SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION

Protopy is a dermatological medicinal product that contains the calcineurin inhibitor tacrolimus at a 0.1% and 0.03% concentration. Protopy 0.1% is indicated for the treatment of moderate to severe atopic dermatitis (AD) in adults who are not adequately responsive to or are intolerant of conventional therapies and Protopy 0.03% is indicated for the treatment of moderate to severe AD in adults or children (2 years of age and above) who failed to respond adequately to conventional therapies.

On 21 April 2005 the European Commission in view of the potential risk of malignancies requested the Opinion of the CHMP on the benefit/risk profile of Protopy. Following this request, the CHMP reviewed the available data on this safety issue, including post-marketing reports, data from non-clinical studies, clinical trials and epidemiological studies.

Lymphoma is a recognised and listed adverse effect for systemically administered calcineurin inhibitor products. This effect is thought to be mediated by the immunosuppression caused as a result of systemic treatment with the product. Systemic exposure is limited with the topical use of tacrolimus, however a local immunosuppressive effect in the skin cannot be excluded.

Case reports of malignancies (including skin cancer, cutaneous T-Cell lymphoma (CTCL), Non-Hodking lymphoma (NHL) and systemic malignancies) have been received during the clinical development and post-marketing experience in association with the use of Protopy. The data presented did not show a definite association with lymphoma or any malignancy. However there appeared to be an increase in numbers of patients with CTCL, relative to what would be expected. The CHMP agreed that the diagnosis of these skin malignancies is difficult and may mimic AD. However, having reviewed the available data, the CHMP concluded that not all cases could be considered to be cases of pre-existing malignancy disease, and an association with tacrolimus could not be excluded in some of the cases.

With regard to the skin cancers, the CHMP concluded that treatment with tacrolimus was not likely to have caused these skin malignancies. However, considering that tacrolimus is effective through its suppression of T cells which are involved in immune surveillance, it is possible that tacrolimus could have an effect on the behaviour of cutaneous lesions which were either pre-malignant or cases of early malignancy. The mode of action of tacrolimus is stated to be by inhibition of calcium dependent signal transduction pathways in T cells which results in prevention of transcription and synthesis of IL-2, IL-3, IL-4, IL-5 and other cytokines. As tacrolimus is an effective immunosuppressant that acts by suppressing T lymphocytes in the skin, the CHMP was of the opinion that an effect of tacrolimus on the development or progression of a variety of skin lesions could not be excluded.

After reviewing the available data the CHMP concluded that the balance of risks and benefits for Protopy is considered favourable. In order to address the safety concerns in relation to the cases of malignancies the CHMP concluded that warnings reflecting the cases of malignancies and the need for monitoring of patients treated with Protopy should be included in the product information. In order to reduce the likelihood of mis-diagnosis and in order to better ensure the appropriate use of the medicinal product, the CHMP emphasised that the product information should reflect that the initial diagnosis and initial prescription should be undertaken by physicians with experience in the treatment of AD. Additionally, the CHMP concluded that Protopy should not be used in immunocompromised adults or children and that Protopy should not be applied to lesions that are considered to be potentially malignant or pre-malignant and that lymphadenopathy present at initiation of therapy should be investigated and kept under review.

The CHMP also expressed concerns about the degree of use of Protopy in children under the age of 2 (not approved) when the immune system is still developing. Therefore the CHMP requested that the MAH should take the appropriate measures in order to ensure that Protopy is not used in this age group.

In addition, the CHMP concluded that further data are required to better elicit the long-term safety of Protopy in respect of its association with malignancies. The CHMP endorsed the ongoing registry study presented by the Marketing Authorisation Holder - APPLES study (paediatric registry). The CHMP requested that the MAH should present 6 monthly updates on the status of recruitment of this study. The CHMP concluded as well that the risk of cutaneous malignancies should be assessed through case-control studies. The CHMP also concluded that the potential role of tacrolimus in the pathogenesis of CTCL should be further investigated through mechanistic studies.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET

Whereas

- The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004 for Protopy

- The Committee acknowledged that cases of malignancy (including skin cancer and lymphoma) have been reported in patients treated with Protopy. In view of the available data (including pre-clinical, clinical and epidemiological) the CHMP concluded that a potential association with the use of Protopy cannot be ruled out and therefore further data are needed to ensure an acceptable long-term safety profile.

- The Committee, as a consequence, concluded that the following information should be included in the Summary of Product Characteristics and relevant sections of the Package Leaflet of Protopy:

    - The treatment with Protopy should only be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis.
    - The treatment should be intermittent and not continuous.
    - A statement to highlight that tacrolimus should not be applied to lesions, which are considered to be potentially malignant or pre-malignant.
    - Protopy should not be used in immunocompromised adults or children.
    - A warning to advise that any lymphadenopathy present prior to initiation of therapy should be investigated and kept under assessment.
    - A statement that Protopy should not be used in children under 2 years.
    - A statement reflecting the cases of malignancies reported in the post-marketing

The CHMP has recommended the amendment to the terms of the Marketing Authorisation for Protopy for which the revised Summary of Product Characteristics and Package Leaflet are set out respectively in annexes I and IIIB.