

Subject: Protopic and Elidel Presentation for Regulatory Briefing on January 14, 2005

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The Division of Pediatric Drug Development (DPDD) recommends a boxed warning for both Protopic and Elidel. This recommendation is based on the totality of scientific information available thus far which includes animal carcinogenicity signal both in mice and monkeys, post-marketing tumor-related adverse event reports coupled with the increased absorption in atopic dermatitis resulting in greater systemic exposure. The evidence raises serious safety concerns in children regarding the potential for carcinogenicity in humans treated with these agents. These products are being widely used to treat atopic dermatitis, a non-life threatening disease, and heavily advertised for use in young children without appreciation by parents and physicians regarding the potential for carcinogenic risk. We believe regulatory action is needed at this time since a definitive answer to the carcinogenic risk of these products will not be known for years and the difficulty of designing a clinical study that will provide a definitive answer to this question

For background, Protopic Ointment (tacrolimus) and Elidel Cream (pimecrolimus) are indicated for the short-term and intermittent long-term treatment of atopic dermatitis in patients ≥ 2 years of age who are either unresponsive or intolerant of alternative, conventional therapies or in whom the use of these therapies is deemed inadvisable due to potential risks. Protopic and Elidel are calcineurin inhibitors and immunosuppressants. Although their exact mechanism of action is not known, they exert direct immunosuppressive effects as evidenced by inhibition of T cell activation and inhibition of various interleukins and interferon gamma.

Although these products are applied topically, they may be systemically absorbed. Detectable drug levels in the blood are more frequently observed in children than in adults. This higher systemic drug exposure in children may be related to their greater body surface area to mass ratio.

Scientific evidence for systemic immunosuppression from topical application of these products is available in both humans and animals.

In animals, the carcinogenicity signal is strong, consistent, and dependent on dose and treatment duration. In mice, lymphoma formation was reported with application of Protopic and with Elidel dissolved in ethanol, at 26x and 47x MRHD (maximum recommended human dose) based on AUC comparisons, respectively. In addition, the median time to skin tumor formation was decreased in hairless mice following chronic Protopic administration with concurrent exposure to UV irradiation. Furthermore, the latency time to lymphoma formation was shortened to 8 weeks after administration of Elidel in ethanol to mice at a dose of 179-217x MRHD based on AUC comparisons.

In humans, post-marketing tumor-related adverse events related to these products continues to be reported. Since marketing approval (12/08/00 for Protopic and 12/13/01 for Elidel), 7 cases of lymphoma have been reported, four with Protopic and three with Elidel. Five of these 7 cases occurred in adults; one, in a 2 year old child; and one in a patient of unreported age. Duration of use is known in 5/7 cases (several weeks, 5 months, 6 months in 2 and 1 ½ years in another); occurrence was reported at the site of drug application in one. In addition, there is one case of cutaneous Kaposi's sarcoma which developed at the site of Protopic application and that became metastatic in an HIV positive adult. To date, 6 cases of skin cancer (of which three were recurrences) have been reported in adults, five with Protopic and one with Elidel. In 4/6 cases, the latency time to skin cancer was reported: 1-2 weeks, 3-4 weeks, 8 weeks and 3 months. Of these 6 cases, there was a history of atrophic lichen sclerosis in two cases and occurrence at the site of drug application in 2 different cases. Of note, the incidence of skin papillomas, a risk factor for precancerous lesions and cancer, was reported pre-marketing in children treated with Elidel (in the Adverse Reactions section of the Elidel package insert, the incidence of skin papillomas in the 6-week pediatric study was 0.4% (1/267) with Elidel and 0 (0/136) with vehicle control; in the 1-year safety study, it was 3.3% (9/272) with Elidel and <1% of 75 patients treated with vehicle control). Post-marketing, 2 cases of papilloma have been reported with Elidel, one in a child and one in an adult. Additional post-marketing tumor-related cases in children include one case each of facial tumor, type unspecified, with Elidel cream, Sezary's syndrome after three years of Protopic use, hepatoblastoma after one year of Protopic use and one case of sudden increase in size of metastatic angiosarcoma after three months of Protopic use.

Additional supportive evidence of immunosuppression in pediatric patients includes the increased incidence of specific infections that occurred with these products compared to vehicle alone in the pediatric clinical trials conducted pre-marketing. These results are reported in the Pediatric Use and Adverse Reactions sections of the Package Inserts. Of the cases of infections reported post marketing in pediatric patients, the most significant case was that of an 8-month old male who developed eczema herpeticum with pseudomonas sepsis and subsequent cardiac arrest. Protopic ointment was applied over his entire body for 6 months. Of note, the serum tacrolimus level was 3.5 ng/ml two weeks after Protopic had been discontinued. The patient survived.

It is known that oral or parenteral administration of immunosuppressant drugs is associated with an increased incidence of infection and cancer, particularly lymphoma. Tacrolimus injection (Prograf), cyclosporine and azathioprine, all of which include an indication for prevention of organ transplant rejection, contain a boxed warning. Although a systemic preparation of tacrolimus, Prograf, is available, there currently is no marketed systemic preparation of Elidel. Of note, a recent non-human primate study conducted with an oral formulation of Elidel which is under development, demonstrated the occurrence of lymphoma in all dose groups studied, including the lowest dose which represented 30x MRHD for the topical product. Therefore, a NOEL for lymphoma was not established in this study. Of further concern, lymphoma was reported in one of four recovery animals despite discontinuation of treatment. In this study, lymphoma was associated with a latent infection by an Epstein Barr related virus which is the same

mechanism described in immunosuppressed humans following transplantation. In addition, three of nine monkeys developed concurrent leukemia.

The immunosuppressive effects of these topical products in animals, manifested primarily as lymphoma formation, are strong, consistent and compelling. The biological relevance of these animal findings to humans exposed to these drugs cannot be excluded. In addition, immunosuppression is the proposed mechanism of action of Protopic and Elidel.

These products are indicated for the intermittent but chronic treatment of a non life-threatening condition, atopic dermatitis. The abraded skin characteristic of atopic dermatitis increases systemic absorption of these drugs and, as noted above, children have higher systemic blood levels of these drugs compared to adults, and, thus, greater systemic drug exposure. Given that these topical products may be applied chronically in a young child over an extensive surface area of abraded skin, there is potential for significant cumulative drug exposure. As demonstrated in the animal carcinogenicity studies, the development of lymphoma was dependent on cumulative drug exposure, being a function of dose and treatment duration. The increasing number of post-marketing tumor-related adverse events is concerning because they too, like the animal carcinogenicity findings and the known carcinogenicity potential with systemic administration of these drugs to humans, relate to the mechanism of action of this drug class, i.e., immunosuppression.

CFR 201.57 provides the Agency with the legal and regulatory authority to require a boxed warning based on serious animal toxicity in the absence of clinical data. FDA has previously exercised this authority. Such was the case for Forteo (teriparatide injection) and Flagyl (metronidazole tablets). Therefore, there is precedent. A boxed warning is the most effective *labeling tool* FDA has to convey a potential safety signal or risk. It is also recommended that the PPI for these products inform patients/parents/caregivers of the potential cancer risk based on the animal carcinogenicity findings and the post-marketing adverse events.

The use of these products continues to increase, including use in the very young, although they are not approved in patients less than 2 years of age. For example, from June, 2003-May, 2004, the number of prescriptions dispensed for Protopic, increased by 16% and for Elidel, by 46%, compared to the previous year. In this same time period, patients aged 1-2 years, accounted for 8% and 13% of Protopic and Elidel prescriptions, respectively.

The increasing use may be related to aggressive and inappropriate advertising with portrayal of these products as safer than steroids and the implication that they can be used as first-line therapy and for unlimited periods of time.

A presentation entitled: "ELIDEL Redefining Successful Therapy...A Blockbuster in the Making!" was delivered by Kurt Graves, Chief Marketing Officer, Novartis, on their 2003 R&D day. Included in this presentation were plans to develop the drug for flare

prevention among other indications (e.g., chronic hand dermatitis) and to expand usage to infants with atopic dermatitis.

In conclusion, based on the scientific information available to date which raises serious safety concerns regarding the potential for carcinogenicity of these agents in humans, the Division of Pediatric Drug Development recommends that a boxed warning be included in the Package Inserts for Protopic and Elidel.