Public Assessment Report

Decentralised Procedure

Amorolfine Hydrochloride 5% Medicated Nail Lacquer

Amorolfine hydrochloride

UK/H/4887/01/DC

PL 37268/0005

Applicant: PHARMAZAC SA
Amorolfine Hydrochloride 5% Medicated Nail Lacquer

PL 37268/0005

LAY SUMMARY

On 5th October 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation to PHARMAZAC SA for the medicinal product Amorolfine 5% Medicated Nail Lacquer (PL 37268/0005; UK/H/4887/01/DC). This medicine is only available on prescription from your doctor.

Amorolfine Hydrochloride 5% Medicated Nail Lacquer contains the active ingredient amorolfine (as the hydrochloride), which belongs to a group of medicines known as antifungals. It kills a wide variety of fungi that can cause nail infections.

Amorolfine Hydrochloride 5% Medicated Nail Lacquer is used to treat fungal infections of the nails.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Amorolfine Hydrochloride 5% Medicated Nail Lacquer outweigh the risks; hence a Marketing Authorisation was granted.
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Module 6 Steps taken after initial procedure
### Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Amorolfine Hydrochloride 5% Medicated Nail Lacquer</th>
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<tr>
<td><strong>Type of Application</strong></td>
<td>Article 10.3, Hybrid Application</td>
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<tr>
<td><strong>Active Substance</strong></td>
<td>Amorolfine hydrochloride</td>
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<td><strong>Form</strong></td>
<td>Medicated Nail Lacquer</td>
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<td><strong>Strength</strong></td>
<td>5%</td>
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<td><strong>MA Holder</strong></td>
<td>PHARMAZAC SA, 31 Naousis Str., 10447 Athens, Greece</td>
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<td><strong>RMS</strong></td>
<td>UK</td>
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<td><strong>CMS</strong></td>
<td>Greece</td>
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<td>Day 210: 28&lt;sup&gt;th&lt;/sup&gt; June 2012</td>
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Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4

Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT
Amorolfine Hydrochloride 5% Medicated Nail Lacquer
Amorolfine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Amorolfine 5% w/v Medicated Nail Lacquer contains 5.574g of amorolfine hydrochloride per 100ml equivalent to 5.000g (5% w/v) amorolfine base

3. LIST OF EXCIPIENTS
Ethanol anhydrous, Ammonio Methacrylate Copolymer (type A), Ethyl acetate, Butyl acetate, Triacetin

4. PHARMACEUTICAL FORM AND CONTENTS
Medicated nail lacquer
5ml vial
Each package contains: swabs, spatulas and nail files.

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Cutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
EXP

9. SPECIAL STORAGE CONDITIONS
Protect from heat. Keep bottle tightly closed after use.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
11. NAME AND ADDRESS OF THE MARKETING AUTHORITY

PHARMAZAC SA
31 Naoussis street,
104 47, Athens
Greece

12. MARKETING AUTHORITY NUMBER(S)

<To be completed nationally>

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

<To be completed nationally>

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Amorolfin Hydrochloride 5% Medicated Nail Lacquer
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</th>
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<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
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<tr>
<td>Lot</td>
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<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
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<tr>
<th>6. OTHER</th>
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<tr>
<td>Protect from heat. Keep bottle tightly closed after use.</td>
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Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member State (CMS) consider that the application for Amorolfine Hydrochloride 5% Medicated Nail Lacquer in the treatment of onychomycoses caused by dermatophytes, yeasts and moulds could be approved.

This application was submitted according to Article 10.3 of 2001/83/EC, as amended, claiming to be a generic medicinal product of Loceryl Nail Lacquer 5% (PL 00031/0285); originally granted to Roche Products Limited on 4th July 1991. The reference licence has gone under a Change of Ownership (CoA) procedure and was authorised to the current Marketing Authorisation Holder, Galderma UK Limited (PL 10590/0042) on 19th April 1999. The reference product has been authorised in the European community for more than 10 years, so the period of data exclusivity has expired.

With UK as the RMS in this Decentralised Procedure (UK/H/4887/001/DC), PHARMAZAC SA applied for the Marketing Authorisation for Amorolfine Hydrochloride 5% Medicated Nail Lacquer in Greece.

Amorolfine belongs to a new chemical class, and its fungicidal action is based on an alteration of the fungal cell membrane targeted primarily on sterol biosynthesis. The ergosterol content is reduced, and at the same time unusual sterically nonplanar sterols accumulate.

Amorolfine is a topical antifungal that has a broad spectrum of activity, including against yeasts, dermatophytes, moulds, dematiacea and dimorphic fungi. Its activity is fungicidal for most species.

Amorolfine from nail lacquer penetrates into and diffuses through the nail plate and is thus able to eradicate poorly accessible fungi in the nail bed. Systemic absorption of the active ingredient is very low with this type of application.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a hybrid medicinal product of an originator product that has been licensed for over 10 years.

No bioequivalence data were submitted with this application, in line with CPMP/EWP/239/95 Notes for Guidance on the Clinical Requirements for Locally Applied Locally Acting Products Containing Known Constituents. This application is based on the identicality of the physico-chemical properties to the reference product. No therapeutic equivalence data is considered necessary as this is a cutaneous solution, so a biowaiver can be applied.

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable justification has been provided for the non-submission of a Risk Management Plan.

All member states agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 210 – 28th June 2012). After a subsequent national phase, the UK granted a Marketing Authorisation for this product on 5th October 2012 (PL 37268/0005).
### II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Amorolfine Hydrochloride 5% Medicated Nail Lacquer |
| Name(s) of the active substance(s) (USAN)         | Amorolfine hydrochloride                           |
| Pharmacotherapeutic classification (ATC code)    | D01AE16 - Other antifungals for topical use        |
| Pharmaceutical form and strength(s)              | Medicated Nail Lacquer, 5%                         |
| Reference numbers for the Decentralised Procedure| UK/H/4887/001/DC                                    |
| Reference Member State                           | United Kingdom                                     |
| Concerned Member State                           | Greece                                              |
| Marketing Authorisation Number(s)                | PL 37268/0005                                      |
| Name and address of the authorisation holder     | PHARMAZAC SA, 31 Naousis Str., 10447 Athens, Greece |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Amorolfin hydrochloride

Chemical Names: Cis-4-[3-(4-tert-amylphenyl)-2-methylpropyl]-2,6-dimethylmorpholine, hydrochloride
Cis-4-[3-[4-(1,1-dimethylpropyl)-phenyl]-2-methylpropyl]-2,6-dimethylmorpholine, hydrochloride

Structure:

![Molecular structure of Amorolfin hydrochloride](image)

Molecular formula: C_{21}H_{36}ClNO

Molecular weight: 353.98

Physical form: white powder

Solubility: Easily soluble in ethanol, soluble in methylene chloride and slightly to very slightly soluble in water.

The drug substance is the subject of a European Drug Master File (EDMF). A letter of access has been provided by the drug substance manufacturer.

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

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Satisfactory Certificates of Analysis for all working standards have been provided. Batch analysis data are provided and comply with the proposed specification.
Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the active substance is stored in the packaging proposed.

**DRUG PRODUCT**

**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients ethanol anhydrous, ammonio methacrylate copolymer (type A), ethyl acetate, butyl acetate and triacetin.

All excipients comply with the relevant European Pharmacopoeia monographs with the exception of butyl acetate which complies with an in-house specification. Satisfactory Certificates of Analysis have been provided for these excipients.

The above excipients do not contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

**Pharmaceutical Development**

The objective of the pharmaceutical development programme was to formulate a stable lacquer containing 5% amorolfine (as amorolfine hydrochloride) that could be considered a generic medicinal product of Loceryl Nail Lacquer 5% (Galderma UK Limited).

Suitable pharmaceutical development data have been provided for this application.

Comparative physico-chemical properties have been provided for the proposed and originator products.

**Manufacture**

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Satisfactory process validation data on pilot-scale batches have been provided. The applicant has committed to perform process validation on future commercial-scale batches.

**Finished Product Specifications**

The finished product specification is satisfactory. Test methods have been described and adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

**Container Closure System**

The finished product is presented in amber glass type I bottle stopped by a high density polyethylene (HDPE) cap with a Teflon liner. The pack size is 5ml vial.

All packs contain cleansing swabs, spatulas and nail files and they all have “European Conformity” or “CE” markings”, in line with EC Directive 93/42/EEC (concerning Class I medical devices).

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with relevant guidelines.
Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf life of 30 months with storage conditions “Protect from heat” and “Keep bottle tightly closed after use” are set. These are satisfactory.

Bioequivalence/bioavailability
No bioequivalence studies have been submitted and none are required to support an application of this type.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SPC, PIL and labelling are pharmaceutically satisfactory.

User testing results have been submitted for the PIL for this product. The results indicate that the PIL is in accordance with Article 59 of Council Directive 2001/83/EC, as amended, and is well structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) Form
The MAA form is pharmaceutically satisfactory.

Expert Report
A pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of this product from a pharmaceutical point of view.

III.2 NON-CLINICAL ASPECTS
PHARMACODYNAMICS, PHARMACOKINETICS, TOXICOLOGY
The pharmacological, pharmacokinetic and toxicological properties of amorolfine hydrochloride are well-known.

No new non-clinical data have been supplied with this application and none are required for applications of this type. The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A suitable justification has been provided for the non-submission of the environmental risk assessment.

There are no objections to the approval of this product from a non-clinical point of view.

III.3 CLINICAL ASPECTS
Pharmacokinetics
No bioequivalence data were submitted with this application, in line with CPMP/EWP/239/95 Notes for Guidance on the Clinical Requirements for Locally Applied locally Acting Products Containing Known Constituents. This application is based on the identiticality of the physico-chemical properties to the reference product. No therapeutic equivalence data is considered necessary because it is a cutaneous solution, so a biowaver
can be applied.

As identical physicochemical properties to the reference product can be established, a biowaiver is granted, in-line with CPMP/EWP/QWP/1401/98 Guideline on the Investigation of Bioequivalence.

**Pharmacodynamics**
No new data have been submitted and none are required for applications of this type.

**Clinical efficacy**
No new data have been submitted and none are required for applications of this type.

**Clinical safety**
No new data have been submitted and none are required for applications of this type.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling**
The SmPC, PIL and labelling are medically satisfactory and consistent with those for the reference product.

**Clinical Expert Report**
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Marketing Authorisation Application (MAA) Form**
The MAA form is medically satisfactory.

**Clinical Conclusion**
There are no objections to the approval of this product from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Amorolfine Hydrochloride 5% Medicated Nail Lacquer are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No non-clinical data were submitted and none are required for applications of this type. A suitable justification has been provided for non-submission of an Environmental Risk Assessment.

EFFICACY
No bioequivalence data were submitted with this application and none are required. Equivalence has been demonstrated through comparable physico-chemical properties between the proposed product and the originator product. No therapeutic equivalence studies have been performed and none are required as the product is a cutaneous solution.

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for the originator product.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with amorolfine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk balance is, therefore, considered to be positive.
## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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