In an era of enhanced FDA scrutiny, the decision by the Pediatric Advisory Committee to recommend a black box warning for tacrolimus (Protopic, Fujisawa) and pimecrolimus (Elidel, Novartis) may prove to be a responsible decision. But the warning is affecting dermatologists in the clinic. Below is a review of the committee’s decision and rationale, a look at some of the data influencing their decision, and some tips for dealing with the new warnings in the clinic.

What We Don’t Know
In reaching its decision, the committee reviewed data from numerous studies, many from unpublished clinical trials. A recurring theme in comments from panelists is that the need for caution derives more from what is unknown about the risks of TCIs than any compelling evidence or documented risk. Among the reasons cited for increased concern is the fact that prescription writing for the TCIs increased nearly 400 percent in four years, and there is growing interest in and clinical use of the TCIs in patients younger than two. Both Protopic and Elidel are indicated for patients two and older. The larger surface area and less developed immune systems of pediatric patients add to concerns.

The committee did not formally vote on the need to communicate a public message of risk, yet according to meeting minutes, all but one of the committee members agreed a message was necessary. The consensus of the committee was that such a message should include these points:

1. The potential increased risk of cancer from treatment with TCIs is based on animal data.
2. There is inadequate human data at this time to ascertain cancer risk from use of TCIs.
3. TCIs should be used as second-line therapy.
4. TCIs should not be used in patients under age two.
5. Sun exposure to treated areas should be minimized.
6. Safety of TCIs in immunosuppressed patients has not been fully evaluated.

Fifteen panelists voted in favor of a black box warning for TCIs; there was one negative vote and one abstention. Additionally, 16 committee members voted against any additional regulatory action beyond healthcare and consumer education and the black box warning. One member voted in favor of smaller individual prescriptions to minimize over-use.

What We Do Know
In arriving at their conclusions, committee members reviewed a wide range...
of data including previously unpublished studies and case-reports in press. The presentations reporting and summarizing these data are available on the FDA website.1

**Animal Studies.** Studies of oral and topical administration of TCIs in various animals demonstrated a carcinogenic risk at very high doses relative to humans. Mice receiving 258-340 times the maximum human area-under-the-curve (AUC) of pimecrolimus orally developed lymphoma, while those receiving 60-133 times the AUC demonstrated no observed effect level (NOEL). For tacrolimus administered orally, both the rat at nine times the maximum human AUC and the mouse at three times the AUC were negative for lymphoma signal.2

With dermal application, lymphoma developed in mice receiving 26 times the maximum human AUC of tacrolimus and in mice receiving either 47 times or 179-217 times the maximum human AUC of pimecrolimus. Mice receiving 10 times the maximum human AUC of tacrolimus dermally demonstrated NOEL. Mice receiving 17 times the maximum human AUC of pimecrolimus also demonstrated NOEL while those receiving 3.3 times the AUC were negative for lymphoma signal.3

A primate carcinogenicity study involved oral doses of pimecrolimus 0, 15, 45, and 120mg/kg/day administered for 39 weeks. The 120mg/kg dosage group was discontinued after 19 weeks due to mortality. All dose groups demonstrated some level of opportunistic infections as well as immunosuppressive related lymphoproliferative disorder (IRLD), the expression of which was dose-dependent. IRLD frequently progresses to lymphoma, and the mechanism of lymphoma formation appears to be the same in humans as in monkeys. Three high-dose monkeys with IRLD developed leukemia; it is unknown if the mechanism of leukemia formation is the same for monkeys and humans.4 Additionally, IRLD was associated with lymphocryptovirus (Epstein-Barr related virus).

Previous studies documenting a risk of lymphoma due to immunosuppression related to oral tacrolimus therapy prompted a black box warning for Prograf (Fujisawa).4

**Human Studies.** Review of the data submitted in the new drug application (NDA) for pimecrolimus cream 1% shows that adult application generally produced low (<0.5ng/ml) blood concentrations of pimecrolimus, with maximum systemic concentration observed between days two and four. These data did not suggest higher blood concentrations of pimecrolimus with increasing body surface area treated.

In pediatric patients, application similarly produced low (<0.5ng/ml) blood concentrations of pimecrolimus. Again, maximum systemic concentration occurred between days two and four. But pediatric subjects differed from the adult group in that a relatively higher proportion of pediatric subjects (30 to 75 percent) displayed blood concentrations above 0.5ng/ml. Infants (under two years of age) demonstrated relatively higher blood concentrations of pimecrolimus compared to older children and adults.4

NDA studies for topical tacrolimus ointment 0.1% show that systemic exposure is low compared to the exposure from oral dosing. Pediatric patients achieved maximum concentrations of tacrolimus at day one of topical administration. However, the data demonstrate that some subjects showed relatively high exposures.4

While the data for both agents suggest no significant differences in systemic exposure between adult and pediatric patients (two to 12 years of age), they do show that systemic exposure tends to increase with increasing body surface area treated. Importantly, despite speculation, no one knows how much topically applied pimecrolimus or tacrolimus enters the lymphatic system or the consequence.4

**Clinical Experience: Reported Adverse Events.** Cases submitted to the voluntary adverse effects reporting system (AERS) for tacrolimus suggest risks of systemic absorption—generally with long-term exposures. In one case a patient with Netherton’s syndrome developed renal failure secondary to topical absorption of tacrolimus 0.1% for one year—well beyond the indicat-
ed use. On admission, the patient’s tacrolimus level was 34.4ng/ml. An 11-month-old patient with GVHD secondary to BMT treated with tacrolimus 0.1% ointment died. The level of tacrolimus at the time of death was 75ng/ml.

In the pediatric and adolescent literature, there are additional reports of adverse events, including the development of lentigines at the application site following continuous use of topical tacrolimus from five months to three years.

AERS reports also document tumor formation in patients treated with either tacrolimus or pimecrolimus. For pimecrolimus, there are nine reported cases—three in children 16-years-old or younger—around the world. These include reports of non-Hodgkins lymphoma in a two-year-old, a papilloma of the chin in a two-year-old, and a “tumor” in a “child.” Among adults, reports include squamous cell carcinoma; T-cell lymphoma, panniculitis-like; basal cell carcinoma; intraductal papilloma; and two cases of lymphoma.

For tacrolimus, there are 21 reported cases of tumor development worldwide—three in children 16-years-old or younger. The adolescent cases include metastatic angiosarcoma in a 16-year-old and malignant lymphoma/Sezary’s Syndrome in another 16-year-old. Hepatoblastoma occurred in a five-year-old. Four cases of SCC; Kaposi’s sarcoma; anaplastic large cell lymphoma, T-cell “type”; metastatic melanoma; two cases of lymphoma; a possible lymphoma; T-cell lymphoma, panniculitis-like; sweat gland tumor; two cases of non-Hodgkin’s lymphoma; BCC; esophageal carcinoma; and two cases of nodular follicular lymphoma comprise the adult cases.

The role of TCIs in each individual case is uncertain, noted Marilyn R. Pitts, PharmD, but they are “collectively a signal for a possible association.”

**TCIs in Practice**

Recommendations by the Pediatric Advisory Committee of the FDA regarding the safety of topical calcineurin inhibitors (TCIs) are based largely on animal data and early pharmacokinetic studies rather than in vitro data—the suspected risk of carcinogenicity makes long-term studies impossible. The new warnings have forced many clinicians to spend more time educating patients and parents and fielding questions about TCI safety. The public may not recognize that the bulk of the available data deal with animal models or generally unusual application or exceedingly long-term use of TCIs. Though these data do not form a complete picture, they may be elements of a puzzle yet to be solved. To add another potential complication to eczema management, late last month, the FDA was meeting to evaluate the safety of topical corticosteroids.

With this in mind, dermatologists should carefully convey to patients/parents what we do and don’t know about cancer risks—perhaps launching from the committee’s seven key points. It’s important as ever to stress the need to use medications as directed and to avoid over-application or extended use of TCIs beyond the prescriber’s recommendation.

Medical decision-making ultimately rests with the clinician in consultation with the patient/parents. Depending on the affected site, the degree of the dermatitis, and/or the level of patient discomfort, clinicians might favor a short-course of TCI therapy over topical corticosteroids or a TCI in combination with a topical corticosteroid, provided all parties understand the known and possible risks and side effects and administer therapy as indicated.

2. Hill B. Topical Immunosuppressants (Calcineurin Inhibitors) - Animal Toxicology.
5. Cohen JI. Epstein-Barr Virus: Cancer and Immunosuppression.
7. Pitts M. Post-Marketing Cases of Tumors Reported with the Topical Immunosuppressants (Calcineurin Inhibitors).

**New in Your Practice**

**Touch of Elegance.** Looking for an odorless, cosmetically elegant UVA/UVB chemical-free sunblock to recommend to patients? Dermatologic Cosmetic Laboratories’ new UVA/UVB Chemfree Superblock SPF 30 may be your answer. This very water resistant sunblock contains highly refined, micronized forms of titanium dioxide and zinc oxide, which allows for more even and complete skin coverage.

Additionally, the presence of squalane provides light moisturization to minimize the appearance of lines and wrinkles, DCL says. Patients will find UVA/UVB Chemfree Superblock SPF 30 is easy to apply, dries quickly, and does not leave a white or heavy coating, they add.

**A Clear Solution.** A one-week course of 0.5% fluorouracil cream prior to cryosurgery helps to reduce and clear a greater number of actinic keratosis lesions for a longer period of time, according to a recent study presented at the AAD’s annual meeting in New Orleans (P2314). In fact, six months following cryosurgery, patients averaged a 67 percent reduction in AK lesion count (vs. 45.6 percent in the placebo/cryosurgery group), while 30 percent of patients achieved complete clearance (vs. 7.7 percent). However, at 12-month evaluations, patients did not maintain total clearance of AKs.