Submission to the Medicines Classification Committee

Request for data on the safety of amorolfine as a restricted medicine for consideration of reclassification to pharmacy-only to harmonise with Australia

Amorolfine is a morpholine derivative with antifungal activity. It acts by interfering with the synthesis of sterols essential for the functioning of fungal cell membranes. It is active *in vitro* against a wide variety of pathogenic and opportunistic fungi including dermatophytes, *Blastomyces dermatitidis*, *Candida spp.*, *Histoplasma capsulatum*, and *Sporothrix schenckii*. Amorolfine also has variable activity against *Aspergillus spp*.

Despite its *in vitro* activity, amorolfine is inactive when given systemically which has limited its use to topical applications for superficial infections. After topical administration, systemic absorption is negligible and thus topical treatment rarely produces systemic effects (Sweetman 2009).

Amorolfine classification in Australia and NZ

In June 2010 amorolfine was re-classified in Australia as:

- Schedule 4 (prescription); except when included in Schedule 2 (pharmacy-only) or in preparations for the treatment of tinea pedis
- Schedule 2 (pharmacy-only); in preparations for topical use except in preparations for the treatment of tinea pedis

The current classification in NZ is:

- Prescription; except for external use
- Restricted; for external use in medicines containing more than 0.25%
- Pharmacy-only; for external use in medicines containing 0.25% or less except in medicines for tinea pedis
- General sale; for external use in medicines for tinea pedis only

The purpose of this submission is to give safety information on topical amorolfine as a restricted medicine so the committee can consider reclassification to a pharmacy-only medicine to harmonise with the Australian classification.

Amorolfine products currently marketed in NZ

There is only one amorolfine product currently available in NZ. Loceryl nail lacquer which contains 5% amorolfine was approved in 1992 for the treatment of onychomycosis caused by dermatophytes, yeasts and moults. Onychomycosis is one of the most common dermatological conditions, and accounts for one third of fungal skin infections and one half of nail disease. This infection occurs predominantly in adults and is rarely found in children, with incidence increasing with age (Scher 1999).

Loceryl nail lacquer is amorolfine 5% dissolved in a lacquer base. The solvents evaporate quickly leaving a thin durable film of amorolfine lacquer on the nail surface. Loceryl should be applied to the affected finger or toenails once or twice weekly. Treatment should be continued uninterrupted until the nail is regenerated and the affected areas are cured. Treatment generally needs to be continued for 6 to 12

months. The package insert and label have a series of instructions and illustrations showing consumers how the lacquer is to be applied.

Safety Profile

The Loceryl datasheet states that adverse effects are rarely experienced and relatively minor, predominantly itching and arythema (0.6%) when used as monotherapy. A copy of the datasheet is attached as annex 1. Topical amorolfine has a well established safety profile with the only contraindication being hypersensitivity to the product. The datasheet states that Loceryl is not indicated for use in children or during pregnancy or lactation. This appears to be based on lack of clinical experience in these populations. The datasheet discusses embryotoxicity in rats and rabbits exposed to high oral doses of systemic amorolfine ($\geq$10 mg/kg/day), although this is of little relevance to topical amorolfine which has negligible systemic absorption. There are no listed drug interactions or interactions with common substances or foods. The datasheet states that concomitant use of cosmetic nail varnish or artificial nails is not recommended.

Loceryl 5% nail lacquer -adverse reactions

There has only been one adverse drug reaction report to CARM for amorolfine 5% (Loceryl nail lacquer), which was in 1999. The report was for non-severe nausea and fatigue in a 49 year old male. This was classified as not serious and unlikely to be related to amorolfine, and the medication was continued. Likewise, in Australia there has only been one adverse reaction report for Loceryl since 2005 involving loss of smell in a 69 year old male.

Points from the Australian National Drugs and Poisons Schedule Committee regarding re-classification to pharmacy-only

In their submission to the Australian committee the applicant considered that amorolfine fit all criteria for schedule 2 (pharmacy-only) given that:

- Amorolfine was suitable for self-treatment of onychomycosis
- Low potential for harm from inappropriate use and very low abuse potential
- Low or well characterised incidence of adverse effects and contraindications for which advice or counselling is available
- High therapeutic index and a wide therapeutic window
- The risk of masking a serious disease and of compromising medical management of a disease was extremely low
- No requirement for ongoing or close medical management during use
- The condition is easily recognisable by consumer and capable of being monitored and self-managed by the consumer, with advice if necessary

The Australian evaluator suggested the applicant's claim that onychomycosis was self-diagnosable was doubtful and emphasised the significance of pharmacist intervention to aid the assessment of the patient and referral to a doctor if no proper diagnosis could be made. Subsequently, the applicant contended that the basis for this reclassification was that onychomycosis, like many other topical fungal skin infections, can be successfully treated by consumers. This was accepted by the TGA assessor who added that while some consumers may request advice with the first purchase, it would usually not be required for repeat purchases over the period of treatment (up to 12 months).

The evaluator agreed that the risk of masking an underlying serious medical condition through topical treatment of onychomycosis was negligible since onychomycosis alone was rarely, if ever, a symptom of an underlying serious pathology. In the unlikely event that onychomycosis was misdiagnosed and amorolfine nail lacquer was used inappropriately, there was negligible risk to health.

The TGA evaluator also agreed with the applicant's claims that the symptoms of skin irritation and allergic sensitivity were easily recognisable by the consumer and appropriate advice to discontinue treatment and seek medical help was provided in the package insert.

The TGA report noted that toxicity and safety of amorolfine was well addressed by the applicant and supported that amorolfine was safe with low toxicity, and there is no potential for development of resistant mutant fungal strains, or potential for misuse or abuse.

A copy of the Australian National Drugs and Poisons Schedule Committee record of reasons is attached as annex 2.

References

Scher, R.K (1999) Onychomycosis: therapeutic update. *Journal of the American Academy of Dermatology* 40: S21-S26

Sweetman, S.C. (2009) *Martindale The Complete Drug Reference*. UK Pharmaceutical Press.