

## **Elidel and Protopic: Issues surrounding the FDA black box warning**

There has been much concern over the recent Food and Drug Administration (FDA) advisory warning placed on the topical immunomodulators, Protopic (tacrolimus) and Elidel (pimecrolimus). In their advisory, the FDA recommended further monitoring of both adverse events and malignancies following use of these medications for the treatment of atopic dermatitis and discouraged use of these medications in children under the age of 2 years, as these creams have not been approved for use in this age group.

The basis for the warning stems from the following:

- The fact that these medications, when absorbed systemically, can cause immunosuppression similar to topical steroids.
- Some animal studies showed an increase in malignancy following systemic (by mouth or IV), not topical (on the skin), administration using doses as high as 30 times the normal dose.
- An increase in prescriptions written for children under 2.
- Reports of significant adverse events, mostly skin infections, including some hospitalizations.

The malignancy risk at present is theoretical, and there is no current evidence indicating an increase in malignancies following use of these creams. The number of malignancies reported in children following topical use of these medications is low — less than the expected rate for the general population. None of the reported malignancies have been B cell lymphomas, the type expected to develop following long term suppression of the immune system. For Protopic, 17 malignancies were reported in all age groups, three of these were found in children (non-Hodgkin's lymphoma, Kaposi's sarcoma, squamous cell carcinoma). For Elidel, eight malignancies occurred in all age groups four of which were found in children (none were B cell lymphomas). No malignancies were reported in children younger than 2 years of age. As a precaution, however, minimal sun exposure and avoidance of tanning beds are advised to decrease the risk of sun-related skin cancers while using these medications.

The potential increased susceptibility to bacterial or viral skin infections is difficult to determine because children with eczema are more prone to develop skin infections in general. Nevertheless, there may be a slight increase in viral skin infections, namely herpes simplex virus (the fever blister virus) and molluscum contagiosum, in children using these medications for eczema.

The current recommendations are that Elidel and Protopic be used for short-term and intermittent therapy as second-line agents for eczema patients who are older than 2 years of age, who don't respond to or don't tolerate other medications, and who do not have a suppressed immune system.