Position Statement on Topical Calcineurin Inhibitors

April 2005

On February 15, 2005 the US Food and Drug Administration (FDA) Pediatric Advisory Committee met to discuss the risk evaluation, labeling, risk communication and dissemination on potential risks among pediatric patients treated for atopic dermatitis with topical dermatological calcineurin inhibitors. During this meeting all available data collected from clinical programs and post marketing surveillance were examined for evidence of increased risks of cancer development, particularly lymphoproliferative conditions. Representations were made by Fujisawa and Novartis, manufacturers of these products, and independent testimony from experts in lymphoma and immunology were heard.

After review of all submissions, the Pediatric Advisory Committee felt there was a theoretical risk of the occurrence of malignancies based solely on animal data, although they recognized the lack of such a signal in humans to date. Their recommendation to the FDA was that topical calcineurin inhibitor labels should include a "black box" warning. The Therapeutic Product Directorate (TPD) of Health Canada has recommended that a "Dear Doctor" letter be sent to all physicians in Canada outlining these concerns.

Topical calcineurin inhibitors (tacrolimus and pimecrolimus) have been studied collectively in over 38,000 subjects, including 14,000 children under the age of 17 years. Furthermore, over 6.7 million patients have used either tacrolimus or pimecrolimus since approval for market. To date, there have been two cases (squamous cell carcinoma and colonic carcinoma) reported with pimecrolimus; and no cases reported with tacrolimus in the clinical trial programs. In the spontaneous reporting programs, there are six cases (four lymphomas, two nonmelanoma skin cancers) reported with pimecrolimus; and nine cases of lymphoma with tacrolimus and 10 other types of tumors. The expected incidence of lymphoma within the clinical trial programs is 3; and the expected incidence of lymphoma in the spontaneous programs is 61. The patients ranged in age from two to 75 years, with a median age of 41.5 years. However, none of the cases of malignancy were reported in children less than two years old. Four cases were reported in children: the pediatric malignancy cases reported by Fujisawa included a case of hepatoblastoma in a five year-old, a case of metastatic angiosarcoma in a 16-year-old and a case of Sezary syndrome in a 16 year-old. The malignancy pediatric case reported by Novartis was a lymphoblastic lymphoma in a two-year-old. The number of lymphomas observed in treated patients is below the expected number of lymphomas in both pediatric and adult populations and for cases where enough information was available, they were assessed by external experts as unlikely to be linked to the use of topical calcineurin inhibitors.

Thus, the current information available does not support an increased risk for lymphoma development associated with the use of topical calcineurin inhibitors. Furthermore, there is currently no evidence of an increased risk of other malignancies either.

The Canadian Dermatology Association (CDA) believes that topical calcineurin inhibitors are an important therapeutic class for the treatment of atopic dermatitis in children and adults. The CDA believes that the FDA and TPD recommendation for a warning of this nature is not supported by clinical evidence and experience.

For topical calcineurin inhibitors:

- There is no evidence of an increased rate of lymphoma when compared to the general population.
- The clinical and histological patterns of the observed lymphomas are not consistent with typical immunosuppression-related lymphomas.
- There is minimal absorption of topical calcineurin inhibitors, with non-detectable or negligible blood levels, making long-term intense immunosuppression unlikely.
- There is no evidence of interference with effectiveness of immunization, delayed hypersensitivity skin responses, or rates of systemic infections.

The CDA recognizes that these agents are a novel therapeutic class, and that continued study and tracking of patients who use these agents are necessary to ensure that these agents are used properly and safely. Both manufacturers are conducting extensive long-term safety studies to measure such parameters. The Canadian Dermatology Association supports these ongoing studies because the benefits to the population far outweigh the current evidence of risks. However the CDA will continue to monitor the situation closely in the future, in order to best safeguard the skin care needs of Canadians.

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Ratified by Board of Directors May 8, 2006
CDA continues to monitor the situation – to date no changes have been made.