Public Assessment Report

Decentralised Procedure

Amorolfin 5% Medicated nail lacquer

(amarolfine hydrochloride)

Procedure No: UK/H/6017/001/DC

UK Licence No: PL 44157/0001

Oystershell nv
LAY SUMMARY
Amorolfine 5% Medicated nail lacquer
(amorolfine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Amorolfine 5% Medicated nail lacquer (PL 44157/0001; UK/H/6017/001/DC). This product will be referred to as Amorolfine in the remainder of this summary, for ease of reading.

This summary explains how Amorolfine was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use this product.

For practical information about using Amorolfine, patients should read the package leaflet or contact their doctor or pharmacist.

What is Amorolfine and what is it used for?
Amorolfine 5% w/v Nail Lacquer is a hybrid medicine. This means that it is similar to a ‘reference medicine’, already authorised in the European Union (EU) called Loceryl 5% w/v Medicated Nail Lacquer (PL 10590/0042). Amorolfine can be used to treat fungal infections of the nails.

How does Amorolfine work?
Amorolfine contains the active ingredient amorolfine hydrochloride, which belongs to a group of medicines known as antifungals. Amorolfine kills a wide variety of fungi that can cause nail infections.

How is Amorolfine used?
Amorolfine is to be used externally and should be applied to the affected finger or toe nail(s).

Please read Section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

This medicinal product can be obtained from a pharmacy.

What benefits of Amorolfine have been shown in studies?
Amorolfine is a hybrid medicine that is applied to finger or toe nails. Studies showed that Amorolfine was physically and chemically equivalent to the reference product, Loceryl 5% w/v Medicated Nail Lacquer, and therefore the benefits and risks are taken as being the same as those of the reference medicine.

What are the possible side effects of Amorolfine?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Amorolfine, see section 4 of the package leaflet available on the MHRA website.

Why was Amorolfine approved?
The MHRA decided that Amorolfine’s benefits are greater than its risks and recommended that it be approved for use.
What measures are being taken to ensure the safe and effective use of Amorolfine?

A risk management plan (RMP) has been developed to ensure that Amorolfine is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Amorolfine including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Amorolfine

Belgium, Germany, Luxembourg and the UK agreed to grant a Marketing Authorisation for Amorolfine on 02 March 2016. A Marketing Authorisation was granted in the UK on 17 March 2016.

The full PAR for Amorolfine follows this summary.

For more information about treatment with Amorolfine, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in May 2016.
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I. INTRODUCTION
Based on the review of the data on quality, safety and efficacy the Member States considered that the application for Amorolfine 5% Medicated nail lacquer (PL 44157/0001; UK/H/6017/001/DC) is approvable.

The product is available in a pharmacy (P), and is indicated for the treatment of mild cases of distal and lateral subungual onychomycoses caused by dermatophytes, yeasts and moulds; treatment is limited to 2 nails.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Belgium, Germany, Luxembourg as Concerned Member States (CMSs). The application was submitted under Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application. The reference medicinal product for this application is Loceryl 5% w/v Medicated Nail Lacquer, originally granted to Roche Products Limited (PL 00031/0285) on 4 July 1991. The reference licence underwent a Change of Ownership (CoA) procedure and was authorised to the current Marketing Authorisation Holder, Galderma UK Limited (PL 10590/0042), on 19 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.

Amorolfine 5% Medicated nail lacquer contains the active ingredient, amorolfine hydrochloride which is a topical antimycotic. It 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.

No new non-clinical or clinical studies were conducted for this application, which is acceptable given that this was a hybrid application for a similar product that has been licensed for over 10 years. A therapeutic equivalence study is not necessary to support this application for a topical solution.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release 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.

All Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 210 – 02 March 2016). After a subsequent national phase, the UK granted a Marketing Authorisation (PL 44157/0001) for this product on 17 March 2016.
II QUALITY ASPECTS

II.1 Introduction
The product is presented as a clear, colourless to pale yellow solution. Each 1 ml of solution contains 55.74 mg of the active substance amorolfine hydrochloride (equivalent to 50 mg amorolfine).

Other ingredients consist of pharmaceutical excipients, Eudragit RL 100, triacetin, butyl acetate, ethyl acetate and ethanol. Appropriate justifications for the inclusion of each excipient have been provided.

All excipients used comply with their respective European Pharmacopoeial monograph with the exception of butyl acetate which is controlled to an in-house specification. Satisfactory Certificates of Analysis for each excipient have been provided. The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in, or used in the manufacturing process for the proposed product. Furthermore, no genetically modified organisms are used in the manufacture of any of the excipients.

The finished product is licensed for marketing in an amber glass (Type I or Type III) bottle with a high density polyethylene (HDPE) cap, polytetrafluoroethylene (PTFE) liner and tamper evident ring. Each pack consists of one bottle and cleansing swabs, spatulas and nail files. The product is packaged in pack size of 2.5 ml.

Specifications and Certificates of Analysis for all packaging components used have been provided. The glass bottles comply with Ph. Eur. requirements as well as the EU Directive 2002/72/EC.

II.2. Drug Substance
INN: Amorolfine hydrochloride
Chemical name: Cis-4-[4-(1,1-Dimethylpropyl)phenyl]-2-methylpropyl]-2,6-dimethylmorpholine hydrochloride

Amorolfine hydrochloride is the subject of a European Pharmacopoeia (Ph. Eur.) monograph.

All aspects of the manufacture and control of the active substance, amorolfine hydrochloride, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.
II.3. Medicinal Product
Pharmaceutical Development
The aim of the pharmaceutical development programme was to produce robust, reproducible product that could be considered a generic medicinal product of Loceryl 5% w/v Medicated Nail Lacquer (Galderma UK Limited). Suitable pharmaceutical development data have been provided for this application.

The physico-chemical properties of the drug product have been compared with the reference product. These data demonstrate that the proposed product can be considered a generic medicinal product of Loceryl 5% w/v Medicated Nail Lacquer (Galderma UK Limited).

Comparative dissolution data were provided for the test and reference products. The dissolution profiles were found to be similar.

A bioequivalence or therapeutic equivalence study has been waived on the basis that the proposed product is a solution for topical use and the active is not systemically absorbed. Comparative in vitro dissolution and other physico-chemical parameters have been presented and are similar to the reference product Loceryl 5% w/v Medicated Nail Lacquer (Galderma UK Limited).

Manufacture of the product
A satisfactory batch formula has 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. Process validation data on commercial scale batches have been provided.

Finished Product Specification
The finished product specification proposed is acceptable. The test methods that have been described have been adequately validated. Batch data have been provided that comply with the release specification.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 3 years with storage conditions ‘Store below 30°C’, ‘Protect from heat’ and ‘Keep the bottle tightly closed and upright’.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The test product is pharmaceutically equivalent to the reference product, which has been licensed in the UK for over 10 years. Given the route of administration and pharmaceutical form, it is not necessary to perform a therapeutic equivalence study.

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

III NON-CLINICAL ASPECTS
III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of amorolfine are well-known. As this is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.
III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
The active substance amorolfine hydrochloride has a log Kow > 4.5. The applicant is requested to submit Persistent Bioaccumulative and Toxic (PBT) substance assessment according to the EMA guideline. The requested outstanding information requires further studies to be completed before a final conclusion can be made on the ERA. Therefore, the applicant has committed to provide a revised ERA post-approval.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical point of view.

IV CLINICAL ASPECTS
IV.1 Introduction
No new clinical data have been submitted and none are required for applications of this type. A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified physician.

IV.2 Pharmacokinetics
No new data have been submitted and none are required for applications of this type.

Amorolfine 5% w/v Nail Lacquer is a hybrid application for a similar version of Loceryl 5% w/v Nail Lacquer. The use of the reference product is well-established in the UK. Both the reference product and the test product contain the same quantitative and qualitative composition of the active ingredient, amorolfine hydrochloride.

In accordance with the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) the applicant is not required to submit a bioequivalence study if the product is to be administered as a topical solution containing the same active substance, in the same concentration as the currently authorised product. The applicant has not submitted a bioequivalence study, which is satisfactory.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none are required for applications of this type.

IV.4 Clinical efficacy
No new data have been submitted and none are required for applications of this type.

IV.5 Clinical safety
No new safety data have been submitted or required for this generic application. As amorolfine hydrochloride is a well-known substance with an acceptable adverse event profile, this is satisfactory.

IV.6 Risk Management Plan (RMP)
The Marketing Authorisation Holder (MAH) has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and
interventions designed to identify, characterise, prevent or minimise risks relating to Amorolfine 5% Medicated nail lacquer.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic contact dermatitis</td>
<td>Text in Summary of Product Characteristics (SPC) (Based on SmPC Amorolfine Oystershell 5% Nail Lacquer)</td>
<td>None proposed.</td>
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<tr>
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<td>4.3. Contraindications</td>
<td></td>
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<td>4.8. Undesirable effects</td>
<td></td>
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<tr>
<td>Nail disorders (e.g. nail discoloration, broken nails, brittle nails)</td>
<td>Text in Summary of Product Characteristics (SPC) (Based on SmPC Amorolfine Oystershell 5% Nail Lacquer: 4.2 Posology and method of administration 4.4 Special warnings and precautions for use 4.8. Undesirable effects)</td>
<td>None proposed.</td>
</tr>
<tr>
<td>Missing Information: Children and patient under 18 years old</td>
<td>Text in Summary of Product Characteristics (SPC) (Based on SmPC Amorolfine Oystershell 5% Nail Lacquer: 4.2 Posology and method of administration)</td>
<td>None proposed.</td>
</tr>
<tr>
<td>Missing Information: Elderly patient</td>
<td>Text in Summary of Product Characteristics (SPC) (Based on SmPC Amorolfine Oystershell 5% Nail Lacquer: 4.2 Posology and method of administration)</td>
<td>None proposed.</td>
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</table>
IV.7 Discussion on the clinical aspects
No new clinical data were submitted and none are required for this type of application.

There are no objections to the approval of this application from a clinical viewpoint.

The grant of a Marketing Authorisation is recommended for this application.

V 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 patient information leaflet (PIL) was English.

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.

VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s product Amorolfine 5% Medicated nail lacquer and the reference product Loceryl 5% w/v Medicated Nail Lacquer (Galderma UK Limited), are interchangeable. Extensive clinical experience with amorolfine hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The benefit/risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

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.

The approved labelling for Amorolfine 5% Medicated nail lacquer is presented below:

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS [LABEL]**

1. Name of the medicinal product and route of administration
   Amorolfine 5% Medicated nail lacquer
   Cutaneous use

2. Method of administration
   Read the package leaflet before use.

3. Expiry date
   Exp

4. Batch number
   Lot

5. Contents by weight, by volume or by unit
   2.5 ml

6. Other
PARTICULARS TO APPEAR ON THE OUTER PACKAGING {CARTON}

1. Name of the medicinal product

Amorolfin 5% Medicated nail lacquer
Amorolfin

2. Statement of active substance(s)

1 ml solution contains 55.74 mg amorolfin hydrochloride (equivalent to 50 mg amorolfin).

3. List of excipients

Excipients: Eudragit RL 100, Triacetin, Butyl acetate, Ethyl acetate, Ethanol

4. Pharmaceutical form and contents

2.5 ml medicated nail lacquer
+ nail files, re-usable applicators and cleansing swabs.

5. Method and route 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 sight and reach of children.

7. Other special warning(s), if necessary

For external use only.

8. Expiry date

Exp:

9. Special storage conditions

Store below 30°C. Protect from heat. Keep the bottle tightly closed and upright.
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 authorisation holder

Oystershell nv
Booiebos 24
9031 Drongen
Belgium

12. Marketing authorisation number(s)

PL 44157/0001

13. Batch number

Lot

14. General classification for supply

Medicinal product not subject to medical prescription.

15. Instructions on use

For treatment of mild fungal nail infections. Apply to the infected nail once a week.

16. Information in braille

amorolfin 5%
Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
<thead>
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<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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