Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

P2: 2004/29670
P4: 2004/20986
Application No: 2004/266/5

[redacted]
Biotechnolgy Manager
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Dear Sir/Madam

SUBJECT: Tacrolimus (Protopic)

Please find enclosed a copy of the relevant edited extract from the Minutes of the 239th (2005/2) Meeting of the Australian Drug Evaluation Committee. These have now been ratified.

The ratified Minutes of the deliberations are forwarded to the Chairman, National Drugs and Poisons Schedule Committee, for information and further action, if appropriate.

Yours sincerely

[redacted]
Secretary
Australian Drug Evaluation Committee

17th June 2005

EXTRACT FROM THE RATIFIED MINUTES
OF THE 239th (2005/3) MEETING OF THE
AUSTRALIAN DRUG EVALUTION COMMITTEE
HELD ON 3 – 4 FEBRUARY 2005

2.11 Tacrolimus – PROTOPIC – Janssen-Cilag Pty Ltd

2.11.1 Application Details

The ADEC considered a submission from Janssen-Cilag Pty Ltd to register a new dose form, new route of administration, new patient population (children) and new indication for PROTOPIC Ointment, containing tacrolimus 300 µg/g and 1 mg/g. The proposed indication was "0.03% and 0.1% for adults, and only 0.03% for children two years of age and above, for the short-term and intermittent long-term treatment of moderate to severe atopic dermatitis in patients who are not adequately responsive to or intolerant of conventional therapies".

2.11.2 Evaluations

There was no objection to registration from the Quality and Biopharmaceutics Evaluator. The base was occlusive and contained soft paraffin. Bioavailability parameters were not calculable, as tacrolimus in serum samples from healthy adult volunteers was routinely below the limit of quantification. The PSC had no objection to registration.

Overall, results of the nonclinical studies were not considered sufficient to preclude approval of registration, given that Protopic was proposed for use in patients not adequately treated with conventional therapies. However, no adequate studies had been carried out in young animals to support the use of tacrolimus ointment in children.

The Clinical Evaluator supported registration. Both strengths were superior to placebo and, in children, superior to 1% hydrocortisone acetate ointment. Application site adverse reactions were higher for tacrolimus ointment compared to placebo and steroids. Systemic adverse reactions included flu syndrome and headache.

2.11.3 Delegate's Proposed Action

The Delegate proposed to reject the submission due to nonclinical deficiencies. These included an inadequate exploration of use in young animals, inadequate data on long-term use in primates, evidence of no margin of safety in the single model of efficacy presented, and no nonclinical data on combination therapy (which may be expected in clinical use). Toxicity could arise from local effects or from systemic absorption.

2.11.4 ADEC Discussion

There were eight pharmacodynamic studies, twelve pharmacokinetics studies, four phase II studies and eight phase III studies. There were data deficiencies in a number of studies and in the submission as a whole.

The efficacy studies showed that 0.03%, 0.1% and 0.3% w/w ointments (registration of the latter strength was not sought) were superior to placebo. Several studies compared tacrolimus to various topical corticosteroids and showed suppression of atopic dermatitis. No data suggested that tacrolimus 0.3% was more effective than

tacrolimus 0.1%, and some studies showed no difference between tacrolimus 0.1% and 0.03% formulations.

The proposed directions for use include application as a thin layer to any part of the body, excluding mucous membranes. There was no maximum to the proportion of body surface area that should be treated and no maximum usage rate. This was of concern as the pharmacokinetic data indicated that up to 30% of patients would experience significant transdermal absorption of tacrolimus, including reaching systemic concentrations not dissimilar in some circumstances to the trough concentrations that are attained after oral tacrolimus dosing to prevent acute rejection. There was reference to, but no evidence of, pharmacokinetic data from children as young as two years of age. In the absence of a dosage device, the quantity of tacrolimus applied could be unknown, variable, and excessive. For young children with a high surface area to body-mass ratio and severely affected skin, the quantity applied and absorbed could be substantial. This was relevant to the consideration of the exposure margins that induced lymphoma in the nonclinical studies. Cumulative exposure to tacrolimus, an immunosuppressant, with intermittent and long-term use was also relevant.

Tacrolimus does not produce dermal atrophy when compared to corticosteroids. In appropriate patients, use of tacrolimus would be steroid-sparing and also avoid the use of cyclosporin.

Application commonly caused skin burning, erythema and pain. Initial use was associated with flare-up of symptoms. There was a higher incidence of flu-type syndrome and headache among patients using tacrolimus. A Member noted that Australian use of extemporaneously prepared topical tacrolimus restricted use to application to the face and frequent clinical review was required. Use of sunscreen was also emphasised.

As tacrolimus was an immunosuppressant there was the potential for adverse effects of this class, such as inflammatory lesions, nephrotoxicity and carcinogenesis.

The ADEC agreed with the concerns of the Nonclinical Evaluators that there were no studies in young animals. While the Nonclinical Evaluators acknowledged that there was no apparent photosensitisation in guinea pigs and hairless mice in the studies undertaken, photocarcinogenicity was enhanced by the presence of tacrolimus. Potential for malignancy with long-term exposure was noted and the lymphomas that were seen in mouse studies were unequivocal.

The ADEC noted the current FDA Public Health Advisory to inform health care providers and patients about a potential cancer risk from use of topical tacrolimus. In the USA Protopic was now recommended as a second-line agent for short-term and intermittent treatment of atopic dermatitis in patients unresponsive to, or intolerant of, other treatments.[1] There were other restrictive recommendations. The ADEC had not seen efficacy trials supporting tacrolimus as a second-line agent and this limitation was not possible in Australia. Some of the lymphoma conditions were apparently

[1] http://www.fda.gov/cder/drug/advisory/elidel_protopic.htm (dated 10 March 2005)(accessed 11 March 2005)

occurring in patients much younger than would be expected, which the Sponsor suggested could be due to misdiagnosis or use of tacrolimus in children younger than two years of age. The Committee thought that this was only a partial explanation.

There were limited long-term data. The planned long-term observational data, to be collected in the northern hemisphere, may not adequately address the risks of photosensitivity and photocarcinogenicity which were of particular concern in Australia and New Zealand.

Regarding the proposal that Protopic "should be prescribed by physicians with experience in the topical treatment of atopic dermatitis", the ADEC considered that this was non-specific; if approved, the ADEC recommended that prescribing should be limited to dermatologists.

The formulation included a new excipient, propylene carbonate. It is widely used in sunscreen products and there were no concerns on its use.

See Item 8.6 for discussion on pimecrolimus (Elidel).

2.11.5 Summary Basis for the ADEC Recommendation

Tacrolimus provided symptomatic treatment of atopic dermatitis without the dermal thinning that occurs with corticosteroids.

The ADEC considered that the nonclinical data were inadequate. There were no studies in young animals for a product proposed for use in patients as young as two years of age. Exposure comparisons to adult animals did not reflect the potential higher local and systemic exposure of children due to their relatively larger body surface area to mass ratio and higher absorption though damaged skin. The ADEC noted that in routine clinical use there would be little control over the applied dose. The ADEC also had concerns regarding risks with long-term use. There were emerging clinical concerns about the risk of malignancy. Additional long-term data were required, including from populations with sunlight exposure typical of Australia.

2.11.6 Resolution

The ADEC resolved to recommend to the Minister and the Secretary that:

RESOLUTION NO 8744

The application submitted by Janssen-Cilag Pty Ltd to register PROTOPIC Ointment, containing tacrolimus 300 µg/g and 1 mg/g, as a new dose form, route of administration, patient population and indication, for the indication:

For the short-term and intermittent long-term treatment of moderate to severe atopic dermatitis in patients who are not adequately responsive to or intolerant of conventional therapies.

should be rejected due to concerns regarding non-clinical safety, including an inadequate data package, and emerging clinical concerns regarding lymphoma and other local tumours.

→ Protopic file 2004/90
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U.S. Food and Drug Administration Department of Health and Human Services

FDA News

FOR IMMEDIATE RELEASE
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FDA Approves Updated Labeling with Boxed Warning and Medication Guide for Two Eczema Drugs, Elidel and Protopic

The Food and Drug Administration (FDA) today announced the approval of updated labeling for two topical eczema drugs, Elidel Cream (pimecrolimus) and Protopic Ointment (tacrolimus). The labeling will be updated with a boxed warning about a possible risk of cancer and a Medication Guide (FDA-approved patient labeling) will be distributed to help ensure that patients using these prescription medicines are aware of this concern. The new labeling also clarifies that these drugs are recommended for use as second-line treatments. This means that other prescription topical medicines should be tried first. Use of these drugs in children under 2 years of age is not recommended.

Eczema or atopic dermatitis is one of the most common skin disorders seen in infants and children, affecting 10 to 15 percent of the childhood population. Although the cause of atopic dermatitis is not known, it is thought that there may be an allergic or immune mediated component. Patients have chronic itching and dry skin, which results in redness and damage to the skin due to rubbing and scratching. Both products are applied to the skin to help control eczema. It is not known exactly how the products work, but they have various effects on the body's immune system.

"We are taking steps to ensure that healthcare providers and patients are aware of the possible long-term risks of these products so that they will be used appropriately", said Dr. Steven Galson, Director of FDA's Center for Drug Evaluation and Research (CDER). "Today's actions are aimed at making sure that health care providers and consumers understand the new warnings and that it is important that these products be used as recommended in the label."

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On February 15, 2005, FDA's Pediatric Advisory Committee recommended that the labeling should be updated with a boxed warning and a Medication Guide about the possible cancer risk for these drugs. FDA had issued a Public Health Advisory in March 2005 advising physicians about the possible cancer risk. At the same time, FDA indicated it would ask the sponsors to update the labeling to address this possible risk. Although a causal link has not been established, rare reports of cancer (for example, skin and lymphoma) have been reported in patients who had been receiving these products.

The boxed warning informs healthcare professionals that the long term safety of these drugs has not been established. Although studies are being conducted by the manufacturers of both drugs to try to answer questions about cancer risk, it could be many years before the research is concluded. In the meantime, there is a benefit associated with these drugs when used appropriately. For instance, they may be effective when other prescription topical medications do not work or are not advisable for the patient. The drugs are intended to be used for short periods, but if a patient requires a longer period of treatment, the treatment can be repeated after a period of time off treatment. Patients are advised to call their doctor if symptoms worsen, they develop an infection, or if symptoms do not improve within the six weeks of treatment.

The Medication Guide will provide consumer friendly information to patients about how to use the drugs safely. Pharmacists are required to provide the Medication Guide to patients when dispensing the drug. Patients are advised to read the entire Medication Guide and talk to their healthcare provider if they have further questions.

Novartis manufactures Elidel cream and Astellas Pharma, Inc (formerly Fujisawa Healthcare) is the manufacturer of Protopic ointment.

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Elidel Information

- Label
- Medication Guide

Protopic Information

- Label
- Medication Guide

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