**Information for Healthcare Professionals**

# Tacrolimus (marketed as Protopic)

## 6/2006: The issues described in this alert have been addressed in product labeling.

**FDA ALERT [03/2005] The FDA has issued a public health advisory to inform healthcare professionals and patients about a potential cancer risk from use of Protopic (tacrolimus). This concern is based on information from animal studies, case reports in a small number of patients, and knowledge of how drugs in this class work. It may take human studies of ten years or longer to determine if use of Protopic is linked to cancer. In the meantime, this risk is uncertain, and FDA advises Protopic should be used only as labeled, for patients after other prescription treatments have failed to work or cannot be tolerated.**

*This information reflects FDA's preliminary analysis of data concerning this drug. FDA is considering, but has not reached a final conclusion about, this information. FDA intends to update this sheet when additional information or analyses become available.*

*To report any unexpected adverse or serious events associated with the use of Protopic, please contact the FDA MedWatch program at 1-800-FDA-1088 or http://www.fda.gov/medwatch/report/hcp.htm*

### Considerations

Physicians with patients using Protopic, or who are considering prescribing the drug, should consider the following:

- Use Protopic only as a **second-line agent** for short-term and intermittent treatment of atopic dermatitis, a form of eczema, in patients unresponsive to, or intolerant of other prescription treatments.
- Avoid use of Protopic in children younger than 2 years of age. The effect of Protopic on the developing immune system in infants and children is not known.
- Use Protopic only for short periods of time, not continuously. The long term safety of Protopic is unknown.
- Children and adults with a weakened or compromised immune system should not use Protopic.
- Use the minimum amount of Protopic needed to control the patient's symptoms. In animals, increasing the dose resulted in higher rates of cancer.

**Data Summary**

Although tacrolimus is not genotoxic and does not interact directly with DNA, it may have a potential to impair local immunosurveillance. Carcinogenicity studies conducted with topical application of tacrolimus in mice demonstrated a dose-dependent development of lymphoma. The systemic administration of tacrolimus in kidney and liver transplant patients has been associated with increased susceptibility to infection and development of lymphoma and skin malignancies.

As of December 2004, the FDA had received 19 cases of postmarketing reports linking Protopic with cancer-related adverse events. Three cases occurred in children up to 16 years of age, and 16 cases occurred in adults. Two deaths in adults were reported related to complications of the cancers, and 8 hospitalizations were reported, including 2 in pediatric patients.

The 19 postmarketing cases included 9 lymphomas, 10 cutaneous tumors, of which 7 occurred at the site of Protopic application, as well as cases of squamous cell carcinoma, cutaneous sarcoma, malignant melanoma and other tumor types. The median time until diagnosis after initiation of treatment with Protopic was 150 days, with a range between 21 days and 790 days. Six cases also reported lymphadenopathy. Two cases reported pre-existing serious conditions, and 4 cases reported a recurrence or aggravation of a pre-existing malignancy. Three additional cases were confounded by other possible risk factors, including environmental exposure, or pre-existing conditions that may have been pre-malignant.

The systemic form of tacrolimus (Prograf) is known to cause both skin cancers and lymphoma in humans by suppressing the body's normal immune defenses against cancer. The cancer risk increases with higher doses and longer treatment courses of Prograf. Protopic is sometimes absorbed through the skin, though usually at very low amounts. Occasionally, children who have been treated with Protopic have had measurable blood levels of the drug, in the range of patients treated with Prograf. The potential for systemic immunosuppression is unknown and the role of Protopic in the development of cancer-related events in the individual postmarketing cases is uncertain at this time.

*Report serious adverse events to FDA's MedWatch at 1-800-FDA-1088; or www.fda.gov/medwatch/report/hcp.htm*

*Questions? Call Drug Information, 1-888-INFO-FDA (automated) or 301-827-4570*
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