Public Assessment Report
Scientific discussion

Terbinafine Dermapharm
(terbinafine hydrochloride)

SE/H/1066/01/DC

This module reflects the scientific discussion for the approval of Terbinafine Dermapharm. The procedure was finalised at 2011-08-12/Day 162. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

Dermapharm AG has applied for a marketing authorisation for Terbinafine Dermapharm cream, 10 mg/g claiming essential similarity to Lamisil Creme, 10 mg/g, cream marketed in Germany by Novartis Consumer Health GmbH. The product contains terbinafine hydrochloride as active substance. For approved indications see the Summary of Product Characteristics.

Terbinafine Dermapharm is a product for topical application on the skin. Hence, pharmacokinetic bioequivalence studies are not relevant to extrapolate efficacy and safety data from the originator product. The applicant has therefore performed a clinical study as an alternative to a conventional bioequivalence study. The composition of Terbinafine Dermapharm differs only slightly from the originator product Lamisil cream.

II. QUALITY ASPECTS

II.1 Introduction

Terbinafine Dermapharm is presented in the form of a cream containing 10 mg of terbinafine hydrochloride. The excipients are benzyl alcohol, cetostearyl alcohol, cetyl palmitate, isopropyl myristate, polysorbate, sodium hydroxide, sorbitan stearate and water. The cream is filled in aluminium tubes.

II.2 Drug Substance

Terbinafine hydrochloride has a monograph in the Ph. Eur.

Terbinafine hydrochloride is a white or almost white powder which is very slightly or slightly soluble in water, freely soluble in anhydrous ethanol and in methanol, slightly soluble in acetone. The structure of terbinafine hydrochloride has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism, chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Terbinafine Dermapharm, 10 mg/g, cream is formulated using excipients described in the current Ph. Eur. All raw materials used in the product are of non-animal origin.
The product development has taken into consideration the physico-chemical characteristics of
the active substance, such as poor aqueous solubility.

The manufacturing process has been sufficiently described and critical steps identified. Results
from the process validation studies confirm that the process is under control and ensure both
batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the
finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the
shelf life claimed in the SPC, with no special storage precautions.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved
based on a full application with regard to preclinical data, no further such data have been
submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

No pharmacokinetic studies have been performed for this product. Terbinafine Dermapharm is
a product for topical application on the skin. Hence, conventional bioequivalence studies are
not possible or relevant due to low systemic exposure to terbinafine. The lack of
pharmacokinetic studies is acceptable. After topical administration of terbinafine, e.g. as a
cream, generally less than 5% of the dose is absorbed.

IV.2 Pharmacodynamics

The pharmacodynamic actions of terbinafine are well known and no specific studies are
required.

IV.3 Clinical efficacy

The applicant submitted one pivotal clinical efficacy and safety study to support this hybrid
application. The study was a double-blind, randomised, multi-centre study comparing
terbinafine cream 1% vs. Lamisil® cream and vs. vehicle in patients with tinea pedis. The
objective was to show therapeutic equivalence (non-inferiority) of the test preparation as
compared to Lamisil® and superiority of both active medications over the vehicle. A total of
325 patients were included in the study based on a positive microscopy and clinical symptoms.
A laboratory mycological investigation was also performed at Day 0 and 48% of the patients
had a negative result at baseline but were still included in the efficacy analyses. The cream was
applied for 7 days and the primary efficacy variable (proportion of patients with clinical and
mycological therapeutic success) was assessed at Day 21.

In the applicant’s analysis of the primary efficacy variable, the proportion of patients with
clinical and mycological cure at Day 21 was 64.3% for Ter-C, 59.7% for Lam-C and 47.6%
for vehicle, for the ITT data set. Non-inferiority of Ter-C vs. Lam-C could be proven for both
the PP and the ITT data sets and superiority of Ter-C over vehicle could also be shown, but not
for Lamisil vs. vehicle. The clinical and mycological success rate (primary efficacy variable)
was relatively low (60-65%) for the active treatments while the vehicle had a high success rate (almost 50%). For secondary efficacy variables, a statistically significant difference between active treatments and vehicle was only demonstrated for a few items.

In this study, patients who were not having a dermatomycosis, and thus, should not benefit from treatment with topical terbinafine were still included, treated, and included in the primary analysis. This is in accordance with clinical practice, where the tinea pedis diagnosis is generally based on typical clinical symptoms while a positive culture is not necessary for initiation of therapy. Even if the overall success rate was less than expected, the results show that Terbinafine Dermapharm would be at most 7-8% worse than the comparator Lamisil, and the point estimates are favouring Terbinafine Dermapharm. Furthermore, superiority could be demonstrated for Terbinafine Dermapharm vs. the vehicle. The ideal non-inferiority analysis including only patients with positive culture at baseline lacks statistical power, but the point estimates (54 vs. 52% for Terbinafine Dermapharm and Lamisil, respectively) do not indicate that the primary analysis should be biased towards non-inferiority.

Bearing in mind that the formulation of the test product Terbinafine Dermapharm is very similar to Lamisil cream, it is not likely that the efficacy of this product would differ from that of Lamisil. The similarity in formulations and the study results indicating an efficacy similar to Lamisil cream altogether support that the efficacy for Lamisil cream can be extrapolated to Terbinafine Dermapharm.

IV.4 Clinical safety
Terbinafine for local application as an antifungal treatment is currently available in several products, e.g. cream, solution and gel. Terbinafine is also available as a systemic treatment in Lamisil tablets. The systemic absorption of terbinafine is generally low from the locally applied products and adverse effects are mainly local.

In the clinical study performed by the applicant the rate of AEs was low and very few AEs were suspected to be related to study treatment. Tolerability tests showed that all treatments were rated as having good or very good tolerability in the majority of the patients. There were no relevant differences between Terbinafin Dermapharm and Lamisil.

IV.5 Discussion on the clinical aspects
The formulation of Terbinafine Dermapharm cream is very similar to Lamisil cream. Even if the overall success rate in the clinical study was less than expected, non-inferiority vs. Lamisil cream could be demonstrated in the primary analysis and superiority could be demonstrated for Terbinafine Dermapharm vs. the vehicle. The similarity in formulations and the study results altogether support that the efficacy for Lamisil cream can be extrapolated to Terbinafine Dermapharm. No safety issues have been observed and tolerability of the product was satisfactory.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was German.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The risk/benefit ratio is considered positive and Terbinafine Dermapharm, 10 mg/g, cream is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Terbinafine Dermapharm, cream, 10 mg/g was successfully finalised on 2011-08-12.
Public Assessment Report – Update

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