Name of drug: Loceryl Nail Lacquer, amorolfine (5%) as the hydrochloride in a lacquer base consisting of methacrylic acid copolymer, glycerol triacetate, butyl acetate, ethyl acetate, ethanol absolute.

INN: Amorolfine

Chemical Name: cis-4-{(RS)-3-[4-(1,1-dimethylpropyl)Pheny1]-2-methylpropyl}-2,6-dimethyl morpholine hydrochloride.

Molecular formula: C$_{21}$H$_{35}$NO-HCl

CAS Registry Number: 78613-38-4

Molecular weight: 353.98.

Chemical class: Antifungal agent.

Chemical structure:

Composition

Amorolfine hydrochloride is a white to off white powder, having at most a slight odour. It has a very high lipophilicity with a partition coefficient of >1000 in n-octanol buffer (pH 7.5). Amorolfine hydrochloride is slightly soluble in water (932mg/100mL at 23°C). It is less soluble in hydrochloric acid due to a common ion effect (solubility 320mg/100mL in artificial gastric fluid, pH 1.2 at 37°C). Amorolfine hydrochloride is practically insoluble in artificial intestinal juice at pH 7.4. The pKa of amorolfine hydrochloride is 6.6.

PHARMACOLOGY

Actions

Class Amorolfine is a topical antimycotic. Amorolfine belongs to a new chemical class. Its fungistatic or fungicidal effect 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.

Site and mode of action Amorolfine has a broad spectrum of action. It is effective against:
Yeast: Candida, Cryptococcus
Dermatophytes: Tricophyton, Microsporum, Epidermophyton
Moulds: Alternaria, Hendersonula, Scopulariopsis
Dematiacea: Cladosporium, Fonsecaea, Wangiella
Dimorphic fungi: Coccidioides, Histoplasma, Sporothrix

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

In rats, progressive cataract formation was seen after high oral doses (40 and 60 mg/kg/day in 26- and 13-week studies, respectively). Females were more affected than males. In both sexes, further deterioration occurred during the recover period. Cataract formation also became apparent after 26 weeks in dogs treated orally with 40mg/kg/day. The mechanism of cataract formation is unknown.

Additional data from a study in pigmented rats with dermal application of 0.25% amorolfine cream indicated neither a direct cataractogenic nor a co-cataractogenic potential. The systemic exposure of the rats during this study resulted in plasma concentrations 7 to 10 fold greater than expected in humans.

**Pharmacokinetics.**

Amorolfine from nail lacquer penetrates and diffuses through the nail plate.

In one clinical study, patients being treated for a large number of infected nails tended to have measurable levels of amorolfine between 0.1 and 0.5 ng/mL whereas other patients have levels below the level of quantification (0.1 ng/mL). In this study, nails were not filed before application of the lacquer. One patient consistently had greater than 0.5 ng/mL (maximum 1.05 ng/mL).

**Clinical Trials**

Clinical efficacy of amorolfine has been demonstrated in three main multicentre studies in around 700 patients. The percentage of clinical responders (cure / improvement) ranged from 70% to 80% in all three studies.

In an open, comparative, randomised clinical study conducted in 340 patients with severe infections involving mainly toe-nails, clinical efficacy has been demonstrated when amorolfine 5% nail lacquer was applied twice weekly in conjunction with griseofulvin 500mg twice daily for the first 2 months of a 12 month treatment course. The reduction in treatment with griseofulvin decreased the risk of intolerance to griseofulvin. Clinical efficacy has not been demonstrated in severe onychomycosis (involving the lunula) for amorolfine 5% nail lacquer when used alone.

Data directly comparing efficacy of once versus twice weekly application of LOCERYL is not available. Two studies on a related formulation have suggested a slight increase in mycological and clinical cure rates when lacquer was applied twice weekly rather than once weekly, but increases were not statistically significant.

**INDICATIONS**

Onychomycoses caused by dermatophytes, yeasts and moulds.

**CONTRAINDICATIONS**
Loceryl nail lacquer must not be reused by patients who have shown hypersensitivity to the treatment. Since there are no data on the use of LOCERYL in pregnant and lactating women, the use of LOCERYL nail lacquer should be avoided during pregnancy and lactation.

**PRECAUTIONS**

Occasionally, a slight transient burning sensation in the area of the nails was observed after application of nail lacquer. The application of lacquer to skin areas surrounding the nails should be avoided.

**Use in pregnancy – Category B3**

Exposure of pregnant rats and rabbits to systemic amorolfine (> 10 mg/kg/day/orally) resulted in increased resorptions (embryotoxicity). The significance of these findings to human embryotoxicity is not known. There are no data on the use of amorolfine in pregnant women.

**Use in lactation**

In a peri- and postnatal study in rats, an increased mortality of newborn pups was observed at 10 mg/kg/day orally. There is no information on whether amorolfine passes into human breast milk. There are no data on the use of amorolfine in lactating women.

**Use in children**

Owing to the lack of clinical experience available to date, children – particularly young children and infants – should not be treated with amorolfine.

**Carcinogenicity and Genotoxicity**

No animal carcinogenicity studies have been conducted on amorolfine. Amorolfine was not shown to be genotoxic in a standard battery of assays for gene mutations and chromosomal changes.

**ADVERSE REACTIONS**

Of the 502 patients treated with amorolfine nail lacquer monotherapy, 3 (0.6%) experienced local adverse events such as itching and erythema. Of the 172 patients evaluated for safety in the combination group during the monotherapy period, 3 (1.8%) experienced the following adverse reactions: pruritis and vesicles (1), periungual scaling (1) and nail discoloration (1). In a sensitization study involving 122 subjects, about one-tenth of patients experienced delayed hypersensitivity skin reactions.

Rare cases of nail disorder (nail discolouration, brittle nails (onychorrhesis) or broken nails) have been reported during treatment with Loceryl nail lacquer. However these reactions may also be linked to the onychomycosis itself.

Very rarely (≤1/10000) burning sensation and contact dermatitis.

**DOSAGE AND ADMINISTRATION**

The patient should apply the nail lacquer to affected finger or toe nails once or twice weekly. Twice weekly application may be more effective, see Clinical Trials. Application is as follows:

1. Before the first application of LOCERYL 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 LOCERYL Nail Lacquer, the affected nails should be filed down again as required, and in any case they must first be cleansed with a cleaning pad to remove any remaining lacquer.

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

2. With one of the reusable spatulas supplied, apply the nail lacquer to the entire surface of the affected nails. For each nail to be treated, dip the spatula into the nail lacquer without wiping off any of the lacquer on the bottle neck. After use, clean the spatula as well as the neck of the bottle with the same cleaning pad used before for nail cleaning. Immediately after application, the bottle should be tightly closed. Allow the nails to dry.

3. When working with organic solvents (thinners, white spirit, etc) wear impermeable gloves in order to protect the LOCERYL lacquer on the nails.

Treatment should be continued without interruption until the nail is regenerated and the affected areas are finally cured. The required duration of treatment depends essentially on intensity and localisation of the infection. In general, it is six months for fingernails. Longer periods are probably required for toenails.

Cosmetic lacquers, artificial nails, or occlusive dressings should not be used during treatment with LOCERYL Nail Lacquer.

Because fungal nail infections are hard to treat, treatment may be required for 6-12 months or longer and a full cure cannot be expected in all cases. After 6 months of treatment, improvement can be expected in 70% to 80% of people, with full cure expected in approximately one in three people.

Clinical efficacy has not been demonstrated in severe onychomycosis (involving the lunula) for amorolfine 5% nail lacquer when used alone.

OVERDOSE

No information is available concerning overdosage in humans.

PRESENTATION AND STORAGE CONDITIONS

Loceryl is supplied in a kit containing the following:
1 amber glass bottle of 2.5 or 5mL nail lacquer
30 cleaning pads impregnated with 70% isopropyl alcohol in foil packets
10 spatulas
30 nail files

Keep in a cool dry place. Store below 30°C

SPONSOR
Galderma Australia Pty Ltd
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POISONS SCHEDULE – S2 – PHARMACY MEDICINE

TGA APPROVAL
03 September 1997
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