LANT-DE-111 (Module 5, vol 6) - healthy volunteers

This study measured the plasma concentration of terbinafine in 20 subjects after one application of terbinafine 1% FFS. It was a Swiss, open label, study where three tubes of 4 g terbinafine were applied to a large area of the back equivalent to three times the surface area of both feet. A LC-MS assay was used with a limit of detection of 1 ng/ml. Sampling was initially every 30 min, then at longer intervals up to 168 h post dosing. Plasma concentrations of terbinafine were below the limit of detection in 11/20 patients. In the remaining 9, terbinafine was only detected at one sampling time, all between 2 h and 168 h after application. From the peak concentration it was calculated that drug exposure was <0.5% of the exposure from a single 250 mg tablet of terbinafine given orally.

LANT-DE-112 (Module 5, vol 7) - tinea pedis

This study measured the plasma concentration of terbinafine in patients with tinea pedis after one application of terbinafine 1% FFS. There were 14 patients who enrolled and all completed the study. A single application of 5 mg/cm^2 was given to both feet. Plasma was sampled and analysed as for LANT-DE-111, above. The mean dose applied was 3.6 g, corresponding to 36 mg of terbinafine. Only one patient had a detectable plasma concentration, of 1.1 ng/ml 12 h after administration.

3.2 Bioavailability, distribution and half-life

LANT-DE-103 (Module 5, vol 7) - skin residence
This study attempted to measure skin residence time in two subjects after one application of terbinafine 10% FFS. None of the four tests in the exploratory phase could assess residence time. The tests used were Fourier-transformed infrared spectroscopy, chronometry, transepidermal water vapour gradient, and photography.

LANT-DE-104 (Module 5, vol 1) - skin penetration
This study measured skin penetration, residence time and resistance to washing in six subjects after one application of terbinafine 5% FFS. The primary objective was to measure penetration into the stratum corneum. There were four treatment groups of terbinafine 5% not washed, terbinafine 5% washed at 30 min, terbinafine 5% washed at 12 h, and Lamisil cream applied for four days. Treatments were applied to the back over an area 8x16 cm and the comparisons were intra-subject.

The concentration of terbinafine in removed film was measured initially hourly then less frequently up to 96 h. The recovery from the film was 100% at 1 h falling to 19% by 24 h. Approximately 24 times more terbinafine was recovered from the film in 24 h than from Lamisil cream. At 24 h the mean terbinafine concentration on the skin surface was 17% of the applied dose and 2% at 48 h. The amount of terbinafine delivered to the stratum corneum over the first 24 h was 16%, 14%, 6% and 2% of the dose at each time point for the film, compared to 6%, 4% 1% and 0.3% for the same time points for the cream. Washing at 30 min reduced the mean terbinafine concentration on the skin surface under the film by 86%. Washing at 12 h reduced the remaining mean terbinafine concentration on the skin surface under the film by 98%. The concentration of drug in the lower stratum corneum compared to the upper was about 16% to 39% at times between 1 h and 24 h. The amount of terbinafine in stratum corneum at 12 h is >10 μg/cm^2 after a single application of 5% FFS, decreasing to 0.3 μg/cm^2 at 96 h. The mean concentration at 96 h is higher than at 24 h after application of Lamisil cream.

LANT-DE-107 (Module 5, vol 2-3) - occlusion
This study measured the effect of occlusion and removal of the film on skin penetration in 12 subjects after one application of terbinafine 5% FFS. It was an intra-subject comparison of terbinafine 5% FFS under standard conditions and under occlusion. The primary endpoint was to measure kinetics in the stratum corneum. A single dose of 640 mg was given to each of four areas of 128 cm^2. There were 11 successive skin strippings with D-squame on the same area with a detection limit by LC/MS/MS of 2.5 ng/disk, or 0.7 ng/cm^2

The concentration of terbinafine decreased rapidly over 24 h followed by a less rapid decline over 24-96 h. The C_{max} in the stratum corneum occurred at 2 h and was 18% of the applied dose. Penetration into the lower stratum corneum was 18-31% of the total in the stratum corneum. The concentration of terbinafine in the stratum corneum was considered much higher than the minimum inhibitory concentration against dermatophytes. Under normal application, terbinafine persisted 48-72 h on the skin but 72-96 h under occlusion. Occlusion, comparable to inter-digital areas, increased concentrations about 2.7 fold.

LANT-DE-110 (Module 5, vol 4) - stratum corneum
This study measured bioavailability of terbinafine in 18 subjects after one application of terbinafine 1% FFS. The primary objective was to study stratum corneum concentrations of terbinafine by skin stripping. A single application of terbinafine 1% FFS was compared to Lamisil cream 1% applied daily for seven days. The sampling focused on the elimination phase with samples at 4 h, 24 h, 48 h and multiple time points up to 312 h post application.

After a single application of terbinafine 1% FFS the amount of terbinafine recovered in stratum corneum expressed as % of applied dose was 53% at 4 h, decreasing to 6% at 24 and 48 h and <1% at 72 h. The concentration of terbinafine with the FFS preparation was 4-24 times higher than the concentration after the application of seven doses of Lamisil cream at the same time points. Even by 312 h, the applicant considered the minimum inhibitory concentration of terbinafine for dermatophytes, 1 ng/ml, to be exceeded. At 312 h, the stratum corneum concentration was 24 ng/cm^2 which, assuming a thickness of 0.1 mm, gives a concentration in skin of 2.4 µg/ml. The concentration measurements over time suggest that the film stays on the skin for approximately 72 h. Very roughly, a single application of the film probably delivers about five times more terbinafine than seven daily applications of Lamisil cream to the stratum corneum.

3.3 Metabolism and excretion
Same as terbinafine in currently marketed products.

3.4 Special groups
Pharmacokinetics within the stratum corneum are considered unlikely to be affected in subpopulations, see clinical expert report.

3.5 Kinetic interactions
Considered unlikely because of low systemic availability, see clinical expert report**.**

3.6 Pharmacokinetics - clinical assessor's comment
Rough calculations suggest a single application of the film delivers about five times more terbinafine to the stratum corneum than seven daily applications of Lamisil cream.

4. EFFICACY
4.1 General and GCP
The company states that all trials adhered to GCP guidelines. There were three randomised, placebo controlled, parallel group, studies in patients with tinea pedis, listed below. See also see clinical expert report**.**

Patients with chronic, hyperkeratotic plantar tinea pedis were excluded, as they would require oral therapy.

4.2 Studies CSFO327 2201, LANT-DE-201 & LANT-DE-305
Study CSFO327 2201, (Module 5, vol 10)- proof of concept
This was a proof of concept study using terbinafine FFS 10% (called in the trial protocol Lamisil NTF (new topical formulation).

It was a randomised, double-blind, placebo controlled, parallel group, single centre study in patients with inter-digital tinea pedis confirmed by direct microscopy.

There were 85 patients enrolled after delayed exclusions, all of whom received the drug. Only 53 patients were analysed in the main per protocol and ITT analysis. The reason for omission was that cultures taken on day 1 were missing or negative for dermatophytes. Patients were issued with a 10 g size tube, although for later trials a 4 g tube was produced, as this was found sufficient.

The primary efficacy variable was a composite of negative microscopy + negative culture + total signs and a symptoms score of ≤2, provided no individual sign or symptom was >1. This was assessed at week four visit.

The results indicate an effect on the primary endpoint compared to placebo, P=0.052. Treatment was more effective than placebo on microscopy and culture, P<0.001., and there was a trend to clinical improvement, P=0.083. There was no significant difference between the two groups in clinical cure rate, defined as total signs and symptoms score of 0. Effective treatment rate was 43% for terbinafine 10% and 17% for placebo. The negative culture and negative microscopy rates were both 97% for terbinafine and 33% and 39%, respectively, for placebo.

Study LANT-DE-201, (Module 5, vol 11)- dose finding
This was a randomised, double-blind, placebo controlled, parallel group, dose response, multi-centre Phase II study in patients with inter-digital tinea pedis confirmed by direct microscopy. It was carried out in France and Bulgaria.

It was a dose finding study with five arms of terbinafine 1%, 5%, 10% FFS, vehicle (one application to both feet), and Lamisil 1% cream as an open label active comparator (7 days once a day).

There were 536 patients randomised and treated. After 115 delayed exclusions, 421 patients received the drug. Of these, four were lost to follow-up leaving 417 in the full analysis set. There were twice as many men as women. The mean age was 42 years, range 11-81. The per protocol set contained data on 397 patients.

The primary efficacy variable, effective treatment rate, was assessed at week 6. The pathogens detected were mostly T. rubrum (52-79% of cases, depending on treatment arm) or T. inter-digitale. Approximately 80% had lesions on both feet and about 25% had lesions extending to the soles or side of feet.

In the PPS the mycological results at week 6 were:

Fig 1.Number and % of patient with negative microcroscopy and culture, week 6

	neg microscopy		**neg culture**		**neg micro + culture**		
	n	**%**	**n**	**%**	**n**	**%**	**95% CI**
Ter 1% FFS (N= 107)	77	83%	90	97%	77	83%	75-91
Ter 5% FFS	82	83%	87	88%	79	80%	72-88

(N= 99)							
Ter 10% FFS (N= 93)	93	87%	97	91%	90	84%	77-91
Vehicle	19	42%	15	33%	12	27%	14-40

The mean signs/symptoms score at baseline varied from 5.0-5.4 and fell to 1.5, 1.3, 1.5 and 3.0 for terbinafine 10%, 5%, 1% FFS and vehicle respectively by week six. The differences between doses were not significant. The 95% CI for terbinafine 1% was 1.2-1.9 and for vehicle 2.3-3.7.

In the full analysis set of data the effective treatment rates at week six were 65%, 68%, 59% and 17% for terbinafine 1%, 5%, 10%, and vehicle. All three active treatments were significantly better than placebo.

The effective treatment rates for Lamisil cream 1% were 41% (28-55, 95%CI) at week one and 76% (64-87%) at week six. The negative microscopy, culture and mycological cure rates at week six for Lamisil cream 1% were 96%, 94% and 94%.

Study LANT-DE-305, (Module 5, vol 12)
This was a randomised, double-blind, placebo controlled, parallel group, single dose, multi-centre Phase III study in patients with inter-digital tinea pedis confirmed by direct microscopy. It was carried out in France (27 centres) and Germany (27 centres).

The primary efficacy variable was eradiation of fungal infection and relief of symptoms and signs by week six, terbinafine FFS 1% compared to placebo.

There were 324 patients randomised, 223 to terbinafine FFS 1% and 101 to FFS vehicle. There were 51 (16%) delayed exclusions because of lack of confirmation by culture. Of the 273 patients in the full analysis set, 252 (92%) completed to week six. There were 21 discontinued, of whom 11 were lost to follow-up and five had unsatisfactory efficacy. Discontinuation rate prior to week six was 7.9% for terbinafine and 7.2% for placebo.

The average age was 43 years, range 12-82, with only six patients less than 20 years old. The mean duration of tinea pedis was 5-6 years, median 2-4, with median duration of current infection 7-9 weeks. For the majority, the infection was bilateral and about 40% had lesions extending to the soles or side of feet. T. rubrum was present in 73%, T. inter-digitale in 20%, both in 3%. Most patients had mild to moderate erythema, pruritis and scaling, but only 8% had pustules. Some 96% of patients applied the treatment in the active group and 98% in the placebo group.

The primary endpoint was reached in the full analysis data set in 63% of terbinafine patients and 17% on placebo, which was highly significant.

At one week, the negative culture rate was 71% for terbinafine and 28% for placebo; the negative microscopy rate was 27% for terbinafine and 16% for placebo.

At six weeks, the negative culture rate was 83% for terbinafine and 33% for placebo; the negative microscopy rate was 74% for terbinafine and 25% for placebo.

4.6 Efficacy - clinical assessor's conclusions

The proof of concept study illustrates that terbinafine FFS is effective. Subsequent dose response data show that a 1% concentration is as effective as 10%, with similar efficacy to Lamisil 1% cream applied daily for seven days.

It is possible that a lower concentration of terbinafine could be equally effective as 1% FFS.

The stratum corneum data indicate that even two weeks after dosing, the minimum inhibitory concentration of terbinafine for dermatophytes is exceeded. Very roughly, a single application of the film probably delivers about five times more terbinafine than seven daily applications of Lamisil cream to the stratum corneum. It is likely that a concentration of 0.2% FFS could be as effective as 1%.

The number of patients studied between the ages of 15 - 18 is inadequate for a risk benefit assessment. The age limit in Section 4.2 was therefore amended to "Adults aged 18 years of age and over".

The possibility of re-treatment, or the management of repeat or resistant infections, was not investigated, therefore section 4.2 was amended to state that there are no data on repeated treatment and a second treatment cannot be recommended.

5. SAFETY

5.1 Population exposed

In the 12 controlled studies there were 162 healthy volunteers and 959 patients with athlete's foot. Of these, 142 volunteers and 371 patients received terbinafine 1% FFS. Single applications were followed for six weeks in the two main trials. More than one application has not been studied.

5.2 Deaths

There was one death from stroke in a patient on placebo.

5.3 Serious adverse events

Serious adverse events were reported in two patients, hernias, not thought to be related to study medication.

5.4 Non-serious adverse events

The overall adverse events rates were 9%, 11%, 8% and 12% for terbinafine 1%, 5%, 10% and vehicle FFS. Most frequent adverse events were no more common with active than vehicle control, these results were presented in the clinical expert report **Page 66**. Sensitisation, irritation and phototoxicity were studied separately in secondary pharmacology studies, see above.

5.5 Withdrawals

There were no patient withdrawals because of safety concerns.

5.6 Laboratory safety

There were no significant laboratory changes associated with terbinafine. Two patients had urinary tract infections which were thought to be unrelated to study medication. Laboratory parameters were measured in 55 healthy volunteers and 14 patients in preliminary pharmacology studies. Because of the lack of significant absorption, laboratory parameters were not measured in the main efficacy studies. There were no significant ECG changes.

5.7 Special groups
There were only three children included below the age of 15.

5.8 Drug interactions
Not studied and probably not relevant.

5.9 Post marketing surveillance
Not available.

5.10 Overdose
LANT-DE-111 (Module 5, vol 6)
This study measured the plasma concentration of terbinafine in 20 subjects after one application of terbinafine 1% FFS, where three tubes of 4 g terbinafine were applied to a large area of the back equivalent to three times the surface area of both feet. There were nine cases of pruritis, three of feeling hot, one burning, and one of nausea. All were mild except for one case of moderate back pain. All were suspected of being related to the study drug and disappeared within one week with no treatment. The total dose of the tube is small compared to one oral tablet.

5.11 Post-marketing surveillance
Not yet marketed. Topical Lamisil has been used by an estimated 186 million patients, including 59 million between 1999 and 2003. Rare allergic reactions have been reported.

5.12 Safety – non-prescription status
Lamisil cream, solution/spray and DermGel have been approved in 51, 47 and 35 countries, respectively. The Company's justification for Pharmacy status appears adequate.

5.13 Safety – clinical assessor's comment
Although it is likely that a lower concentration of terbinafine could have been used, the safety profile for the single application of 1% FFS does not appear to be a concern. Additional post-marketing data from Lamisil cream, solution/spray, provide additional reassurance.

The safety data appear sufficiently reassuring to grant non-Prescription Only Medicine status and Pharmacy (P) status is recommended.

7. EXPERT REPORT
This was written by a suitably qualified expert.

8. SUMMARY OF PRODUCT CHARACTERISTICS

8.1 The number of patients studied between the ages of 15 - 18 is inadequate for a risk benefit assessment, therefore the age limit in Section 4.2 was changed to "Adults aged 18 years of age and over".

8.2 Following recommendation by the medical assessor, Section 4.2 now states that there are no data on repeated treatment and a second treatment cannot be recommended.

9. PATIENT INFORMATION LEAFLET

Following assessment, the following changes were made to the patient information leaflet:
In the description of the product, "opaque viscous solution" was changed to "cloudy liquid".
Section 1 - change "can extend to adjacent areas of" to "can spread to".
Section 2 - change "external use only" to "treating the skin of the feet only".
Section 3 - change the reference from 15 to 18.
Section 3 - add to the end "do not use the product a second time if it did not work"

10. PRECLINICAL ASSESSMENT

There are no new non-clinical concerns identified with Terbinafine 10 mg/g (1%) Film Forming Solution (as the hydrochloride).

The inclusion of the novel excipient acrylates/octylacrylamide copolymer does not raise any non-clinical concerns.

11. CONCLUSIONS

It is possible that a lower concentration of terbinafine could be equally effective as 1% FFS.

The stratum corneum data indicate that even two weeks after dosing, the minimum inhibitory concentration of terbinafine for dermatophytes is exceeded. Very roughly, a single application of the film probably delivers about five times more terbinafine than seven daily applications of Lamisil cream to the stratum corneum. It is likely that a concentration of 0.2% FFS could be as effective as 1%.

Overall, Lamisil FFS 1% is clearly more effective than vehicle and a single application is approximately as effective as seven daily applications of Lamisil 1% cream.

The safety data appear sufficiently reassuring to grant non-Prescription Only Medicine status and Pharmacy (P) status is recommended.

The risk-benefit appears favourable.

12. PRE-CLINICAL AND CLINICAL ASSESSORS' RECOMMENDATIONS

It is recommended that marketing authorisation is granted provided the product particulars are modified as requested above. Pharmacy (P) status is recommended.

SPC Lamisil

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

1. Oral LAMISIL is indicated in the treatment of ringworm (Tinea corporis, Tinea cruris and Tinea pedis) where oral therapy is considered appropriate due to the site, severity or extent of the infection.
2. Oral LAMISIL is indicated in the treatment of Onychomycosis.

4.2. Posology and method of administration

Adults

250mg daily

The duration of treatment varies according to the indication and the severity of the infection.

Skin infections

Likely durations of treatment are as follows:

Tinea pedis (inter-digital, plantar/moccasin type):	2 to 6 weeks
Tinea corporis:	4 weeks
Tinea cruris:	2 to 4 weeks

Onychomycosis

The duration of treatment for most patients is between 6 weeks and 3 months. Treatment periods of less than 3 months can be anticipated in patients with fingernail infection, toenail infection other than of the big toe, or patients of younger age. In the treatment of toenail infections, 3 months is usually sufficient although a few patients may require treatment of 6 months or longer. Poor nail outgrowth during the first weeks of treatment may enable identification of those patients in whom longer therapy is required.

Complete resolution of the signs and symptoms of infection may not occur until several weeks after mycological cure.

Children

A review of safety experience with oral LAMISIL in children, which includes 314 patients involved in the UK LAMISIL Post Marketing Surveillance study, has shown that the adverse event profile in children is similar to that seen in adults. No evidence of any new, unusual or more severe reactions to those seen in the adult population have been noted. However, as data is still limited its use is not recommended.

Use in the elderly
There is no evidence to suggest that elderly patients require different dosages or experience side-effects different to those of younger patients. The possibility of impairment of liver or kidney function should be considered in this age group (see Precautions).

Method of administration
Via the oral route.

4.3. Contra-indications
Hypersensitivity to LAMISIL.

4.4. Special warnings and special precautions for use
Rarely, cases of cholestasis and hepatitis have been reported, these usually occur within two months of starting treatment. If a patient presents with signs or symptoms suggestive of liver dysfunction such as pruritis, unexplained persistent nausea, anorexia or tiredness, vomiting, fatigue, abdominal pain or dark urine, or pale stools hepatic origin should be verified and LAMISIL therapy should be discontinued (see 4.8 Undesirable effects).

Single dose pharmacokinetic studies in patients with pre-existing liver disease have shown that the clearance of LAMISIL may be reduced by about 50%. The therapeutic use of LAMISIL in patients with chronic or active liver disease has not been studied in prospective clinical trials, and therefore cannot be recommended.
LAMISIL should be used with caution in patients with psoriasis, as very rare cases of exacerbation of psoriasis have been reported.

Patients with impaired renal function (creatinine clearance less than 50ml/minute or serum creatinine of more than 300 μmol/l) should receive half the normal dose.

4.5. Interactions with other medicinal products and other forms of interaction
The plasma clearance of terbinafine may be accelerated by drugs which induce metabolism (such as rifampicin) and may be inhibited by drugs which inhibit cytochrome P450 (such as cimetidine). Where co-administration of such agents is necessary, the dosage of LAMISIL may need to be adjusted accordingly.

In vitro studies have shown that terbafine inhibits the CYP2D6-mediated metabolism. This in vitro finding may be of clinical relevance for patients receiving compounds predominantly metabolised by this enzyme, such as tricyclic antidepressants (TCAs) ß-blockers, selective serotonine reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAO-Is) Type B.

Other studies undertaken in vitro and in healthy volunteers suggest that terbinafine shows negligible potential to inhibit or induce the clearance of drugs that are metabolised via other cytochrome P450 enzymes (e.g. Cyclosporin, Tolbutamine, Terfenadine, Triazolam, oral contraceptives). However, some cases of menstrual disturbance (breakthrough bleeding and irregular cycle) have been reported in patients taking LAMISIL concomitantly with oral contraceptives.

4.6. Pregnancy and lactation

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

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

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

4.7. Effects on ability to drive and use machines

None.

4.8. Undesirable effects

Frequency estimate: very common ≥ 10%
common ≥ 1% to< 10%, uncommon ≥ 0.1% to < 1%,
rare ≥ 0.01% to < 0.1%, very rare < 0.01%

Side effects are generally mild to moderate, and transient. The most common are gastrointestinal symptoms (dyspepsia, fullness, loss of appetite, nausea, mild abdominal pain, diarrhoea), allergic skin reactions (rash, urticaria) and headache.

Musculo-skeletal disorders including arthralgia and myalgia have been reported. These may occur as part of a hypersensitivity reaction in association with allergic skin reactions.

Rare cases of serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity and angioneurotic oedema) have been reported. If progressive skin rash occurs, LAMISIL treatment should be discontinued.

Uncommon: taste loss and taste disturbance have been reported in approximately 0.6% of patients treated with LAMISIL. This usually resolves slowly on drug discontinuation. Very rare cases of prolonged taste disturbance have been reported, sometimes leading to a decrease of food intake and significant weight loss

Rare cases of serious hepatic dysfunction, including jaundice, cholestasis and hepatitis have been reported. if hepatic dysfunction develops, treatment with LAMISIL should be discontinued (see also precautions).

Rare: paraesthesia, hypoaesthesia, dizziness, malaise and fatigue

Very rare: Haematological disorders such as neutropenia, thrombocytopenia and agranulocytosis

Very rare: Exacerbation of psoriasis (see section 4.4)

Very rare: Psychiatric disturbances such as depression and anxiety

Very rare: cases of vertigo

Very rare: precipitation and exacerbation of cutaneous and systemic lupus erythematosus have been reported.

4.9. Overdose

A few cases of overdose (up to 5g) have been reported, giving rise to headache, nausea, epigastric pain and dizziness. The recommended treatment of overdose consists of eliminating the drug, primarily by the administration of activated charcoal, and giving symptomatic supportive therapy if needed.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

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

PRECLINICAL

There are no new nonclinical concerns identified with Terbinafine 10 mg/g (1%) Film Forming Solution (as the hydrochloride). The inclusion of the novel excipient acrylates/octylacrylamide copolymer does not raise any nonclinical concerns.

EFFICACY

The indication is treatment of tinea pedis (athlete's foot).

Lamisil Once 1 % Cutaneous Solution and Lamisil NCH 1 % Cutaneous Solution have been shown to eradicate the fungal infection and relieve the symptoms of Athlete's foot. Subsequent dose response data show that a 1% concentration is as effective as 10%, with similar efficacy to Lamisil 1% cream applied daily for seven days.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and some benefit has been shown to be associated with Lamisil Once 1 % Cutaneous Solution or Lamisil NCH 1 % Cutaneous Solution. The risk benefit is therefore considered to be positive.

LAMISIL ONCE 1 % CUTANEOUS SOLUTION and
LAMISIL NCH 1 % CUTANEOUS SOLUTION
PL 00030/0213-4

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 6 May 2004
2	Following assessment of the application the MHRA requested further information relating to the quality dossier on 25 February 2005 and information relating to the clinical dossier on 10 March 2005
3	The applicant responded to the MHRA's requests, providing further information on 19 April 2005
4	Following assessment of the response the MHRA requested further additionally information relating to the clinical dossier on 4 May 2005 and the quality dossier on 2 August 2005, 11 August 2005 and 17 August 2005
5	The applicant responded, providing further information, on 5 August 2005, 30 August 2005 and 27 October 2005
6	The application was determined on 4 November 2005

Product Summary for Lamisil® Once™ 1% cutaneous solution (PL 00030/0213)

1. NAME OF THE MEDICINAL PRODUCT

Lamisil® Once™ 1% cutaneous solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains 10 mg terbinafine (as hydrochloride).

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cutaneous solution.

Clear to slightly opaque viscous solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment for tinea pedis (athlete's foot)

4.2. Posology and method of administration

Adults 18 years of age and over: single administration.

Lamisil Once should be applied once on both feet, even if lesions are visible on one foot only. This ensures elimination of the fungi (dermatophytes) that might be found in areas of the foot where no lesions are visible.

Patients should wash and dry both feet and hands before applying the product. They should treat one foot, then the other.

Starting between the toes, patients should apply a thin layer evenly between and all around the toes, as well as cover the sole and sides of the foot for up to 1.5 cm. The product should be applied in the same way to the other foot, even if the skin looks healthy. The product should be left to dry to a film for 1-2 minutes. Patients should then wash their hands. Lamisil Once should not be massaged into skin.

For the best results, the treated area should not be washed for 24 hours after application. It is therefore recommended to apply Lamisil Once after a shower or bath and wait until the same time the following day before washing the feet again.

Patients should use the quantity they need to cover both feet as instructed above. Any unused medication is to be discarded.

Relief of clinical symptoms usually occurs within a few days. If there are no signs of improvement after one week, patients should see a doctor. There are no data on repeated treatment with Lamisil Once. Therefore a second treatment cannot be recommended within a particular episode of athlete's foot.

Children:
Lamisil Once has not been studied in the paediatric population. Its use is therefore not recommended in patients below 18 years of age.

The elderly:
There is no evidence to suggest that elderly patients require different dosages or experience side effects different from those in younger patients.

4.3. Contraindications

Hypersensitivity to terbinafine or any of the excipients (see 6.1. List of excipients).

4.4. Special warnings and precautions for use

Lamisil Once is not recommended to treat hyperkeratotic chronic plantar tinea pedis (moccasin type).

Lamisil Once is for external use only. It should not be used on the face; it may be irritating to the eyes. In case of accidental contact with the eyes, rinse eyes thoroughly with running water. Do not swallow.

In the unlikely event of allergic reaction, the film should be removed with an organic solvent such as denatured alcohol and the feet washed with warm soapy water.

Contains alcohol; keep away from naked flames.

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

No drug interactions are known with use of topical Lamisil formulations.

4.6. Pregnancy and lactation

Animal studies did not reveal any teratogenic or embryofoetotoxic potential of terbinafine. No cases of malformations in humans have been reported with terbinafine to date. However, since clinical experience in pregnant women is very limited, Lamisil Once should be used only if clearly indicated during pregnancy.

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

4.7. Effects on ability to drive and use machines

Cutaneous application of Lamisil Once does not affect the ability to drive and use machines.

4.8. Undesirable effects

Undesirable effects include mild and transient reactions at the site of application. In very rare instances, allergic reactions may occur.

Skin and subcutaneous tissue disorders:

Very rare (<1/10,000, including isolated reports): allergic reactions such as rash, pruritus, dermatitis bullous and urticaria.

General disorders and administration site conditions

Uncommon (>1/1,000, <1/100): application site reactions such as skin dryness, skin irritation or burning sensation.

4.9. Overdose

Overdose is very unlikely to happen since the product is for single dose, cutaneous use, and the tube only contains the necessary quantity for one application. Accidental ingestion of one 4 g tube of product which contains 40 mg terbinafine is much lower than one 250 mg Lamisil tablet (oral unit dose). Should several tubes be ingested however, adverse effects similar to those observed with an overdose of Lamisil tablets (e.g. headache, nausea, epigastric pain and dizziness) are to be expected.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antifungal for topical use (ATC code D01 A E15)

Terbinafine is an allylamine which has a broad spectrum of antifungal activity in 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 is fungicidal against dermatophytes and moulds. The 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 P450 system. Terbinafine does not influence the metabolism of hormones or other drugs.

Studies in patients have shown that a single dose application of Lamisil Once 1 % cutaneous solution on both feet demonstrated efficacy in patients with tinea pedis (athlete's foot) presenting lesions between the toes, and extending to adjacent skin areas of the sides and soles of the feet. The rate of relapse/reinfection at 3 months after treatment was low: 1 person out of 8 (12.5%).

5.2. Pharmacokinetic properties

Once applied to the skin, Lamisil Once 1 % cutaneous solution forms a film on the skin. Terbinafine in the film stays on the skin for up to 72 hours. The film quickly delivers terbinafine to the stratum corneum: at 60 minutes after application, 16 to 18% of the applied dose will be present in the stratum corneum. Delivery progressively continues and terbinafine persists in the stratum corneum for up to 13 days, at levels which are in excess of the in vitro Minimum Inhibitory Concentration for terbinafine against dermatophytes.

Systemic bioavailability is very low. An application of Lamisil Once 1 % cutaneous solution on the back, on an area of 3 times the area of both feet, resulted in exposure to terbinafine of less than 0.5% of the exposure following oral administration of a 250 mg tablet.

5.3. Preclinical safety data

In long-term studies (up to 1 year) in rats and dogs no marked toxic effects were seen in either species up to oral doses of about 100 mg/kg a day. At high oral doses, the liver and possibly also the kidneys were identified as potential target organs.

In a two-year oral carcinogenicity study in mice, no neoplastic or other abnormal findings attributable to treatment were made up to doses of 130 (males) and 156 (females) mg/kg a day. In a two-year oral carcinogenicity study in rats at the highest dose level, 69 mg/kg a day, an increased incidence of liver tumours was observed in males. The changes, which may be associated with peroxisome proliferation, have been shown to be species-specific since they were not seen in the carcinogenicity study in mice or in other studies in mice, dogs or monkeys.

During the studies of high dose oral terbinafine in monkeys, refractile irregularities were observed in the retina at the higher doses (non-toxic effect level was 50 mg/kg). These irregularities were associated with the presence of a terbinafine metabolite in ocular tissue and disappeared after drug discontinuation. They were no associated histological changes.

A standard battery of *in vitro* and *in vivo* genotoxicity tests revealed no evidence of a mutagenic or clastogenic potential for the drug.

No adverse effects on fertility or other reproduction parameters were observed in studies in rats or rabbits.

Repeated dermal administration of Lamisil Once 1 % cutaneous solution in rats and minipigs produces plasma terbinafine levels which are at least 50-100 times lower than the no-adverse-effect-levels established in terbinafine animal toxicity studies, so use of the product is not expected to produce any systemic adverse effect. Lamisil Once 1 % cutaneous solution was well tolerated in a variety of tolerability studies and did not cause sensitisation.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Acrylates/octylacrylamide copolymer;
Hydroxypropylcellulose;
Medium chain triglycerides;
Ethanol.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store in the original package. There is no special temperature precaution for storage.

6.5. Nature and contents of container

4 g aluminium laminated tube (polyethylene-aluminium-polyethylene) with a polyethylene screw cap.

6.6. Instruction for use and handling (and disposal)

No special requirements.

Administrative Data

7. MARKETING AUTHORISATION HOLDER

Novartis Consumer Health,
Horsham
RH12 5AB,
UK

8. MARKETING AUTHORISATION NUMBER

PL 00030/0213

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

4 November 2005

PATIENT INFORMATION LEAFLET

Lamisil® Once™ 1% cutaneous solution

LAMISIL® ONCE™

1% cutaneous solution
Terbinafine hydrochloride

Please read this leaflet carefully before you start using Lamisil® Once™ 1% cutaneous solution.
It contains important information for you.
Keep this leaflet with the medicine, you may need to read it again.

Athlete's foot is a common fungal infection of the feet and can cause real discomfort. Lamisil Once has been specially developed to treat athlete's foot in one single application. You should follow the instructions for use carefully to obtain the best results.

- *Ask a doctor or a pharmacist for advice if you are in any doubt.*
- *See a doctor or pharmacist if your symptoms do not improve within 1 week after using Lamisil Once.*

This leaflet contains information on:

Lamisil Once is a clear to slightly cloudy gel-like solution, which, upon application on the feet, leaves a smooth, barely visible film that stays on the skin. The film delivers the active substance into the skin. Delivery progressively continues to kill the fungus that causes athlete's foot.

Lamisil Once contains 10 mg of the fungicidal active substance terbinafine (as hydrochloride) per 1 g of solution. The other ingredients are acrylates/octyl-acrylamide copolymer, hydroxypropylcellulose, triglycerides and ethanol.
Lamisil Once is a preparation for a single dose application. It is available in tubes of 4 g.

Product licence holder/manufacturer
Novartis Consumer Health
Horsham, RH12 5AB, UK

1. WHAT IS LAMISIL ONCE AND WHAT IS IT USED FOR?

Lamisil Once is used to treat athlete's foot. It works by killing the fungi which cause athlete's foot.

How do you know that you have athlete's foot?
Athlete's foot (tinea pedis) appears only on the feet (usually both), where it often appears between the toes, and can spread to the sole and sides of the feet. The most common type of athlete's foot causes cracking or scaling of the skin, but you may also have mild swelling, blisters, or weeping sores. This may often be associated with itching or burning sensations.

If you are not sure about the cause of your condition, please talk to your doctor or pharmacist before using Lamisil Once.

2. CHECK BEFORE YOU USE LAMISIL ONCE

When you must not use it:
Do not use *Lamisil Once* if you are allergic to any of the ingredients in this medicine (see the list of ingredients at the beginning of this leaflet).

Take special care with Lamisil Once:
Lamisil Once is for treating the skin of the feet only. Be careful not to get the product on your face and eyes, or damaged skin (other than the treatment site) as it could be irritating. If you get it accidentally into your eyes, rinse thoroughly with running water. If any discomfort persists, see your doctor. Do not swallow.

Lamisil Once is not recommended for long-term fungal infection of the soles and heels of the feet with associated thickening and/or pronounced flaking of the skin. If you think you might have this condition, you should consult your doctor.

If you have fungal nail infection (fungus inside and under the nail), with discoloration of the nails and change in nail texture (thick, flaky), do not use *Lamisil Once* but consult a doctor. You may require prescription medication for your nail infection.

If you are pregnant or breast-feeding:
If you are pregnant, ask your doctor or pharmacist before using *Lamisil Once*.
Do not use *Lamisil Once* while breast-feeding.

Lamisil Once and children:
Do not use this medicine on patients under 18 years of age.

Taking other medicines:
Before using *Lamisil Once* tell your doctor or pharmacist about any other medicines you are taking, or have recently taken, including any you have bought without medical prescription.
Do not apply other medicinal products on the treated areas.

3. HOW TO USE LAMISIL ONCE?

For adults:
Lamisil Once is to be applied only once. You have to apply the product on both feet (between and over the toes, sole and sides of the feet), even if symptoms are visible only on one foot. This ensures the elimination of the fungus responsible for your infection which might be present in other areas of the feet even if no lesions are visible.

When applied on the feet, the medication dries quickly to a colourless film. The tube has enough

medication to treat both feet. Follow the instructions carefully to get the best results.

When you use Lamisil Once:
Lamisil Once delivers the active into the skin where it persists for a number of days to eliminate the fungus that causes athlete's foot. To get the best results, feet should not be washed or splashed for 24 hours after the application. It is therefore recommended to apply *Lamisil Once* after a shower or a bath, and wait 24 hours before washing your feet again.

Before you use Lamisil Once:
- Wash both feet and dry them carefully.
- Wash and dry your hands.
- Remove the cap from the tube.

How to use Lamisil Once:
- This is a single application treatment.
- Apply to both feet. Finish one foot before treating the other.
- Use about half the tube for each foot, as needed to cover skin.
- Apply to each foot with fingers as shown in the accompanying diagrams: apply first between, under, and over all toes. Then apply over sole and sides of your foot

- Treat the other foot in the same way, even if your skin looks healthy.
- Spread evenly. Do not massage into skin.
- Do not apply to skin a second time.
- Leave the product to dry to a film for 1-2 minutes, before wearing your normal footwear.
- Replace the cap on the tube and discard any remaining product. Do not keep or give the remaining product to other people.
- Wash your hands with warm soapy water after the application.

The film left on your skin after applying the product, even if it is barely visible, will continue to work killing the fungi for several days after the single-dose application. Your skin condition should start to improve within a few days. Even though *Lamisil Once* will begin to kill the fungi immediately after single application, it may take up to 4 weeks for your skin to heal completely.

Few people suffering from athlete's foot (1 person out of every 8), experience relapse or reinfection within three months of treatment with this product.

If you have not noticed any signs of improvement within 1 week after applying *Lamisil Once*, please see your doctor or pharmacist who will advise you. Do not use the product a second time for a particular athlete's foot episode if it did not work after the first application.

To help with treatment:
To help the treatment, keep the affected area clean by washing it regularly after the first 24 hours. Dry it carefully without rubbing. Try not to scratch the area although it may be itchy, because this could cause further damage and slow the healing process or spread the infection.

Because these infections can be passed on to other people, remember to keep your own towel and clothes and do not share them with others. To protect yourself from reinfection, these should be washed frequently.

What if you accidentally swallow some of the product?
If you or someone else accidentally swallows the product, *please tell your doctor who will advise you what to do.*

4. POSSIBLE SIDE EFFECTS

All medicines can cause unwanted effects in some people, and it is important to note the following:

In very rare instances, people may be allergic to the product, which could cause skin rash, itching, blistering of the skin, or hives (less than 1 person out of 10,000 is expected to suffer from allergy). In the unlikely event that you experience an allergic reaction or any of the above symptoms when using this product, remove the film with denatured alcohol, wash your feet with warm soapy water, rinse-off and consult your doctor or pharmacist.

Other side effects which may occur at the application site are uncommon (1 to 10 people out of 1,000), and usually mild, transient and harmless. These effects may include skin dryness, skin irritation or burning sensation after application. If you are nevertheless concerned, tell a doctor or pharmacist.

If you notice any side effects not mentioned in this leaflet, please tell your doctor or pharmacist.

5. STORING LAMISIL ONCE

Keep all medicines out of the reach and sight of children.
Do not use or keep this medicine after the expiry date shown on the box and on the tube.
Store in the original container in order to protect from light. There is no special temperature precaution for storage.
Contains ethanol, keep away from naked flames.
This leaflet was last approved on: October 2005.

GB 892644 - 912357

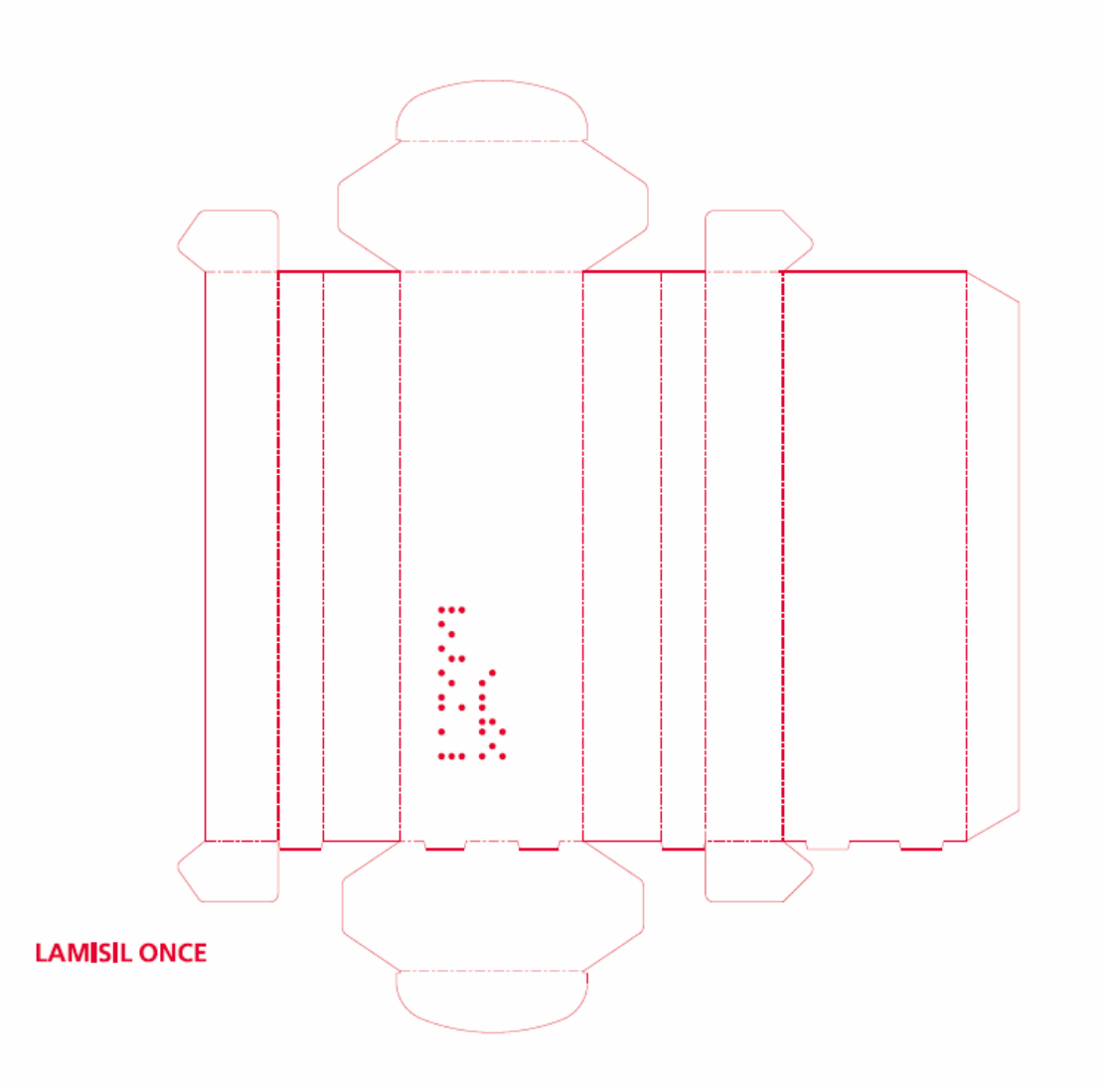
NOVARTIS

LABELLING

Lamisil® Once™ 1% cutaneous solution tube labelling

	Local language	Translation
Preprinted	BN / Exp. Date:	LOT / EXP

Lamisil® Once™ 1% cutaneous solution carton label with Braille


LAMISIL ONCE