CURANAIL 5% NAIL LACQUER (AMOROLFINE HYDROCHLORIDE)
PL 10590/0049

UKPAR

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CURANAIL 5% NAIL LACQUER
PL 10590/0049

LAY SUMMARY

The MHRA granted Galderma (UK) Limited a Marketing Authorisation (licence) for the medicinal product Curanail 5% nail Lacquer (PL 15909/0049) on 7th April 2006. This medicine which is available from Pharmacies is used to treat mild fungal infections of the nail in up to 2 nails.

Curanail 5% Nail Lacquer contains the active ingredient amorolfine (as the hydrochloride), which is one of a group of medicines known as anti-fungals, which kill a wide variety of fungi which can cause infections.

This new product is a duplicate of a previously granted application for Loceryl Nail Lacquer 5% (PL 10590/0042) held by Galderma (UK) Limited which is available on prescription for more serious fungal nail infections. Curanail 5% Nail Lacquer is for milder fungal infections of the nail and has been granted a different legal supply classification, which means it can be sold in pharmacies.

No new or unexpected safety concerns arose from these applications. It was, therefore, judged that the benefits of Curanail 5% Nail Lacquer being available from a pharmacy outweigh the risks. Hence a Marketing Authorisation has been granted.

CURANAIL 5% NAIL LACQUER
PL 10590/0049

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted a marketing authorisation for the medicinal product Curanail 5% Nail Lacquer (PL 10590/0049) to Galderma (UK) Limited on 7th April 2006. The product is available in Pharmacies (P).

The application was submitted according to article 10.c [formerly article 10.1(a)(i)] of Directive 2001/83/EC, cross-referring to Loceryl Nail Lacquer 5% (PL 10590/0042). The cross-reference application was granted on 19th April 1999 as a change of ownership from PL 00031/0285, held by Roche Products Limited which was itself granted a marketing authorisation for on 4th July 1991.

No new quality data was submitted nor was it necessary for this simple application, as the data is identical to that of the previously granted cross-reference product. As the cross-reference product was granted prior to the introduction of current legislation, no public assessment report was generated for it.

The product contains the active ingredient amorolfine hydrochloride which is a broad spectrum topical antimycotic agent that has both fungistatic and fungicidal activity against all pathogens of nail mycosis. The product is indicated for the treatment of mild cases of distal and lateral subungual onychomycoses caused by dermatophytes, yeasts and moulds limited up to 2 nails.

PHARMACEUTICAL ASSESSMENT

This abridged simple application is associated with a reclassification application – see medical assessment for the joint medical/ pharmaceutical assessment.

The company has submitted an expert statement confirming that all pharmaceutical aspects are the same as the cross reference product. The Marketing Authorisation Application form has been updated to reflect the current granted licence. The Drug Substance Specification, method of manufacture and Finished Product Specification are consistent with the current granted MA and this is satisfactory

Conclusion

This MA may be approved as a P product.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for applications of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION

Galderma UK LTD have submitted an abridged application requesting a POM to P reclassification for Curanail 5% Lacquer containing amorolfine hydrochloride. It is proposed that the product will be used to treat onychomycosis affecting the distal nail plate caused by dermatophytes, yeasts and moulds in adults aged 18 years and over with a pack size of 3ml.

Treatment should be without interruption until the nail has regenerated and the affected areas are finally cured. The required frequency and duration of treatment depends on intensity and localisation of the infection. In general, it is 6 months for finger nails and 9-12 months for toe nails. A review of treatment is recommended at intervals of 3 months.

The abridged application is submitted under Article 10.c [formerly article 10.1 (a) (i)] as a so called "informed consent application" cross referring to the previously authorised product Loceryl Nail Lacquer 5 % (PL 10590/0042).

2. BACKGROUND

Loceryl Nail Lacquer was initially authorised in 1991 and marketed by Roche UK from that year. The product is authorised in about sixty countries worldwide, in four of which it is available over-the-counter. In Austria and Singapore it was reclassified in 1993 and in Germany and Australia it was made available OTC in 1997.

In the UK amorolfine hydrochloride is only available as a prescription medicine. This is the first application for pharmacy availability of a product containing this ingredient.

Amorolfine is a broad spectrum topical antimycotic agent that has both fungistatic and fungicidal activity against all pathogens of nail mycosis. It is a morpholine derivative that acts on enzymes involved in ergosterol synthesis in the fungal cell wall leading to changes in membrane permeability and disruption of key fungal metabolic processes.

In 1998 the House of Lords Select Committee on Science and Technology report on resistance to antibiotics and other anti-microbial agents noted the possibility that wider availability of anti-fungal agents without prescription might contribute to the development of resistance. Following this, the (then) MCA reviewed the issue of resistance related to the legal status of anti-fungal medicines in a paper considered by CSM in October 1999. This review concluded:

> *"Although the level of fungal drug resistance is currently thought to be below that observed with bacteria, increased use of anti-fungal agents would lead to increased selective pressure and probably more widespread resistance."*

However, it was noted that there was little robust evidence that non-prescription use of topical anti-fungal agents had been associated with the emergence of resistance.

Other topical antifungal products are already available either as Pharmacy or GSL medicines including clotrimazole, miconazole, terbinafine, econazole and sulconazole. These are indicated for fungal skin infections due to dermatophytes, yeasts, moulds and other fungi,

such as ringworm, athlete's foot, intertrigo, fungal nappy rash, candidal vulvitis and vaginitis. Treatment is generally from one to three weeks in duration.

3. PHARMACEUTICAL COMMENT

3.1 Marketing Authorisation Application (MAA)

The MAA is being assessed separately and in parallel with this reclassification application. There are no issues relating to the abridged application which impinge on the reclassification application. The applicant has provided suitable reassurance that there are no differences in the chemistry and pharmacy data between this product and the cross reference product.

3.2 Pack Size

The proposed pack size for the pharmacy product is 3ml. This is smaller than the current, marketed POM pack of 5ml.

The applicant estimates that the pack would last for three months if used once a week on four nails. If only two nails were affected it could last up to six months. The duration of treatment is usually six months for finger nails and nine to twelve months for toe nails.

It is likely therefore that if toe nails are affected, a repeat supply may be necessary. Individuals seeking a repeat purchase will be asked about duration of treatment so far and if necessary the pharmacist will recommend a treatment review.

A review of treatment after 3 months is recommended. If, however, there is sufficient product remaining in the pack after 3 months, it is possible that users may not return to discuss progress with their pharmacist.

Assessor's comment

The proposed pack size of 3ml is considered acceptable. The patient information leaflet should include information about the importance of a 3 monthly review with the pharmacist, and what to do it the condition does not improve.

4. MEDICAL ASSESSMENT OF SUITABILITY FOR PHARMACY AVAILABILITY

The expert report in support of the pharmacy availability of amorolfine nail lacquer was signed by an independent pharmaceutical and clinical physician. Further information has been supplied on the subject of resistance and is considered acceptable.

4.1 Rationale for treatment

Onychomycosis is sometimes misunderstood to be a trivial cosmetic problem that does not merit treatment. However, the condition has high prevalence as a result of heavy contamination of communal bathing places by infected users. The applicant claims that the high prevalence of the disease justifies the rationale of treatment to reduce the number of infections. Onychomycosis should not therefore be considered a trivial disease, and there is a

sound case for treatment on the grounds of public health considerations and effect on quality of life.

Assessor's comment
This is acceptable.

4.2 Management of onychomycosis

Onychomycosis can be treated with oral and topical agents. Systemically active agents can achieve more thorough penetration of the nail, thus leading to better cure rates. However, oral treatment can cause side effects such as gastrointestinal disturbances and increases in liver enzymes. The risk of systemic side effects and the lengthy duration of treatment required for optimum efficacy mean that systemic therapy is often reserved for severe or relapsing cases, for difficult to treat infections and for patients with immunologic disorders or debilitating diseases.

The advantage of topical anti-mycotic agents is that the potential for undesirable systemic effects and drug interactions are very limited.

Assessor's comment
Systemic therapy is almost always more successful than topical treatment, which should only be used in mild cases of onychomycosis where nail dystrophy and complete nail plate destruction do not occur. However, among topical treatments amorolfine nail lacquer is the most effective preparation. It has been shown to be effective in 50% of cases of both fingernail and toenail infections.

4.3 Indication

The applicant is proposing that Curanail Lacquer be sold for the indication "onychomycosis affecting the distal nail plate caused by dermatophytes, yeast and moulds". The approved indication for the POM product is "onychomycosis caused by dermatophytes, yeast and moulds". Thus, the applicant is proposing to restrict the indication to distal onychomycosis.

There are four clinical types of onychomycosis. The most common form is disto-lateral subungual onychomycosis (DLSO), when the nail bed is affected. DLSO is usually caused by Trichophyton rubrum. The second form is superficial white onychomycosis (SWO), which accounts for 10% of cases. This infection is caused by Trichophyton mentagrophytes, which directly invades the superficial layers of the nail plate. Proximal subungual onychomycosis is the least common type in otherwise healthy individuals. It is more common in immunocompromised patients and is a clinical marker for HIV infection. Vascular disease and diabetes also may present in this way. The fourth form is candidal onychomycosis. Candida species may invade nails previously damaged by infection or trauma.

All these varieties of onychomycosis may eventually progress to total nail dystrophy where the nail plate is almost completely destroyed.

Assessor's comment
According to BNF, PRODIGY and Guidelines for Treatment of Onychomycosis by the British Association of Dermatologist topical antifungal therapy is recommended for the treatment of mild cases of DLSO where the infection is confined to the distal edge of the

nail. BNF suggests topical treatment with amorolfine in cases when up to two nails are affected.

The indication of the P product should be restricted to patients with early onychomycosis when involvement is limited to mild distal disease in up to 2 nails.

4.4 Posology

The posology for the approved POM product is once weekly. The SPC states that "twice weekly application may prove beneficial in some cases". For the proposed P product the posology is once weekly. Thus the applicant is proposing to delete the sentence "Twice weekly application may prove beneficial in some cases" and retain only the once weekly administration in section 4.2. in the SPC.

In an open, randomized study 456 patients with onychomycosis were treated once or twice weekly for up to 6 months with amorolfine. Overall cure rates for those treated twice weekly compare to those treated once weekly were 54.2% vs. 46.0% (p=0.4). Clinical cure or improvement was achieved 74 and 68% of patients receiving twice- and once-weekly treatment, respectively. The mycological cure rate was 76.1% for twice-weekly treatment and 70.6% for once-weekly treatment.

Assessor's comment
Based on these clinical data once weekly administration of amorolfine 5% lacquer in mild cases of DLSO seems to be justified.

It should be noted that patients with severe impairment of peripheral circulation were excluded from this study. There are several underlying conditions, which predispose for fungal nail infection including impaired circulation, diabetes mellitus, immunosuppression. Since these patients need regular supervision of their underlying condition from a doctor, they should be excluded from the P supply of amorolfine.

4.5 Safety

4.5.1 First POM criterion:

- A direct or indirect danger exists to human health, even when used correctly, if utilised without medical supervision

4.5.1.1 Safety related to misdiagnosis

Onychomycotic changes to the nail usually have specific characteristics that can be easily recognised. DLSO can be quickly and simply recognised by individuals by the very characteristic progress of the infection. According to PRODIGY fungal infections of the nail is characterised by nail thickening and discoloration. The texture of the nail changes and the nail may be soft and easily broken.

Pharmacists will be given comprehensive training and educational materials to assist diagnosis in those individuals who present to a pharmacy. The pharmacy protocol gives guidance on how to recognise and distinguish the most commonly found nail disorders. If

there is any doubt on diagnosis, pharmacists will be advised to refer individuals to their GP for a full consultation and diagnostic screen.

The leaflet contains pictures of infected nails, which also help patients in the identification of the condition.

All individuals receiving Curanail Lacquer are advised to return for regular 3 monthly treatment reviews. One of the purposes of the review is to ensure that the treatment is appropriate for the condition.

Approximately 50% of nail abnormalities are caused by fungus. The remaining 50% are caused by a variety of disorders. These include inflammatory skin disease such as psoriasis, eczema and trauma. Often these conditions are associated with other symptoms involving the skin and or nail that can distinguish them from fungal infections.

Assessor's comment
PRODIGY and Guidelines for Treatment of Onychomycosis by the British Association of Dermatologist state that the diagnosis of onychomycosis should be confirmed by mycology before the treatment is commenced. However, in current general practice the diagnosis is based on the clinical picture alone. Other conditions similar to nail infection are accompanied by skin symptoms, which can help in the differential diagnosis.

Moreover, if onychomycosis is misdiagnosed and Curanail Lacquer is used inappropriately, the risk to health is negligible, either directly through use of treatment, or indirectly through lack of treatment of the disorders mistaken for onychomycosis.

4.5.1.2 Resistance

Amorolfine is a broad spectrum antimycotic agent with both fungistatic and fungicidal activity against all pathogens of nail mycosis.

Little specific data are available which demonstrate either an issue of acquired resistance with amorolfine, or similar products treating this indication.

Fungal resistance can be one of the reasons of treatment failure of antifungal drugs. However, currently there is very little data to suggest that resistance to antifungal agents is a problem.

Resistance can be considered to be more of a problem when it involves clinically important microbes. Fungal infections of the toe nails are mainly due to dermatophytes, which are not associated with clinically serious infections. Resistance in moulds is not common and generally, if resistance is found it is intrinsic and not acquired. Infections of the finger nails can be caused by yeasts such as Candida species. There has not been any increase noted in resistance despite many OTC antifungal being available to treat Candida infections.

Assessor's comment
Despite the lack of specific data on resistance to topically administered amorolfine, since amorolfine is not used for systemic treatment of fungal infections, resistance is not considered be a major issue.

4.5.1.3 Safety profile of amorolfine

Amorolfine has a good safety profile with very few side effects reported in clinical studies or in use as a POM medicine. The most frequently reported adverse events are nail disorders and skin irritations.

The absorption of amorolfine to the systemic circulation through nail is negligible. The plasma concentration of amorolfine in patients receiving twice weekly applications of amorolfine nail lacquer for up to 12 months was measured in two studies. At the end of treatment, the majority of patients had no detectable plasma concentrations of amorolfine and others had concentrations of only between 0.1 and 0.3 ng/ml.

Assessor's comment
Between 1991 and 2004 there are 26 reports dealing with 38 reactions for amorolfine on the ADROIT database.

The clinical pharmacology of the product assumes negligible systemic side effects of amorolfine lacquer.

4.5.2 Second POM criterion:

- There is frequent incorrect use which could lead to a direct or indirect danger to human health.

The product information clearly describes the method of administration. Therefore, it is unlikely that the product will be used incorrectly.

To avoid reoccurrence the treatment should be continued until the infected section of the nail has fully grown out. This may take up to 12 months for toenails and individuals may not experience improvement in their conditions before 3 months. With such a long duration of treatment, it is important to maintain patient compliance. Review of the treatment at 3 monthly intervals serves as an opportunity to help with this.

4.5.2.1 Safety related to misuse or abuse

Amorolfine is not considered to be a drug of abuse.

4.5.2.2 Overdosing - accidental or deliberate

There have been isolated reports of individuals applying amorolfine nail lacquer more frequently than it is recommended. Moreover, it is unlikely that this kind of overdosing can lead any serious consequences.

4.5.3 Third POM criterion:

- It is a substance the activity and/or side effects of which require further investigation

Amorolfine is not a substance which requires further investigation. No concerns arise in regard to this criterion.

5 PHARMACY PROTOCOL AND TRAINING

The Pharmacy Protocol and Training proposals have been prepared by a suitably qualified person. The aim is to provide suitable background and educational material for pharmacists and medicines counter assistants.

The material includes background information on onychomycosis, amorolfine and the SPC for Curanail, together with more detailed information on:

- Whether the condition is suitable for treatment with Curanail
- Whether the product is suitable for the customer
- Advice on initial supply of the product
- Advice while using the product
- Other strategies to combat or prevent onychomycosis

Assessor's comment
The proposals are acceptable.

6 PRODUCT INFORMATION

Certain changes were made to the product information (SPC, PIL and labelling) to reflect the non-prescription use of the product.

7 DISCUSSION

The high prevalence of onychomycosis justifies the rationale of the treatment of the condition. Onychomycosis should not therefore be considered a trivial disease, and should be treated to reduce the number of the condition and increase quality of life.

Although systemic therapy is almost always more successful than topical treatment in the management of onychomycosis, topical treatment has proved to be effective in the mild cases of onychomycosis. Among topical treatments amorolfine nail lacquer is the most effective preparation.

Amorolfine has a good safety profile with very few side effects reported in clinical studies or in use as a POM medicine. The clinical pharmacology of the product assumes minimal systemic side effects of amorolfine lacquer. The most frequently reported adverse events are nail disorders and skin irritations.

According to BNF, PRODIGY and Guidelines for Treatment of Onychomycosis by the British Association of Dermatologist topical antifungal therapy is recommended for the treatment of mild cases of DLSO when up to two nails are affected. Based on this, the indication of the P product should be restricted to patients with early onychomycosis when involvement is limited to mild distal disease in up to 2 nails.

There are several underlying conditions, which predispose for fungal nail infections including impaired circulation, diabetes mellitus, and immunosuppression. Since these patients need

regular supervision of their underlying condition from a doctor, they should be excluded from the P supply of amorolfine.

Although according to guidelines the diagnosis of onychomycosis should be confirmed by mycology before antifungal treatment is commenced, this does not reflect current general practice where diagnosis is established based on the clinical picture alone. Furthermore, if onychomycosis is misdiagnosed and Curanail Lacquer is used inappropriately, the risk to health is negligible, either directly through use of treatment, or indirectly through lack of treatment of the disorders mistaken for onychomycosis.

There is little specific data available on resistance to topically administered amorolfine. Available resistance data to antifungals used for nail infections do not raise any concern over the issue of resistance. Furthermore, the fact that amorolfine is not used for systemic treatment of fungal infections, gives further reassurance.

The treatment should be continued without interruption until the nail is regenerated and the affected areas are finally cured. In general, it is six months in case of finger nails and nine to twelve months for toe nails. Re-occurrence of onychomycosis can only be avoided when both the fungi and the spores are eliminated, which will only occur once the infected section of the nail has fully grown out. With such a long duration of treatment, it is important to warn patients to use the product correctly. Treatment review at 3 monthly intervals serves as an opportunity to maintain patient compliance.

8 CONCLUSION

The advice of the Committee is sought on whether amorolfine nail lacquer for the treatment of mild cases of disto-lateral subungual onychomycosis caused by dermatophytes, yeasts and moulds limited up to 2 nails may safely be supplied without prescription.

COMMITTEE ON SAFETY OF MEDICINES RECOMMENDATION – 14th April 2005

The UK Advisory Committee considered whether Curanail 5% Lacquer containing amorolfine 5% falls within a description or class specified for the purpose of Section 58 of the Medicines Act 1968 by Order made under Section 58(1) as being appropriate for supply on a Prescription Only basis in accordance with Section 58(A)(2) of that Act, and advised that the product could be available for non-prescription supply, under the following conditions:

- Treatment of onychomycosis affecting the distal nail plate of not more than 2 nails, caused by dermatophytes, yeasts and moulds in adults aged 18 years and over
- Maximum strength 5%
- Maximum pack size 3ml of product.

Additionally, a number of points relating to the Summary of Product Characteristics, Product Information Leaflet and labelling were raised. The applicant agreed to the changes.

EXTERNAL CONSULTATION PROCESS

ARM 31 proposing pharmacy availability of Curanail Lacquer was issued on 18 July 2005 with a deadline for comments of 30 August 2005.

There were 20 responses, of which 15 were in favour, 1 against the proposal, 1 neither for nor against and 3 with no comment.

Those organisations in favour included the Royal College of General Practitioners, Royal College of Physicians, Royal Pharmaceutical Society of Great Britain, National Pharmacy Association and other pharmacy organisations, together with the Royal College of Nursing and the Skin Care Campaign.

The British Association of Dermatologists did not express a preference and an individual pharmacist was not in favour.

DISCUSSION OF RESPONSES TO CONSULTATION

The majority of responders were in favour of the proposal. The main issue raised was concern over the efficacy of the product. Additional issues were related to the posology and misdiagnosis.

Efficacy and posology

Five responses were received on the issues of efficacy and posology. The Royal College of Physicians do not object the proposal and think that it is reasonable to make this product available for the general public. However, the College expressed concern that the product would be ineffective. The British Association of Dermatologists considers that the patient information leaflet patients should inform patients that the cure rate with Curanail lacquer might be quite low. A pharmacist disagreed with the proposal and commented that topical antifungal nail lacquers were not effective preparations.

The Royal Pharmaceutical Society of Great Britain (RPSGB) pointed out that further information was needed whether efficacy was likely to be affected by administering the product once weekly as opposed to the approved 1-2 times weekly administration.

The Dispensing Doctor's Association commented that the P product should be used twice a week as it was indicated for the POM product.

The British Association of Dermatologists commented that since onychomycosis was improving slowly, it could be expected that patients terminate the treatment early. The Royal Pharmaceutical Society of Great Britain think that it should be emphasised in the PIL that patients should return to the pharmacy at 3-month intervals for further assessment.

Assessor's comment:

The issues of efficacy and the posology have been discussed in the previous paper.

It has been acknowledged that systemic therapy is more successful than topical

treatment. The BNF, PRODIGY and Guidelines for Treatment of Onychomycosis by the British Association of Dermatologist recommend topical antifungal therapy only in mild cases of onychomycosis. BNF suggests topical treatment in cases when up to two nails are affected. Based on this guidance the indication of amorolfine will be restricted for the treatment of mild cases of disto-lateral subungual onychomycosis limited up to 2 nails.

The posology for the POM product is once weekly. The POM SPC also states that twice weekly application may prove beneficial in some cases. The applicant provided additional evidence to show that in mild cases once weekly administration of amorolfine is similarly effective to the twice weekly application.

The PIL should emphasise the need to review progress with the pharmacist 3 monthly intervals.

5.1 Misdiagnosis

The British Association of Dermatologists expressed concern over the appropriateness of the diagnosis without laboratory test. Additionally, it is thought that a large number of patients with onychomycosis from other causes would be getting treatment inappropriately.

Others commented that the pharmacy training will ensure that the product is supplied for appropriate patients. The RPSGB has emphasised the importance of the role of the pharmacist in appropriate diagnosis and have raised a query on the plans to cascade training material to pharmacists.

ASSESSOR'S COMMENT:

The issue of misdiagnosis have been discussed in the previous paper. In current general practice the diagnosis of onychomycosis is based on the clinical picture alone. Other conditions similar to nail infection are accompanied by skin symptoms, which help in the differential diagnosis. In addition, patients with underlying conditions, which predispose for fungal nail infection (impaired circulation, diabetes mellitus, immunosuppression) will be excluded from the P supply of amorolfine and will be referred to their GP.

The role of the pharmacist is important with the initial diagnosis and ensuring correct use. It is important that the applicant liaises with the RPSGB to ensure suitable training material is supplied to all pharmacists.

6. CONCLUSION

No new issues have been identified during consultation. Fifteen of the responders were in favour; one was not in favour of the proposal. One responder expressed concerns and three did not provided comment. The applicant should liaise with the RPSGB in relation to the content and distribution of the training material.

The majority of responders concur with the proposals outlined in the consultation document. In the light of the responses to consultation, Curanail lacquer can be reclassified as a pharmacy medicine for the treatment of mild cases of disto-lateral subungual onychomycosis caused by dermatophytes, yeasts and moulds limited up to 2 nails. The labels and leaflet have been amended consistent with the CSM advice and full mock-ups submitted.

Final Conclusion

Responses to consultation raise no new issues of concern and are considered acceptable for grant of the reclassification.

SPC labels and leaflet have been updated satisfactorily. The application may be approved.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for this application is consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

Amorolfine has been used to treat the symptoms of onychomycosis for many years. The data supplied with this application is identical to the previously approved marketing authorisation for Loceryl Nail Lacquer 5 % (PL 10590/0042).

No new or unexpected safety concerns arise from these applications.

The SPCs, PILs and labelling are satisfactory and consistent with that for the cross-reference product, with appropriate amendments to account for the reclassification of the product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product. Clinical experience with amorolfine is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive. Suitable justification has been provided for the reclassification of this product from Prescription Only Medicine (POM) to Pharmacy (P).

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 01/09/2004.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 29/09/2004.
3	Following assessment of the application the MHRA requested further information relating to the dossier on 25/11/2004, 22/11/2005, 29/11/2005, 04/01/2005, 30/03/2006 and 05/04/2006.
4	The applicant responded to the MHRA's requests, providing further information relating to the dossier on 24/11/2005, 22/12/2005, 13/01/2006, 20/02/2006, 31/03/06, 04/04/2006 and 05/04/2006.
5	The MHRA's assessment report was considered by the Committee on Safety of Medicines (CSM) on 14/04/2005 and CSM recommended approval of the application, under certain conditions, subject to amendments to the product particulars (SPC and PIL) .
6	External Consultation was sought by the MHRA regarding the proposed reclassification of the product on the 18/07/ 2005.
7	The application was determined on 07/04/2006.

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STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

CURANAIL 5% NAIL LACQUER
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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Curanail 5% Nail Lacquer

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Curanail lacquer contains 5% w/v amorolfine in the form of hydrochloride.

Amorolfine is chemically described as *cis*-4-[(RS)-3[4-(1,1-Dimethylpropyl)phenyl]-2-methylpropyl]-2,6-dimethylmorpholine.

Amorolfine hydrochloride	HSE	6.40	%w/w

3. PHARMACEUTICAL FORM

Medicated Nail Lacquer.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of mild cases of distal and lateral subungual onychomycoses caused by dermatophytes, yeasts and moulds limited up to 2 nails.

4.2. Posology and method of administration

Adults and Elderly
The nail lacquer should be applied to the affected finger or toe nails once weekly. The patient should apply the nail lacquer as follows:

1.Before the first application of Curanail 5% nail lacquer, it is essential that the affected areas of nail (particularly the nail surfaces) should be filed down as thoroughly as possible using the nail file supplied. The surface of the nail should then be cleansed and degreased using a cleaning pad (as supplied). Before repeat application of Curanail 5% nail lacquer, the affected nails should be filed down again as required, following cleansing with a cleaning pad to remove any remaining lacquer.

Caution: Nail files used for affected nails must not be used for healthy nails.

With one of the reusable applicators supplied, apply the nail lacquer to the entire surface of the affected nails and allow it to dry. After use, clean the applicator with the same cleaning pad used before for nail cleaning. Keep the bottle tightly closed.

For each nail to be treated, dip the applicator into the nail lacquer without wiping off any of the lacquer on the bottle neck.

Caution: When working with organic solvents (thinners, white spirit, etc.) wear impermeable gloves in order to protect the Curanail 5% nail lacquer on the nails.

Treatment should be continued without interruption until the nail is regenerated and the affected areas are finally cured. The required frequency and duration of treatment depends essentially on intensity and localisation of the infection. In general, it is six months (finger nails) and nine to twelve months (toe nails). A review of the treatment is recommended at intervals of approximately three months.

Co-existent tinea pedis should be treated with an appropriate antimycotic cream.

Children
Due to the lack of clinical experience available, Curanail lacquer is not recommended for patients below the age of 18 years.

4.3. Contraindications

Curanail 5% nail lacquer must not be reused by patients who have shown hypersensitivity to the treatment.

No experience exists of use during pregnancy and nursing, therefore, the use of Curanail 5% nail lacquer should be avoided during pregnancy and lactation.

4.4. Special warnings and precautions for use

Avoid contact of the lacquer with eyes, ears and mucous membranes.

Patients with underlying conditions predisposing to fungal nail infections should be referred to a doctor. Such conditions include peripheral circulatory disorders, diabetes mellitus, and immunosuppression.

Patients with nail dystrophy and destroyed nail plate should be referred to their doctor.

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

There are no specific studies involving concomitant treatment with other topical medicines.

Use of nail varnish or artificial nails should be avoided during treatment.

4.6. Pregnancy and lactation

Reproductive toxicology studies showed no evidence of teratogenicity in laboratory animals but embryotoxicity was observed at high oral doses. The systemic absorption of amorolfine during and after topical administration is very low and therefore the risk to the human foetus appears to be negligible. However, because there is no relevant experience, Curanail 5% nail lacquer should be avoided during pregnancy and breast feeding.

4.7. Effects on ability to drive and use machines

None.

4.8. Undesirable effects

In exceptional cases, a slight, transient burning sensation in the area of the nails was observed after the application of nail lacquer.
Rare cases of nail disorders, i.e. nail discoloration, broken nails, brittle nails have been reported during treatment with Curanail 5% Nail Lacquer. However, these reactions can also be linked to the onychomycosis itself.

4.9 Overdose

Accidental oral ingestion
Curanail is for topical use. In the event of accidental oral ingestion, an appropriate method of gastric emptying may be used.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Curanail is a topical antimycotic. 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 broad spectrum antimycotic. It is highly active (MIC < 2mcg/ml) *in vitro* against

yeasts:	*Candida, Cryptococcus, Malassezia*
dermatophytes:	*Trichophyton, Microsporum, Epidermophyton*
moulds:	*Hendersonula, Alternaria, Scopulariopsis*

dematiacea:	*Cladosporium, Fonsecaea, Wangiella*
dimorphic fungi:	*Coccidioides, Histoplasma, Sporothrix*

With the exception of *Actinomyces*, bacteria are not sensitive to amorolfine. *Propionibacterium acnes* is only slightly sensitive.

5.2. Pharmacokinetic properties

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.

Following prolonged use of Curanail 5% Nail Lacquer, there is no indication of drug accumulation in the body.

5.3. Preclinical safety data

None stated.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Methacrylic acid copolymer, triacetin, butyl acetate, ethyl acetate, ethanol absolute.

6.2. Incompatibilities

None.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Curanail 5% nail lacquer should be stored below 30°C. Protect from heat. Keep bottle tightly closed after use.

6.5. Nature and contents of container

Amber glass bottle with screw thread and plastic screw closure.

Pack Sizes: 3ml

All packs contain cleansing swabs, spatulas and nail files.

6.6. Special precautions for disposal

No special instructions.

7. MARKETING AUTHORISATION HOLDER

Galderma (UK) Limited
Galderma House
Church Lane
Kings Langley
Herts. WD4 8JP
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 10590/0049

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/04/2006

10 DATE OF REVISION OF THE TEXT

CURANAIL 5% NAIL LACQUER
PL 10590/0049

PRODUCT INFORMATION LEAFLET

Curanail

5% Nail Lacquer
Amorolfine

PATIENT INFORMATION LEAFLET

Please read all of this leaflet carefully because it contains important information.
You can buy Curanail® 5% Nail Lacquer without a prescription so that you can treat your nail infection yourself. Please follow the instructions below to get the best results.
Keep this leaflet, in case you need to refer to it later.
• Ask your pharmacist if you need any more information or advice.
You must go and see the doctor, pharmacist or podiatrist if your symptoms get worse or do not improve after 3 months.

P23305-1

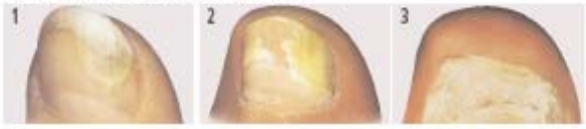
This leaflet describes:
1. What Curanail® 5% Nail Lacquer is and what it is used for
2. What to consider before you use the nail lacquer
3. How to use the nail lacquer
4. Possible side effects
5. Storing the nail lacquer

CURANAIL® 5% NAIL LACQUER

The active substance is amorolfine (as the hydrochloride).
The nail lacquer contains 50 mg/ml (5%) of the active ingredient amorolfine. It also contains the excipients (additional ingredients) methacrylic acid copolymer 150,000, triacetin, butyl acetate, ethyl acetate and ethanol.
Each pack contains 1 bottle filled with 3ml of nail lacquer together with cleansing swabs, re-useable applicators and nail files.
The Marketing Authorisation holder is Galderma (UK) Ltd, Galderma House, Church Lane, Kings Langley, Herts. WD4 8JP, United Kingdom. (PL 10590/0049)
This medicine is made by Laboratoires Galderma, 74540 Alby-Sur-Chéran, France.

1. What Curanail® 5% Nail Lacquer is and what it is used for

The active ingredient amorolfine belongs to a group of medicines known as antifungals. The nail lacquer is used to treat fungal infections affecting up to 2 nails and affecting the upper half or sides of the nail (as shown in the first picture below). If the infection appears to be more like pictures 2 or 3, you should consult your doctor. Amorolfine kills a wide variety of fungi that can cause nail infections. A fungal nail infection is likely to result in discoloured (white, yellow or brown), thick or brittle nails, although their appearance can vary considerably as the following pictures show:

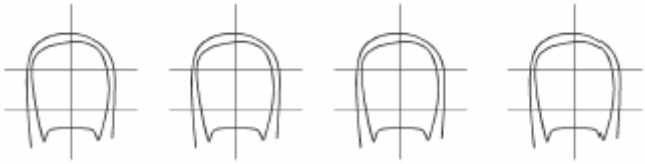


2. What to consider before you use Curanail® 5% Nail Lacquer

Do not use it if:
You are allergic to the nail lacquer or any of the ingredients it contains.
You are pregnant, think you are pregnant, or intend to become pregnant or are breastfeeding.
You are under the age of 18.
Check with your doctor or pharmacist before using if:
You suffer from diabetes.
You are being treated because you have a weak immune system.
You have poor circulation in your hands and feet.
Your nail is severely damaged or infected.
Important information about some of the ingredients of Curanail® 5% Nail Lacquer :
This product contains ethanol (alcohol). Using it too often or applying innaccurately may produce irritation and dry the surrounding skin.
Interactions with other medicines:
You can use the nail lacquer whilst you are taking other medicines.

3. How to use Curanail® 5% Nail Lacquer

Before Commencing Treatment
In the diagram below, shade the area affected by the fungal nail infection. This will help you in remembering how the nail looked originally when your treatment is reviewed. Every three months, shade the area now affected until the infected nail has completely grown out. If more than one nail is affected, select the worst affected nail for this exercise. Take this leaflet to the pharmacist or podiatrist when treatment is being reviewed to inform them of treatment progress to date.

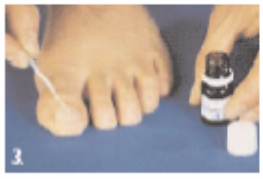


Before Treatment | Three Months | Six Months | Nine Months

Treat your infected nails as described below. NAILS SHOULD BE TREATED ONCE A WEEK. Once weekly application should continue for 6 months for finger nails and 9 to 12 months for toe nails. Nails grow slowly so it may take 2 or 3 months before you start to see an improvement. It is important to carry on using the nail lacquer until the infection has cleared and healthy nails have grown back. The following steps should be followed carefully for each affected nail:

Step 1: Prepare the Nail
Using a new file, gently file down the infected areas of nail, including the nail surface. Protect any healthy nails while you are doing this so that you don't spread the infection.
CAUTION: Do not use the same nail file for infected nails and healthy nails, as this could spread the infection as well. To prevent the spread of infection take care that no one else uses the files from your kit.

Step 2: Clean the nail
Use one of the swabs provided to clean the nail surface. Do not throw the swab away as you will need it later to clean the applicator.



Step 3: Treat the nail
Dip one of the re-usable applicators into the bottle of nail lacquer. The lacquer must not be wiped off on the edge of the bottle before it is applied.
Apply the lacquer.
Apply the nail lacquer evenly over the entire surface of the nail.
Allow to dry.
Let the treated nail(s) dry for approximately 3 minutes.

Following Application:

Clean the applicator

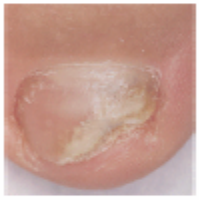
You can use the applicators provided more than once. However, it is important to clean them thoroughly each time so that you don't spread the infection. Use the same swab you used for cleaning your nails. Don't touch the newly treated nails with the swab.

Close the nail lacquer bottle tightly. Dispose of the swab carefully as it is inflammable.

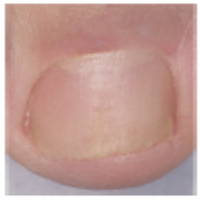
Before using the nail lacquer again, first take the old lacquer off your nails using a clean swab, then file down the nails again. Re-clean with the swab and re-apply the lacquer as described above.

- When dry the nail lacquer is unaffected by soap and water, so you can wash your hands and feet as normal.
- Wear rubber, or other waterproof gloves, to protect the lacquer on your fingernails when you are using chemicals such as paint thinners or white spirit
- It is important to carry on using the nail lacquer until the infection has cleared and healthy nails have grown back. This usually takes 6 months for fingernails and 9 to 12 months for toenails.

  You will see a healthy nail growing as the diseased nail grows out
- Do not use nail varnish or artificial nails during treatment.



Before Treatment



After Treatment

Important
- If you get Curanail® 5% Nail Lacquer in your eyes or ears wash it out with water immediately and contact your doctor, pharmacist or nearest hospital straight away.
- Avoid the lacquer coming into contact with mucous membranes (e.g. mouth and nostrils). Do not breathe it in.
- If you, or anyone else, accidentally swallows the lacquer contact your doctor, pharmacist or nearest hospital straight away.

4. Possible side effects

Like all medicines Curanail® 5% Nail Lacquer can have side effects. Very rarely, you may feel a slight burning sensation in the nail area after applying the nail lacquer. Some people have noticed nail discolouration, or broken or brittle nails during treatment, but these symptoms may be associated with the infection itself.
If you are concerned about this or you notice anything else which you don't understand talk to your pharmacist or podiatrist.

5. Storing Curanail® 5% Nail Lacquer

Keep out of the reach and sight of children.

Keep the pack away from heat and do not store above 30 °C. Keep the bottle tightly closed after use.

Do not use after the date (EXP) printed on the pack.

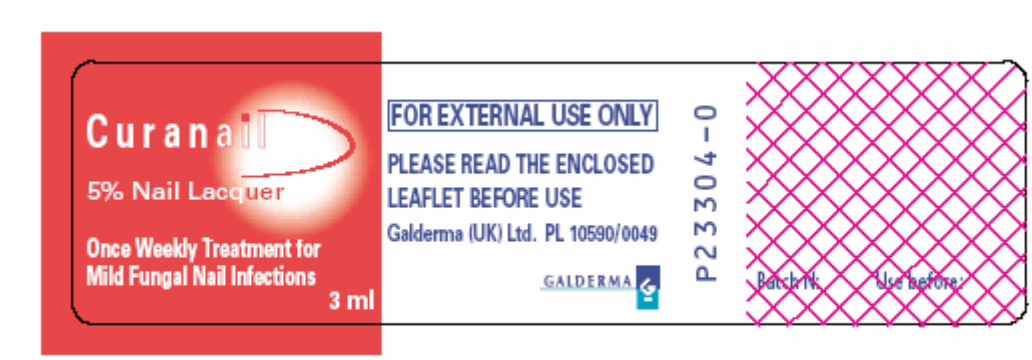
Date of preparation of this information: November 2005

GALDERMA

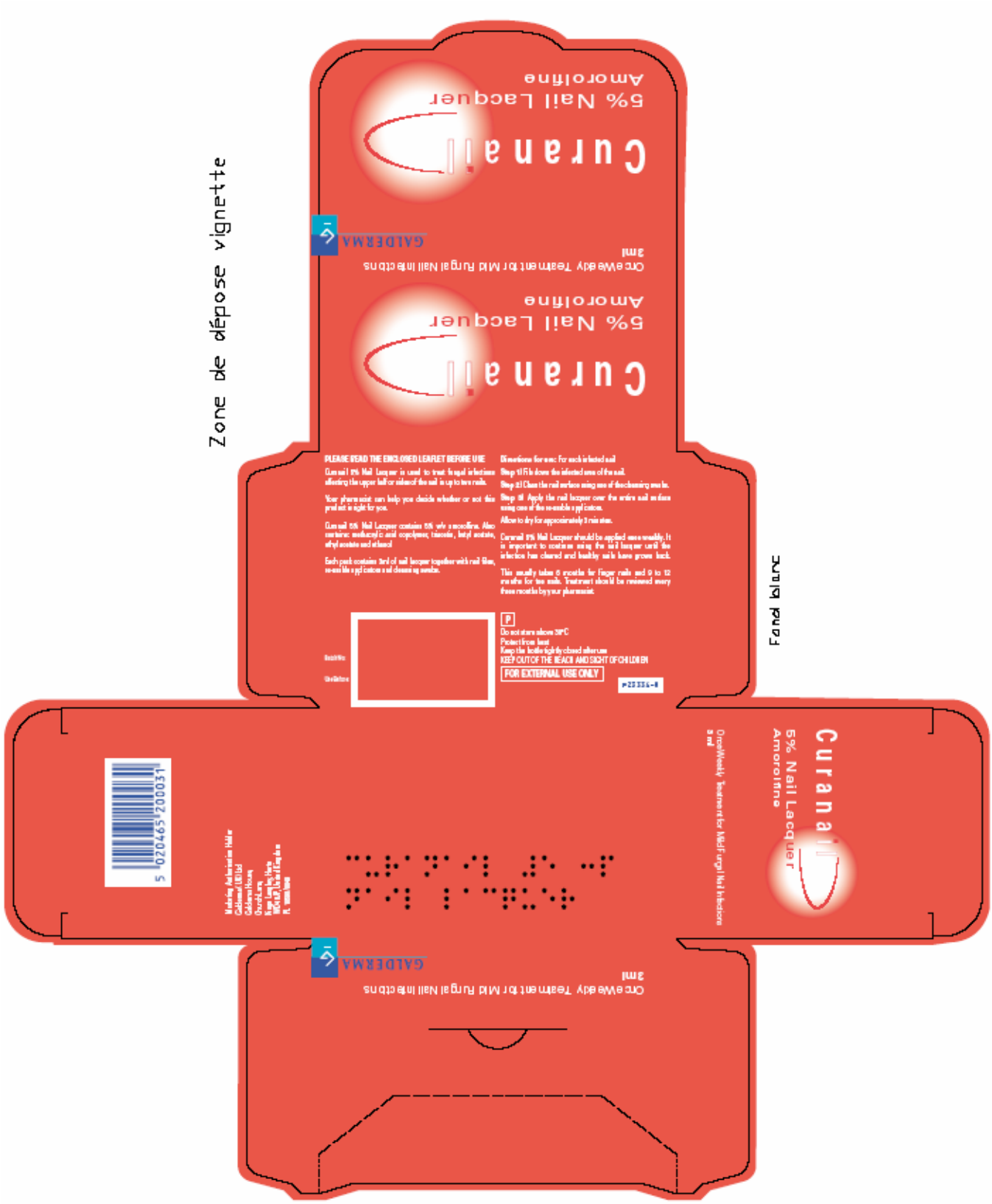
CURANAIL 5% NAIL LACQUER
PL 10590/0049

LABELLING

LABEL



CARTON


Zone de dépose vignette
Fond blanc
Curanail
5% Nail Lacquer
Amorolfine
3ml
GALDERMA
PLEASE READ THE ENCLOSED LEAFLET BEFORE USE
FOR EXTERNAL USE ONLY
5 020465 200031