

## **Background Package**

**Fujisawa Healthcare, Inc.**

**Pediatric Advisory Committee  
Food and Drug Administration  
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*Discussion Topic: Risk evaluation, labeling, risk communication, and dissemination of information on potential cancer risk among pediatric patients treated for atopic dermatitis with topical dermatological immunosuppressants.*

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## **1 INTRODUCTION**

Fujisawa Healthcare, Inc. (FHI)<sup>†</sup>, as the developer and manufacturer of Protopic® (tacrolimus) 0.03% and 0.1% Ointment, is making this submission in order to provide background information for the Pediatric Advisory Committee Meeting scheduled for February 15, 2005. This background information document provides general information relevant to atopic dermatitis; treatment options; epidemiology of cancer; a risk-benefit evaluation of Protopic Ointment; and summarizes the current status of continued surveillance efforts by FHI.

## **2 EXECUTIVE SUMMARY**

Atopic dermatitis is an intensely pruritic, chronic, relapsing inflammatory skin disease, significantly impacting a patient's life, hindering social interaction, lowering self-esteem, leading to work/school absenteeism, negatively affecting family interactions, and producing sleep disturbances and emotional distress. The impact of these signs and symptoms is particularly disabling in patients with moderate to severe disease. Topical calcineurin inhibitors, such as Protopic Ointment, are indicated for patients who have not been responsive to alternative, conventional therapies, or for whom such therapies are deemed inadvisable. Therapeutic options, such as topical or systemic corticosteroids, psoralen plus ultraviolet A (PUVA), or oral immunosuppressants, can be associated with side effects such as skin atrophy, telangiectasia, striae, hypopigmentation, secondary infection, reduction in effectiveness with long-term use, cataracts/glaucoma, endocrine, metabolic, renal and hepatic side effects, immunosuppression and skin cancer.

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<sup>†</sup> For ease of reference, "FHI" may include Fujisawa Healthcare, Inc. and related companies.

Protopic Ointment was the first in a new therapeutic class for the topical treatment of moderate to severe atopic dermatitis and is clearly beneficial for patients. Excellent results have been obtained even in those patients who are the most difficult to treat (e.g., those with severe disease, extensive body surface involvement, facial lesions, disease recalcitrant to steroidal therapy, and patients with long-standing disease). Data to date from more than 19,000 patients in the clinical program, including approximately 7,600 children, and an estimated 1.7 million patients in the US treated with marketed product demonstrate that the risk of developing lymphoma or nonmelanoma skin cancer in patients with atopic dermatitis treated with Protopic Ointment is not elevated by treatment.

As discussed in detail below, there is no evidence that treatment with Protopic Ointment increases the risk of lymphoma and skin cancer in patients with atopic dermatitis, including pediatric patients.

?? Patients with atopic dermatitis treated with Protopic Ointment do not have prolonged exposure to systemic tacrolimus.

- In contrast, the increased risk of lymphoproliferative disease that is reported in transplant patients taking immunosuppressants is associated with prolonged systemic exposure to intense immunosuppression. The increased risk of skin cancer that is reported in transplant patients is associated with chronic immunosuppression.

?? There is no evidence that Protopic Ointment impairs local or systemic immune function in patients with atopic dermatitis.

?? The reporting rates for lymphoma and skin cancer in patients treated with Protopic Ointment are not higher than the expected incidence in the general population.

In summary, FHI believes that Protopic Ointment has a favorable benefit-risk ratio for patients with moderate to severe atopic dermatitis. Current product labeling contains significant precautionary language intended to communicate potential risks. FHI fully supports the effective communication of potential risks to both physicians and patients, and welcomes the opportunity to participate in the further examination of consistent approaches to risk communication across the pharmacological class of topical calcineurin inhibitors.

### **3 BACKGROUND**

#### **3.1 Atopic Dermatitis and Therapeutic Options**

Atopic dermatitis, or eczema, is an intensely pruritic, recurring inflammatory skin disease that affects up to 20% of school-age children [Fleischer et al, 2002]. As with other members of the “atopic triad” (atopic dermatitis, hay fever and asthma), the incidence of atopic dermatitis is rising [Schiffner et al, 2003; Boguniewicz & Leung, 1996]. Atopic dermatitis often presents in early childhood and has a significant negative impact on quality-of-life. The “itch-scratch-itch” cycle disrupts sleep both for the patient and for caregivers, resulting in emotional stress, strained familial interactions, and loss of productivity at school or work. Afflicted patients may have a negative self-image and psycho-social problems. Individuals with atopic dermatitis are predisposed to developing skin infections [Schiffner et al, 2003; Smith, 2001; Kemp, 1999; Linnet & Jemec, 1999; Rudikoff & Lebwohl, 1998; Boguniewicz & Leung, 1996; Finlay, 1996; David & Cambridge, 1986; Aly, 1980; Hanifin & Rajka, 1980]. The economic burden of atopic dermatitis to a family has been equated to that of diabetes and asthma [Su et al, 1997].

Treatment choices for non-responsive patients with atopic dermatitis are limited. Extensive or prolonged use of topical corticosteroids has been known to be associated with cutaneous atrophy, pigment changes, telangiectasis, striae, tachyphylaxis, rebound flares, and systemic effects such as suppression of the hypothalamic-pituitary-adrenal axis. Systemic corticosteroids may cause metabolic and endocrine effects (hypothalamic-pituitary-adrenal axis suppression, Cushing's syndrome, growth inhibition, glucose intolerance), immunosuppression with increased risk of infections, musculoskeletal abnormalities (myopathy, osteoporosis, avascular necrosis of the femoral head), hypertension, CNS effects (sleep disturbances, mania, pseudotumor cerebri), and ophthalmic side effects. Systemic cyclosporine, methotrexate, and azathioprine are associated with adverse effects of renal or hepatic impairment, hypertension, increased susceptibility to infection and lymphoma/malignancy. Ultraviolet therapy with or without psoralen increases the risk of skin cancer [Chrousos, 2005; Hanifin et al, 2004; Roos et al, 2004; Saporito & Menter, 2004; Schiffner et al, 2003; Rudikoff & Lebwohl, 1998; Boguniewicz & Leung, 1996].

Topical calcineurin inhibitors, such as Protopic Ointment and Elidel® (pimecrolimus) 1% Cream, represent a therapeutic pharmacological class that has been shown to be highly effective for the treatment of atopic dermatitis, particularly in the most difficult to treat patients.

### **3.2 Protopic Ointment**

Protopic (tacrolimus) 0.03% and 0.1% Ointment was the first in the class of topical calcineurin inhibitors to be approved and is indicated for *“short-term and intermittent long-term therapy in the treatment of patients with moderate to severe atopic dermatitis in whom the use of alternative, conventional therapies are deemed inadvisable because of*

*potential risks, or in the treatment of patients who are not adequately responsive to, or are intolerant of, alternative, conventional therapies.”* Protopic 0.03% and 0.1% Ointment is indicated for adults, and Protopic 0.03% Ointment is indicated for children 2 to 15 years of age.

In clinical studies involving more than 19,000 patients, including approximately 7,600 children with atopic dermatitis, Protopic Ointment therapy has demonstrated significant clinical improvement including quality-of-life benefits; transient and low systemic exposure; and no evidence of systemic immunosuppression [e.g., Reitamo et al, 2002; Drake et al, 2001; Hanifin et al, 2001; Kang et al, 2001; Paller et al, 2001; Soter et al, 2001; Reitamo et al, 2000; Fleischer, 1999]. In the US, 300 patients in clinical studies have been followed for more than 3 years [Hanifin et al, 2003]. Since launch of Protopic Ointment in January 2001, approximately 1.7 million patients in the US have been treated with Protopic Ointment with approximately 3 million cumulative patient-years exposure.

The most common adverse effects seen in clinical studies were local application site events. Long-term clinical studies have shown that patients treated with Protopic Ointment have a decreased risk of cutaneous bacterial infections. The labeling states that Protopic Ointment may be associated with an increased risk of varicella zoster virus infection, herpes simplex virus infection, or eczema herpeticum; however, further long-term studies have demonstrated a decreased or comparable rate of viral infections when compared to patients managed conventionally [Hanifin et al, 2003; Fleischer et al, 2002; Pournaras et al, 2001; Remitz et al, 2001]. Long-term safety and postmarketing reports have confirmed the safety and efficacy of tacrolimus ointment in the management of moderate to severe atopic dermatitis.



### **3.3 Potential for Systemic Exposure with Tacrolimus: Topical versus Oral Administration**

The question of the potential for systemic exposure to tacrolimus following topical use was thoroughly discussed on November 16, 2000 at the Center for Drug Evaluation and Research Dermatologic and Ophthalmic Drugs Advisory Committee meeting, prior to the approval of Protopic Ointment. Because calcineurin inhibitors administered orally are associated with an increased risk of lymphoproliferative disorders and skin cancer in transplant recipients, the discussion centered on whether the long term use of topical immunosuppressive agents would increase lymphoproliferative disease and skin cancer, particularly in the pediatric population. The question was also discussed at an Advisory Committee hearing on October 30, 2003.

Calcineurin inhibitors, administered orally (e.g., tacrolimus, Prograf® or cyclosporine, e.g., Neoral®), are used as systemic immunosuppressants for the prophylaxis of organ rejection in transplant recipients. Exposure with topical tacrolimus is typically 30-fold lower than that seen with Prograf. For all systemic immunosuppressants that are not DNA-reactive, such as tacrolimus, the potential for development of lymphoma or skin cancer is associated with exposure sufficient to induce a sustained high level of immunosuppression, as well as other transplant-specific factors [Andreone et al, 2003; Berg & Otley, 2002].

Animal data, pharmacokinetic data and clinical trial results from the Protopic Ointment program were presented by both FHI and the FDA, with comments and questions by the November 16 Advisory Committee membership. The risks for pediatric patients were characterized by the Advisory Committee as potential, yet undefined, based on the data presented. The November 16 Advisory Committee recommended that the labeling include appropriate statements relevant to the theoretical risk and precautionary risk

management measures. These recommendations were incorporated into the product labeling at the time of approval.

## **4 INCIDENCE OF CANCER IN RELEVANT POPULATIONS**

### **4.1 Lymphoma**

The term lymphoma is applied to two categories of neoplasms, Hodgkin's disease and non-Hodgkin's lymphoma, with non-Hodgkin's lymphoma being five times more common. There are many subtypes of non-Hodgkin's lymphoma which are classified based on neoplastic cellular differentiation (e.g., B-cell, T-cell, NK cell), cell size and morphology, and other immunophenotypic features (e.g., cellular differentiation markers). Signs and symptoms of both non-Hodgkin's lymphoma and Hodgkin's disease include enlarged lymph nodes, itching, night sweats, fatigue, and intermittent fever. Risk factors associated with lymphoma include immunosuppression, infections (such as Epstein-Barr virus, *H. pylori*), environmental exposures and genetics [American Cancer Society, 2005]. Cutaneous T-cell lymphoma is an unusual and uncommon non-Hodgkin's lymphoma which typically presents as a chronic, indolent skin disease.

#### ***4.1.1 Lymphomas in the General Population***

The age-adjusted incidence of lymphoma in the general population (all ages) in the US was 21.7 per 100,000 per year based on data from the Surveillance, Epidemiology, and End Results (SEER) Program (1997-2001) [Ries et al, 2004]. Approximately 88% of these were non-Hodgkin's lymphoma.

The following table shows the SEER incidence per 1,000,000 by age group for individuals 19 years of age and younger and by type of lymphoma.

| Years of Age | All Lymphoma | Hodgkin's Lymphoma | Non-Hodgkin's Lymphoma | Burkitt's Lymphoma | Miscellaneous lymphoreticular neoplasms | Unspecified Lymphoma |
|--------------|--------------|--------------------|------------------------|--------------------|---|----------------------|
| 0-14         | 14.9         | 6.0                | 5.5                    | 2.3                | 0.4                                     | 0.8                  |
| 0-19         | 24.0         | 13.5               | 7.1                    | 2.1                | 0.3                                     | 0.9                  |
| 1-4          | 7.6          | 0.5                | 4.1                    | 2.0                | 0.4                                     | 0.6                  |
| 5-9          | 13.2         | 4.1                | 5.5                    | 2.7                | 0.2                                     | 0.7                  |
| 10-14        | 24.3         | 13.1               | 7.3                    | 2.6                | 0.3                                     | 1.0                  |
| 15-19        | 51.0         | 35.9               | 12.0                   | 1.5                | 0.3                                     | 1.3                  |

Rates are per 1,000,000 patient years and are age-adjusted to the 2000 US standard by 5-year age groups.  
Note: the rate for all ages is calculated as 217 per 1,000,000 per year.

Based on these data, the majority of cases of lymphoma are reported in adults.

#### ***4.1.2 Posttransplant Lymphoproliferative Disorders Are Unique to Transplant***

Posttransplant lymphoproliferative disorders (PTLD) include a spectrum of B-cell disorders ranging from hyperplasia (e.g., benign polyclonal hyperplasia of lymphocytes) to malignant lymphomas (e.g., non-Hodgkin's lymphoma) which occur in transplant recipients receiving immunosuppressive regimens [Aull et al, 2004; Andreone et al, 2003; Penn, 1999; Reding et al, 1994; Nalesnik et al, 1991; Swinnen et al, 1990]. Generally, PTLD is associated with intensive systemic immunosuppression (multi-immunosuppressants, multiple regimens) with agents such as cyclosporine, corticosteroids, azathioprine, monoclonal/polyclonal anti-lymphocyte antibodies, and tacrolimus (Prograf) [Melosky et al, 1992; Wilkinson et al, 1989]. Symptoms of PTLD includes prolonged weight loss, unexplained high fever, malaise and prolonged lymphadenopathy. Unlike lymphomas that occur in immunocompetent individuals, PTLD is generally treated by reduction or cessation of immunosuppressant therapy [Penn, 1999; Newell et al, 1996]. In the Cincinnati Transplant Tumor Registry, non-Hodgkin's lymphomas accounted for 94% of posttransplant lymphomas (1460/1560) and the majority (86%) demonstrated B-cell differentiation [Penn, 1999].

A major risk factor for PTLN is infection with Epstein-Barr virus (EBV) [Andreone et al, 2003; Penn, 1999; Newell et al, 1996; Preiksaitis et al, 1992]. EBV inserts its DNA into the genome of B-cells of infected individuals. In immunocompetent and many immunocompromised individuals, lymphoproliferation does not occur since the proliferation of these EBV-transformed B-cells is controlled by virus-specific cytotoxic T-cells and natural killer cells. However, this immunosurveillance mechanism can be disrupted by intense immunosuppression (especially those regimens that include antilymphocyte antibody therapy), or cumulative use of multiple immunosuppressants, leading to the uncontrolled proliferation of transformed B-cells.

Extralymphnodal location of PTLN is an important feature of this disease, with the transplanted organ often being the site of PTLN. Evidence suggests that approximately 20 to 30% of PTLN may be of donor origin [Strazzabosco et al, 1997].

The incidence of PTLN varies with the transplanted organ, likely due to differing intensities of immunosuppression required in different transplant settings. Recently reported estimates of the incidence of PTLN in transplant recipients are on the order of 1% of renal, 2% of liver, 3% of heart, 2 to 8% of lung and 7 to 11% of small-bowel transplant recipients [Andreone et al, 2003]. The incidence of PTLN in transplantation studies sponsored by FHI (mean follow-up period, 7.4 months; n=8,066) was 0.41%. The incidence of PTLN is higher in pediatric transplant recipients compared to adults [Shroff & Rees, 2004].

In summary, PTLT is a unique, recognized complication of intense, sustained immunosuppression associated with EBV infection in transplant patients. Transplant recipients with PTLT generally are receiving multiple immunosuppressive agents, and have a higher exposure to specific immunosuppressive agents than their transplant counterparts without PTLT. The PTLT observed in transplant recipients differs from lymphomas observed in the general population with respect to extranodal involvement, location of lesions, and patient management [Andreone et al, 2003; Penn, 1999].

#### ***4.1.3 Cutaneous T-cell Lymphoma in the General Population***

Cutaneous T-cell lymphoma (CTCL), which is also known as mycosis fungoides, typically presents as a chronic, inflammatory dermatosis and includes a spectrum of diseases characterized by skin-homing helper T-lymphocytes (CD4 phenotype); CTCL is difficult to diagnose and initially presents with patches or plaques, which resemble atopic dermatitis. Patients typically present with a recalcitrant dermatitis, which is often not diagnosed as CTCL until years after initial presentation with symptoms, despite skin biopsies and appropriate dermatologic management. The most common pre-existing disease is “eczema”. The interval between the first appearance of skin lesions and diagnosis has been reported to range between 4 and 10 years with an average latency of 6.1 years [Epstein, 1972]. Since patients with CTCL present with a long-standing dermatitis, mimicking atopic dermatitis that fails to respond to conventional topical therapy [Heald & Edelson, 1999], it is not surprising that these patients may be treated with topical calcineurin inhibitors prior to establishing the diagnosis.

For 1984, the incidence in the US was reported as 0.42 cases per 100,000 [Weinstock & Horm, 1988]. CTCL is rare in children, however, an estimated 0.5 to 5% of CTCL cases develop in children [Garzon, 1999]. The risk factors for CTCL are not well-described; however, CTCL is not commonly associated with immunosuppression posttransplant. The retrovirus, human T-cell leukemia virus I (HTLV I), is associated with a variant of CTCL [Heald & Edelson, 1999]. Sézary syndrome is a rare form of CTCL.

## **4.2 Skin Cancer**

Primary skin cancers arise on the skin and are the most common tumors in the US. Skin cancer includes nonmelanoma skin cancer (basal cell and squamous cell carcinomas) as well as malignant melanoma. Nonmelanoma skin cancers typically present on the head, neck and other sun-exposed areas. Risk factors for the development of skin cancer include sun sensitivity (sunburn easily, difficulty tanning, blonde or red hair color); history of excessive sun or ultraviolet light exposure (frequent sunburns, use of tanning beds, or ultraviolet light treatment); x-ray treatment; exposure to certain chemicals including coal tar, arsenic, creosote and pitch; immunosuppression; and prior skin cancer [American Cancer Society, 2005].

### ***4.2.1 Nonmelanoma Skin Cancer in the General Population***

Nonmelanoma skin cancer is a common malignant neoplasm in individuals over the age of 40 years, particularly among adults with light complexions, and its incidence is increasing [Ming et al, 2004; Frieling et al, 2000]. An estimated 1.2 million new cases of nonmelanoma skin cancer occur each year in the United States [American Cancer Society, 2005; Miller & Weinstock, 1994].

The age-specific first incidence of nonmelanoma skin cancer adjusted to the 1988-1992 US white male population in the prospective Physician Health Survey was 533 per 100,000 person-years [Friedling et al, 2000]. The incidence of cutaneous squamous cell carcinoma in the US has been estimated to be 100 to 150 per 100,000 person-years [Alam & Ratner, 2001]. The incidence of skin carcinomas in individuals below the age of 15 is negligible [Pierini & de Pierini, 2000; Ries et al 1999].

#### ***4.2.2 Nonmelanoma Skin Cancer in Transplant Recipients***

Penn [1999] has reported a higher incidence of squamous cell carcinoma in transplant recipients associated with long-term exposure to immunosuppressive agents. Transplant recipients also tend to have an increased incidence of warts, and oncogenic strains of human papillomavirus have been isolated from warts, premalignant and malignant lesions in these patients [Berg & Otley 2002; Penn, 1999].

Margolis et al [2001] reported an adjusted rate ratio (adjusted for age in 10-year intervals, gender, and state of origin) for nonmelanoma skin cancer in solid organ transplant recipients of 4.36 compared to a control, hypertensive patient population (rate=1).

#### ***4.2.3 Nonmelanoma Skin Cancer in the Atopic Dermatitis Population***

The rate of nonmelanoma skin cancer in patients with atopic dermatitis is unknown. In an unpublished study of 2,030 adult patients hospitalized for atopic dermatitis in Denmark (1977-1996) conducted by Olesen et al, the incidence of nonmelanoma skin cancer was 0.79% (16 cases).

Margolis et al [2001] reported an adjusted rate ratio for nonmelanoma skin cancer of 2.14 in patients with eczema requiring at least four physician visits in a 12-month period compared to a control, hypertensive patient population (rate=1). Some (1.1%) of these patients had received ultraviolet light therapy and/or systemic immunosuppressive therapy, regimens known to increase the rate of nonmelanoma skin cancer in patients with psoriasis.

#### ***4.2.4 Precursors to Nonmelanoma Skin Cancer***

Human papillomavirus (HPV)-induced warts and molluscum contagiosum are observed frequently in immunocompromised individuals, such as transplant recipients or those infected with human immunodeficiency virus, and HPV-induced warts can precede development of cutaneous squamous cell carcinoma, particularly in immunocompromised individuals [Stockfleth, 2004].

HPV induced-warts and molluscum contagiosum have been reported in individuals with atopic dermatitis at rates of 2.5 to 17% and 4%, respectively [Williams et al, 1993; Giannetti, 1987; Bonifazi et al, 1985]. There does not seem to be an increased risk of HPV induced-warts in patients with atopic dermatitis, although other viral infections such as herpes simplex virus are seen more frequently in these patients [Williams et al, 1993].



## 5 RISK EVALUATION FOR PROTOPIC OINTMENT

### 5.1 Evaluation of Nonclinical and Human Biomaterial Data

#### 5.1.1 *Animal Carcinogenicity Data*

Carcinogenicity studies were conducted in rodents as a part of the Protopoc Ointment development program and were discussed as part of the Advisory Committee review that occurred in association with approval of the product. As described in the current product labeling, these studies were conducted with 0.03% and 0.1% tacrolimus ointment and demonstrated the following:

?? In a 104-week dermal carcinogenicity study in mice,

- No skin tumors were associated with the topical application of tacrolimus.
- Lymphomas were noted in animals dosed with 0.1% tacrolimus; however, the systemic tacrolimus exposure in these animals was 26X the maximum recommended human dose (MRHD) based on area-under-the-blood concentration-curve (AUC).
- No lymphomas were noted in mice treated with 0.03% tacrolimus ointment (10X MRHD based on AUC).

*Note: These safety factors may be an underestimation since they do not account for the transient exposure which may occur in patients with atopic dermatitis.*

?? In a 52-week photocarcinogenicity study in hairless mice,

- The median time to onset of skin tumor formation was decreased following treatment with tacrolimus ointment at 0.1% or greater.
- The relevance to humans of the finding in hairless mice is unknown.

?? Based on the results of a comprehensive battery of mutagenicity and photomutagenicity tests, tacrolimus is not DNA-reactive.

Rodents are known to have a much more permeable skin than man and other animal species [Reifenrath et al, 1984]. Patients with atopic dermatitis have considerably less daily systemic exposure to tacrolimus compared with rodents in life-time carcinogenicity studies. Given the differences in the absorption profiles between animals and humans, systemic disease in these animal studies must be interpreted with caution.

At the request of FHI, Dr. Samuel Cohen (Professor and Chair, Pathology and Microbiology, Havlik-Wall Professor of Oncology, at Nebraska Medical Center), a researcher with expertise in both rodent carcinogenesis and human oncology, reviewed the data collected as part of the Protopic Ointment development program, as well as published literature. In Dr. Cohen's opinion, dermally administered tacrolimus does not pose a carcinogenic hazard to patients with atopic dermatitis because of the difference in tacrolimus blood levels in patients treated with Protopic Ointment and lymphoma bearing mice and because of the absence of a signal for neoplasia in the atopic dermatitis population receiving Protopic Ointment.

#### ***5.1.2 Recent Explorations of Mechanism of Action of Topical Tacrolimus as an Immunomodulator***

The results of in vitro studies to date have demonstrated that, following topical application in patients with atopic dermatitis, tacrolimus down-regulates aberrant expression of various activation markers, such as high-affinity IgE receptor (Fc $\gamma$ R1), and inhibits cytokine signaling pathways [Wollenberg et al, 2001].

Recently, the effect of tacrolimus on Langerhans cells, the primary antigen-presenting cell in the skin, was explored using epidermal single-cell suspensions prepared from lesional skin of patients with atopic dermatitis treated either with Protopic Ointment (n=9) or hydrocortisone butyrate ointment (n=5) [Schuller et al, 2004]. In contrast to steroid ointment, Protopic Ointment does not induce dendritic cell apoptosis.

Simon et al [2004] examined the cellular infiltrate in lesions from 10 patients with atopic dermatitis treated with Protopic 0.1% Ointment and characterized the cytokine patterns. Skin biopsies were obtained from lesional and non-lesional atopic dermatitis sites as well as normal skin. Protopic Ointment application reduced infiltration of cytokine expressing inflammatory cells, predominantly inflammatory dermal dendritic cells, without evidence of drug-induced systemic immunosuppression.

Although the exact mechanism of action of tacrolimus in atopic dermatitis is unknown, these data suggest that topical tacrolimus acts as a local immunomodulator rather than an immunosuppressant.

## **5.2 Evaluation of Clinical and Postmarketing Safety**

### ***5.2.1 Review of Clinical Data***

More than 19,000 patients, including approximately 7,600 pediatric patients, participated in the clinical development program for Protopic Ointment. Approximately 8,700 of these patients were followed in long-term safety studies after Protopic Ointment was approved; in addition, over 1,800 patients with atopic dermatitis have participated in clinical studies postmarketing. In these clinical studies, there has been no evidence of an

increased risk of lymphoma or lymphoproliferative disorders or skin cancers associated with the use of Protopic Ointment. To date, in clinical studies, there have been no reports of lymphoma or skin cancer in pediatric patients (<16 years of age) treated with Protopic Ointment reported to FHI.

Patients with atopic dermatitis treated with Protopic Ointment do not have prolonged exposure to systemic tacrolimus. Protopic Ointment does not produce high systemic levels of tacrolimus in patients with atopic dermatitis. There was no evidence based on blood concentrations that tacrolimus accumulates systemically upon intermittent topical application for periods of up to 1 year. When blood levels are observed, they are generally minimal, transient, and occur early in treatment. Using historical data for comparison, the bioavailability of topically applied tacrolimus is considered to be less than 0.5% [Undre, Green, et al, 2002; Undre, Rubins, et al, 2002; Alaiti et al, 1998].

There is no evidence that Protopic Ointment in patients with atopic dermatitis impairs dermal or systemic immune function. Clinical studies evaluating delayed type hypersensitivity response, vaccine responses and rates of infection over time in treated patients have demonstrated responses comparable to those observed in non-atopic dermatitis affected individuals.

?? In a 1-year clinical study [Reitamo et al, 2000], evaluation of CD4 and CD8 counts and assessment of cell-mediated immunity using a recall Antigen Test demonstrated that Protopic 0.1% Ointment did not affect cell-mediated immunity, supporting that atopic dermatitis patients applying Protopic Ointment do not have impaired immune response.

?? Arkwright et al [2000] reported that children with atopic eczema less than 9 years of age may have poor antibody response to Pneumococcal vaccination. In contrast, Stiehm et al [2005, in press in JAAD; 2003] reported that the use of Protopic Ointment in pediatric patients (2-12 years of age) with moderate to severe atopic dermatitis did not affect antibody response to a polyvalent pneumococcal vaccine, with all treated subjects exhibiting protective responses to at least 8 serotypes. In this study, levels of immunoglobulins, antibodies, or lymphocyte subsets, and proliferative response to standard antigens were unchanged during Protopic Ointment treatment.

?? In a review of data from five clinical trials involving 1,554 patients with atopic dermatitis treated with Protopic Ointment, Fleischer et al [2002] found no evidence of an increased risk of cutaneous bacterial, viral or fungal infections following treatment for up to 1 year, suggesting that topically applied tacrolimus does not alter local cutaneous immune response.

### ***5.2.2 Postmarketing Safety***

Since launch in the US in January 2001, FHI estimates that 1.7 million US patients have used Protopic Ointment, with approximately 3 million cumulative patient-years exposure. FHI analyzes postmarketing experience worldwide and reports to the FDA adverse events that coincide with the use of Protopic Ointment. FHI has rigorously reviewed the global safety databases, provided safety updates to the FDA, and performed assessments to evaluate the risk of systemic lymphoma or lymphoproliferative disorders and skin cancers in clinical studies and postmarketing reports.

The number of postmarketing reports of lymphoma, including CTCL, and skin cancer have been low and no higher than expected with the general population. There have been no postmarketing events reported to FHI of either lymphoma or skin cancer in pediatric patients (<16 years of age) treated with Protopic Ointment.

### ***5.2.3 Independent Safety Evaluations***

In addition to FHI's standard practice of in-depth, ongoing review of safety data for all products, FHI has augmented its routine, internal safety evaluations with input from external independent experts with expertise in dermatology, epidemiology and PTLD/pediatric oncology. Thomas Diepgen, MD, PhD (Professor & Chairman of Dermatology, Allergology, Environmental Medicine, and Epidemiology at University of Heidelberg) and Thomas Gross, MD, PhD, (Gordon Teter Chair for Pediatric Cancer, Associate Professor of Pediatrics, Ohio State University) were asked to independently review cases of lymphoma (noncutaneous) and cutaneous T-cell lymphoma reported to the company through January 2004. The opinion of these experts was that there was insufficient evidence to suggest an increased risk of lymphoma (including CTCL) in patients with atopic dermatitis treated with Protopic Ointment.

### ***5.2.4 Discussion of Reports***

#### **5.2.4.1 Lymphoma (Including CTCL)**

Through December 31, 2004, FHI is aware of reports of lymphoma (noncutaneous) in 12 patients and reports of CTCL in 7 patients treated with Protopic Ointment. Of these, 5 lymphomas (noncutaneous) and 6 CTCLs were reported in US patients. The patients with CTCL, in general, had a long history of a recalcitrant dermatitis and in most cases, a potential misdiagnosis.

All reported lymphomas occurred in adult patients, with the youngest patient being a 16-year-old Japanese female with CTCL as the final diagnosis. This patient had a 7-year history of a recalcitrant dermatitis unresponsive to systemic steroids and oral cyclosporine, and laboratory findings suggestive of CTCL prior to treatment with Protopic Ointment. This was originally reported as a lymphoma and subsequently diagnosed to be CTCL.

Individual and collective assessments of these reports support neither a relationship to Protopic Ointment use nor an increased risk of lymphoma in patients treated with Protopic Ointment.

#### **5.2.4.2 Skin Cancer**

As part of pharmacovigilance, FHI compared the incidence of nonmelanoma skin cancer in 9,813 adult and pediatric patients with moderate to severe atopic dermatitis treated with Protopic Ointment in US clinical trials with that reported for the general population [see Section 4.2]. There was no evidence of increased risk for the development of nonmelanoma skin cancer. There has been one European spontaneous postmarketing report of skin cancer and none from other regions, including the US.

In addition, there has been no evidence of an increase in the incidence of HPV in studies of patients treated for up to 4 years with Protopic Ointment. The incidence of HPV-induced warts and molluscum contagiosum in long-term clinical trials with Protopic Ointment was similar to or lower than that reported in the literature for patients with atopic dermatitis [see Section 4.2.4; Hanifin et al, 2003; Fleischer et al, 2002].

### **5.3 Continued Commitment to Risk Evaluation**

FHI continues to reaffirm its commitment to further evaluate the long-term safety of Protopic Ointment in patients with atopic dermatitis through a protocol submitted to the FDA for a multinational 8,000 pediatric patient registry study with 10 year follow-up. FHI has initiated two ex-US postmarketing long-term safety studies in patients with atopic dermatitis.

## **6 LABELING AND RISK COMMUNICATION**

The current product labeling for Protopic Ointment contains statements designed to communicate appropriate potential risk. For example:

- ?? The precautions section contains information concerning the risk of lymphoma in transplant patients receiving immunosuppressive regimens.
- ?? The labeling cautions that patients treated with Protopic Ointment who develop lymphadenopathy should have the etiology investigated and should be monitored until resolution. In some cases, in the absence of a clear etiology for the lymphadenopathy, discontinuation of treatment should be considered. Patients who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves.
- ?? Protopic Ointment is not recommended for patients with Netherton's Syndrome, a disease characterized by defects in epidermal barrier function, due to the potential for increased systemic absorption of tacrolimus.

Precautionary risk management actions (per November 16, 2000 Advisory Committee) included recommending the use of Protopic Ointment as second line therapy, recommending the duration of use to short-term and long-term intermittent use, designating the 0.03% concentration for use by children 2 through 15 years of age, and cautioning against exposure to natural or artificial sunlight. This information is included



in the current Protopic Ointment labeling. The November 16 Advisory Committee recommended these precautions after thorough consideration of: the issues related to lymphoma and skin cancer risk, including the question of systemic exposure to topical tacrolimus relative to systemic exposure to oral tacrolimus; the question whether the long-term use of topical immunosuppressive agents increased lymphoproliferative disease and skin cancer; and whether there was additional risk in the pediatric population. These risks for pediatric patients were characterized by the Advisory Committee as potential, yet undefined, based on the data presented.

With regard to the product labeling for Protopic Ointment, FHI believes that the current labeling adequately and appropriately describes the potential risk and contains adequate precautions for risk management. This conclusion is based on the risk evaluation discussed above [see Section 5], which has included a rigorous review of clinical safety data and postmarketing reports as well as evaluations of animal and human safety data by external, independent experts. With regard to animal data, expert review has confirmed that dermally administered tacrolimus does not pose a carcinogenic hazard to patients with atopic dermatitis. Expert review of postmarketing safety data has found insufficient evidence of an increased risk of systemic lymphoma or lymphoproliferative disease, or CTCL, in patients receiving therapy for atopic dermatitis with Protopic Ointment.

Overall, clinical data and postmarketing safety experience have demonstrated that there is no increased risk of developing lymphoma or skin cancer in patients treated with Protopic Ointment. Nonetheless, FHI appreciates that there can be alternative ways of communicating this theoretical risk (e.g., added prominence, consistent wording across the class of topical calcineurin inhibitors). The communication of the theoretical risk must be presented in a balanced and clear way that neither understates nor overstates the

state of scientific knowledge and must take into account the risk/benefits of this class versus therapeutic alternatives.

## **7 CONCLUSION**

FHI's clinical data and postmarketing safety experience have demonstrated that there is no increased risk of developing lymphoma or skin cancer in patients treated with Protopic Ointment. Our goal is to appropriately communicate both risks and benefits so that physicians and patients with atopic dermatitis can make an informed decision about treatment with Protopic Ointment. We welcome the opportunity to provide information for discussion of approaches for consistent risk awareness across the pharmacological class in the open forum of this February 15, 2005 Pediatric Advisory Meeting.

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