



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

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SUBJECT: ODS Postmarketing Safety Review (PID 040608)
Update - All Adverse Events in Children Less Than 2 years, and Update on Malignancy Related
Events in all Age Groups
Drug: Tacrolimus, topical (Protopic®, NDA 50-777)

***** Confidential: Contains IMS Health Data*****

Data Cleared by IMS January 26, 2005 to share with Audience/Intent: Pediatric Advisory Subcommittee members, Public, Media, Web

EXECUTIVE SUMMARY

This document summarizes all reports of adverse events associated with topical tacrolimus use in children less than two years of age; IMS drug usage data in children less than two years of age; and malignancy related adverse event reports in all age groups. The information in this review is provided in preparation of a label revision meeting with OCTAP/DPDD/HFD-960, scheduled for October 4, 2004. We conducted hands-on review of reports with serious outcomes, and reports describing malignancy related adverse events.

We searched the AERS database on September 22, 2004 for all adverse event reports associated with topical tacrolimus use in children less than two years old, as well as malignancy-related reports in all age groups. Since approval on December 8, 2000 we identified 10 reports in children less than two years old, and 17 malignancy-related reports in all age groups. The majority of the reports were domestic, and the children were mostly male, and ranged in age from six weeks to 17 months old, with a median age of 1 year old (n = 10). The children were administered topical tacrolimus primarily to treat atopic dermatitis. Two of the ten cases reported using the 0.1% strength of tacrolimus, and the remaining cases did not report the strength of topical tacrolimus used. Two pediatric cases reported obtaining serum tacrolimus levels, one of which was positive two weeks after discontinuation of the product. The majority of cases reported systemic reactions, of which many were labeled. The remaining cases reported either labeled local reactions, or local and systemic reactions.

Hospitalization was the most serious outcome reported in four of the children less than two years old. One case each described systemic events including eczema herpeticum with septicemia, and meningitis and septicemia.¹ The two remaining hospitalization cases reported malnutrition and hematemesis. The case of malnutrition was complicated by a severely restricted diet, and the case describing hematemesis reported possible tacrolimus exposure through breast milk. However, in the hematemesis case serum tacrolimus levels were negative in the mother, child and the mother's breast milk.

We also looked at drug usage information, and found that the overall number of prescriptions for topical tacrolimus increased from 650,000 in 2001 to 990,000 in 2003. Additionally, the 0.1% strength is dispensed almost 2 ½ times more often than the 0.03% strength. The use of Protopic® in children accounts for 42% of total use. The use in children less than two years old, an age for which topical tacrolimus is not indicated, accounts for 7% of all Protopic® prescriptions. We saw a trend of increasing use in children less than two years old, except during calendar year 2002.

We found 17 cases in all age groups that reported malignancy related events, twelve of the cases new since the September 2003 analysis. The cases were mostly of foreign origin, although seven were domestic. The patients ranged in age from five to 75 years old, with a median age of 41.5 years. Three cases were reported in children; however, none of the children were less than two years old. The most serious outcomes were death (2), hospitalization (7) and life-threatening (1). Two cases reporting death were previously reviewed.² Topical tacrolimus, used mostly as the 0.1% strength, was primarily used to treat atopic dermatitis, with a small number (4) used for non-approved indications. The cases reported a variety of malignancies including, non-Hodgkin's lymphoma, angiosarcoma, cutaneous Kaposi's sarcoma, and squamous cell carcinoma at various sites, with the median onset of symptoms occurring within 106 days (range 28 days to 4 years). Five cases reported lymphadenopathy, four cases reported a recurrence or aggravation of a pre-existing malignancy, and two cases reported pre-existing serious underlying conditions (both cases were analyzed in the September 2003 review).

Most of the adverse events found in the pediatric cases are expected and reflected in the product label, except for septicemia, which we found in two hospitalized children less than 2 years old. The reports of adverse events with serious outcomes, although many of them labeled, warrants further monitoring. The known increased risk of lymphomas in patients treated with immunosuppressive agents, the known immunosuppressive effect of systemic tacrolimus, and the potential systemic absorption of topical tacrolimus provide a biological basis for concern in the 17 malignancy-related cases presented in this review. Consequently, ODS concurs with the October 2003 Advisory Committee's recommendation to enhance topical tacrolimus' product label to inform practitioners and patients of this potential risk,³ and to add to the label specific information concerning septicemia in children.

¹ Eczema herpeticum and infections are labeled events. Meningitis is not a labeled event.

² Bonnel RA. ODS – Post-Marketing Safety Review – Protopic® (NDA 50-7770 – All Adverse Events, September 24, 2003

³ Pediatric Subcommittee of the Anti-Infectives Drugs Advisory Committee, October 29 – 30, 2003

Background/Relevant Product Labeling

Topical tacrolimus was approved as Protopic® ointment on December 8, 2000. It is indicated for short-term and intermittent long-term therapy in the treatment of patients with modest 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.⁴ Protopic® 0.03% is approved for adults and children aged 2 years and older, and Protopic® 0.1% is approved for adults only. The oral and injectable formulations of tacrolimus were approved as Prograf® on April 8, 1994 for the suppression of organ rejection in patients undergoing allogenic liver or kidney transplants.

On September 24, 2003 ODS completed a review of all adverse events reported for topical tacrolimus.⁵ The September 2003 review analyzed 36 pediatric cases, seven of whom were less than two years old. The skin was the single most affected organ system in the pediatric group, as well as in the subgroup of children less than two years old. The September 2003 analysis reviewed five malignancy cases for all age groups. The five malignancies included Kaposi's sarcoma, anaplastic large cell lymphoma, non-Hodgkin's lymphoma-2, and B-cell lymphoma. The reader is referred to the September 2003 review if more details are required. Information from that review was presented at the October 29-30, 2003 Pediatric Advisory Subcommittee of the Anti-Infectives Drugs Advisory Committee, where the committee determined that the current labeling for the calcineurin inhibitors do not contain sufficient information on the product's associated cancer risks in humans.⁶ The Committee recommended boxed warnings, in addition to other risk management tools to inform prescribers, patients and/or caregivers of this risk.⁷

This document is organized into two parts:

- Part I provides updated AERS demographic information, and IMS drug use data for children < 2 years old
- Part II analyzes all cases of malignancy related adverse events

LABELING⁸

The *Pharmacokinetics Section* of the topical tacrolimus label indicates systemic absorption of topical tacrolimus in adult and pediatric patients with atopic dermatitis. The results from a pharmacokinetic study of 0.1% Protopic® ointment in 20 pediatric atopic dermatitis patients (aged 6 to 13 years), show peak tacrolimus blood concentrations below 1.6 ng/ml in all patients. The lowest tacrolimus blood level at which systemic effects can be observed is unknown.

⁴ Electronic PDR – Protopic® - extracted September 2004

⁵ Bonnel RA. ODS – Post-Marketing Safety Review – Protopic® (NDA 50-7770 – All Adverse Events, September 24, 2003

⁶ Pediatric Subcommittee of the Anti-Infectives Drugs Advisory Committee, October 29 – 30, 2003

⁷ Pediatric Subcommittee of the Anti-Infectives Drugs Advisory Committee, October 29 – 30, 2003

The *Pregnancy Section* states “although systemic absorption of tacrolimus following topical applications of Protopic ointment is minimal relative to systemic administration, it is known that tacrolimus is excreted in human milk.”

The *Pediatric Use Section* of the label indicates that the most common adverse events associated with Protopic® ointment application in pediatric patients were skin burning and pruritus. In addition to skin burning and pruritus, the less common events (<5%) of varicella zoster (most chicken pox), and vesiculobullous rash were more frequent in patient treated with Protopic® ointment. The safety and efficacy of Protopic® Ointment have not been established in pediatric patients below 2 years of age, and its use in this age group is not recommended.

The *Adverse Reactions Section* of the label indicates that the most commonly observed local adverse events were skin burning, pruritus and skin erythema. Additionally, other local and systemic effects, such as flu-like symptoms, allergic reactions, skin infection, infections (not specified), herpetic infections, pharyngitis and others are listed in the product label.

The *Precautions Section* indicates that transplant patients receiving immunosuppressive regimens (e.g. systemic tacrolimus) are at increased risk for developing lymphoma; therefore patients who receive Protopic® ointment and who develop lymphadenopathy should have the etiology of their lymphadenopathy investigated. Systemic tacrolimus (Prograf®) has a box warning about the possible formation of lymphoma. Additionally, the *Warnings Section* of Prograf® states that “As in patients receiving other immunosuppressants, patients receiving Prograf are at increased risk of developing lymphomas, and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.”⁹

LITERATURE SEARCH

A MEDLINE search of the English-language literature published from 1966 to 2004 found a case report¹⁰ of topical tacrolimus associated Kaposi’s sarcoma in an HIV + patient, for which a MedWatch report was submitted. This case was reviewed in the ODS September 2003 analysis.¹¹

Part I: AERS Demographic Information, and IMS Drug Use Data for Children Less Than 2 Years Old

On September 22, 2004 we searched the AERS database for all reports of adverse events associated with topical tacrolimus use in children less than two years old. We found ten reports that listed topical tacrolimus as a suspect agent. Seven reports

⁸ Electronic PDR – Protopic®, extracted September 2004

⁹ Electronic PDR – Prograf®, extracted October 2004

¹⁰ Cho M, Puma I, Nguyen D, et al. Development of Kaposi’s sarcoma in an AIDS patient after treatment with topical tacrolimus. *J Am Acad Dermatol.* 2004 Jan;50(1):149-50.

¹¹ Bonnel RA. ODS – Post-Marketing Safety Review – Protopic® (NDA 50-7770 – All Adverse Events, September 24, 2003

were US, and three were foreign. There were seven males, two females, and one of unreported gender. The patients ranged in age from six weeks to 17 months old, with a median age of 1 year old (n = 10). The most serious outcome was hospitalization in four reports. There were no reports of death. Topical tacrolimus was used primarily to treat atopic dermatitis (6), followed by allergic dermatitis (1). Three reports did not provide the indication for use of topical tacrolimus. In eight cases the strength of topical tacrolimus ointment was unreported, however, in two cases the strength was reported as 0.1%. Two cases reported obtaining serum tacrolimus levels, one of which was positive two weeks after discontinuation of the product. The second case reported non-detectable tacrolimus levels. The majority (7) of the cases reported systemic reactions, of which many were labeled. The remaining three cases reported either labeled local reactions, or local and systemic reactions. An analysis of the cases reporting most serious outcome, hospitalization, follows.

Hospitalization Reports in Children Less Than 2 years old (4)

There were four reports of hospitalization associated with topical tacrolimus use in children less than two years old. Three of the cases were US, and one case was foreign. The patients were aged 6 weeks, 6 months, 8 months and 17 months. Three cases were administered topical tacrolimus to treat atopic dermatitis, and one case reported exposure through breast milk, although serum and milk levels were negative. The cases described meningitis, malnutrition, hematemesis + esophagitis + melena, and eczema herpeticum + sepsis. The malnutrition case reported the concomitant use of corticosteroids, and a severely restricted diet in response to a history of multiple food allergies. The most profound case was of an 8-month old with atopic dermatitis who was hospitalized after developing eczema herpeticum after being administered topical tacrolimus 0.1% for six months over his entire body. Although topical tacrolimus was discontinued upon hospitalization, the patient's condition continued to worsen to include the development of a local abscess, as well as septicemia, cardiac arrest and neurological changes. Two weeks after tacrolimus was discontinued a serum tacrolimus level was 3.5 ng/ml. At the time of the report the patient was still hospitalized. A narrative of the cases is located in Appendix 1.

Drug Use

The following table summarizes projected U.S. prescriptions dispensed by retail pharmacies (chain, independent, food stores, and mail order) by calendar years from 2002, through August 2004. *This information is from IMS Health Prescription Audit Plus™ (on-line) and is not authorized for use outside the FDA without IMS Health clearance.*

Prescriptions of Topical tacrolimus Dispensed – By Year

	Jan – Aug 04	2003	2002	2001	Total
Topical tacrolimus 0.03%	181,000	257,000	284,000	223,000	945,000
Topical tacrolimus 0.1%	531,000	733,000	588,000	427,000	2,279,000
Total	712,000	990,000	873,000	650,000	3,224,000

IMS Health National Prescription Audit Plus™, 2002 – 2004, data extracted September 2004

The number of prescriptions for Protopic® has increased from 650,000 in 2001 to 990,000 in 2003. The trend towards increasing prescriptions appears to continue from January to August, 2004. Additionally, Protopic 0.1% is dispensed almost 2 ½ times more often than Protopic 0.03%.

Age: Appearances (already in thousands, do not add three zero's to each figure)

Topical tacrolimus	Jan – Jul 04	2003	2002	2001	Total	Percentage
Less Than 2 years old	54,000	47,000	12,000	37,000	150,000	7%
2 to 11 years	93,000	215,000	164,000	132,000	604,000	29%
12 to 16 years	15,000	38,000	33,000	29,000	115,000	6%
017 years and older	201,000	372,000	327,000	321,000	1,221,000	58%
Total	363,000	672,000	536,000	519,000	2,090,000	100%

IMS Health National Disease & Therapeutic Index™, 2001 to 2004, data extracted September, 2004

We obtained drug usage information stratified by age from IMS Health National Disease and Therapeutic Index™ (NDTI). Drug use age data is based on “appearances” as determined by patient visits to office based practitioners in the continental US. Appearance data is different from the number of prescriptions dispensed. Based on appearance data, IMS Health NDTI™ shows 42% of all topical tacrolimus is used in children aged 16 years and younger, and 7% of use occurred in children less than two years old. When use is analyzed on an annual basis, there appears to be a trend of increasing use in children less than two years old, except for calendar year 2002. The number of prescriptions dispensed for children less than two years old during the first eight months of 2004 already exceeds the number of prescriptions dispensed in this age group in all of 2003. Similar to the September 2003 analysis we did not obtain information concerning the duration of topical tacrolimus use.

Part II: Malignancy Related Reports

On September 22, 2004 we searched the AERS database for all reports of topical tacrolimus associated malignancies in all age groups using the following search terms and levels:

- Granuloma – PT
- Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps) - SOC

We found 18 cases reporting malignancy related adverse events. We excluded one foreign case describing a teratoma in a 29 year old male because follow-up information indicated that Protopic® was started after the teratoma was diagnosed. We reviewed 17 cases. Seven cases were US, and ten were foreign. There were 13 males and four females, ranging in age from five to 75 years, with a median age of 41.5 (n = 17). The reported outcomes included death (2), hospitalization (7) and life-threatening (1). The remaining seven cases reported non-serious outcomes. Topical tacrolimus was used to treat atopic dermatitis (13), vitiligo (1), inverse psoriasis (1), vulval atrophic sclerosis lichen (1) and balanitis (1). The patients primarily used the 0.1% strength, although two

patients reported using both 0.1% and 0.03% preparations. One patient used 0.075% (mixed with petrolatum); and one case, involving a five year old child, did not report the strength of tacrolimus used. Symptoms relating to the diagnosed malignancies appeared 28 days to 4 years from starting topical tacrolimus, with a median time to onset of 106 days (n = 12). Six cases reported the malignancy occurring at the site of tacrolimus application, and five cases reported experiencing lymphadenopathy. Four cases reported a recurrence or aggravation of a pre-existing malignancy, two cases reported pre-existing serious underlying conditions¹² and eight cases reported current or previous topical and/or systemic corticosteroid or immunosuppressive therapy. Additionally, one patient reporting squamous cell carcinoma of the face also reported non-facial exposure to UV phototherapy, and a “reasonable level” of sun exposure by playing outdoor sports. Additionally, another case reporting carcinoma of the mouth reported a 30+ year history of pipe, and a five+ year history of cigarette smoking. The cases reported a variety of malignancy-related events, including:

- Hepatoblastoma, medically significant outcome, 5 year old
- Angiosarcoma, metastatic, hospitalization, 16 year old
- Sezary Syndrome, hospitalization, 16 year old
- Lymphoma, non-serious outcome, 22 year old
- Esophageal cancer with metastasis, non-serious outcome, 49 year old
- Sweat gland tumor, hospitalization, 43 year old
- Squamous cell carcinoma on the face, non serious outcome, 34-35 year old
- Squamous cell carcinoma of the vulva, hospitalization, 75 year old
- Recurrent melanoma, non-serious outcome, 39 year old
- Squamous cell carcinoma of the anterior floor of the mouth, hospitalization, 51 year old
- Lymphadenopathy with possible lymphoma, non-serious outcome, 40 year old
- Anaplastic large cell lymphoma at application site with progression to the lungs, non-serious outcome – 50 year old
- Cutaneous & Pulmonary Kaposi’s sarcoma, death, 28 year old
- Non-Hodgkin’s Lymphoma, life-threatening, 52 year old
- Non-Hodgkin’s Lymphoma, death, 54 year old
- Nodular follicular lymphoma, hospitalization, 50 year old
- Squamous cell carcinoma of the penis, hospitalization, 57 year old

The narratives for the cases are presented in Appendix 2 of this document.

Discussion/Conclusion

¹² Serious underlying conditions included chronic renal insufficiency, and HIV-AIDS

Topical tacrolimus was approved as Protopic® ointment in 2000 to treat modest to severe atopic dermatitis in patients where the use of alternative, conventional therapies is inadvisable. The 0.03% product was approved for adults and children aged 2 years and older, and the 0.1% was approved for adults only. Neither the 0.03% nor the 0.1% product is approved for children less than 2 years old.

We reviewed the demographic data for ten cases of adverse events associated with topical tacrolimus use in children less than two years old. The children were mostly male, and ranged in age from six weeks to 17 months old, with a median age of 1 year old (n = 10). The children were administered topical tacrolimus primarily to treat atopic dermatitis, and two of the ten cases reported using the 0.1% strength of tacrolimus. The current Protopic® labeling describes systemic absorption with the product in both adult and pediatric patients, as well as a variety of systemic and local adverse events. Two pediatric cases reported obtaining serum tacrolimus levels, one of which was positive two weeks after discontinuation of the product. The majority of cases reported systemic reactions, of which many were labeled. The remaining cases reported either labeled local reactions, or local and systemic reactions. The most serious outcome was hospitalization in four cases. One case each described eczema herpeticum with septicemia, and meningitis and septicemia, both in children less than one year old. In these two cases the onset of symptoms occurred six and two months respectively from the start therapy. Topical tacrolimus is labeled for eczema herpeticum, and infections, but not for meningitis. It appears that topical tacrolimus may have had a role in the development of the reactions in these two cases. Two additional hospitalizations were reported that described malnutrition, and hematemesis. The case of malnutrition was complicated by a severely restricted diet, and the case describing hematemesis reported possible tacrolimus exposure through breast milk. However, in the hematemesis case serum tacrolimus levels were negative in the mother, child and the mother's breast milk. It is unknown what role, if any topical tacrolimus played in the development of the reactions in the last two cases.

We also looked at drug usage information, and found that the overall number of prescriptions for topical tacrolimus increased from 650,000 in 2001 to 990,000 in 2003. Additionally, the 0.1% strength is dispensed almost 2 ½ times more often than the 0.03% strength. The use of Protopic® in children accounts for 42% of total use. The use in children less than two years old, an age for which topical tacrolimus is not indicated, accounts for 7% of all Protopic® prescriptions. When we looked at annual usage, we saw a trend of increasing use in children less than two years old, except during calendar year 2002. The trend appears to continue during the first eight months of 2004, where we noted the amount of topical tacrolimus dispensed in children less than two years old already exceeding the amount dispensed in this age group for all of 2003.

We found seventeen cases in the AERS database that reported malignancy related events, twelve of the cases new since the September 2003 analysis. The cases were mostly foreign, although seven were reported from the US, and the patients ranged in age from five to 75 years old, with a median age of 41.5 years. Three cases were reported in children; however, none of the children were less than two years old. The two cases reporting death were previously

reviewed.¹³ Seven new cases reported hospitalization, and one case reported a life-threatening outcome. The remaining cases reported non-serious outcomes. Topical tacrolimus, used mostly as the 0.1% strength, was primarily used to treat atopic dermatitis, with a small number (4) used for non-approved indications.

There were a variety of malignancies reported including, but not limited to non-Hodgkin's lymphoma, angiosarcoma, cutaneous Kaposi's sarcoma, and squamous cell carcinoma at various sites. Symptoms related to the diagnoses of malignancy-related events occurred within a median time of 106 days (range 28 days to 4 years). It is interesting to note that six cases reported the malignancy occurring at the site of tacrolimus application, although the significance of this finding is unknown. Five cases reported lymphadenopathy, four cases reported a recurrence or aggravation of a pre-existing malignancy, and two cases reported pre-existing serious underlying conditions (both cases were analyzed in the September 2003 review). Although the role of topical tacrolimus in these malignancy cases is unknown, patients exposed to systemic immunosuppressive therapy (e.g. tacrolimus) have shown an increased risk of lymphoma development, particularly of the skin. Currently the findings from these 17 cases of malignancy-related events, twelve new cases since the September 2003 analysis do not allow us to draw conclusions regarding whether topical tacrolimus is the cause of the reported malignancy, or whether these malignancies occurred as part of the natural history of the underlying condition (in some patients).

Most of the adverse events found in the pediatric cases are expected and reflected in the product label, except for septicemia, which we found in two hospitalized children less than 2 years old. The reports of adverse events with serious outcomes, although many of them labeled, warrants further monitoring. Additionally, we have presented 17 cases of malignancy-related adverse events occurring in children and adults, none occurring in children less than two-years old. The known increased risk of lymphomas in patients treated with immunosuppressive agents, the known immunosuppressive effect of systemic tacrolimus, and the potential systemic absorption of topical tacrolimus provide a biological basis for concern in the 17 malignancy-related cases presented in this review. Consequently, ODS concurs with the October 2003 Advisory Committee's recommendation to enhance topical tacrolimus' product label to inform practitioners and patients of this potential risk, and to add to the label specific information concerning septicemia in children.

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cc:

NDA: 50-777

Electronic only cc:

¹³ Bonnel RA. ODS – Post-Marketing Safety Review – Protopic® (NDA 50-7770 – All Adverse Events, September 24, 2003

HFD-400/Seligman

HFD-430/Avigan/Karwoski/Nguyen/Topical tacrolimus (Drug File)

HFD-540/Nikhar/Wright/Kozma-Fornaro

Appendix 1: Hospitalization Narratives

2004 US, FDA 4425551-5, MCN 2004US000854. A 17 month old female with a history of multiple food allergies and chronic atopic dermatitis was being managed with topical corticosteroids, emollients and topical tacrolimus 0.1%. During treatment the patient presented with a three-month history of an itching skin eruption, thinning scalp hair, swelling in the extremities, lack of weight gain and progressively lower percentiles on a normal growth curve. The patient was hospitalized with a diagnosis of kwashiorkor nutritional deficiency. Upon history taking it was revealed that, in response to the allergy testing, the patient was placed on a severely limited diet. This was a literature report.

Reviewers comment: This child's hospitalization appears to have been related to the severely restricted diet the child was placed on, and unrelated to the use of topical tacrolimus. It is interesting to note that this 17 month old child was treated with the adult strength of topical tacrolimus.

2004 US, FDA 4421520-X, MCN 2004US00821. A 6 month old girl was administered topical tacrolimus (strength unreported) for two months to treat atopic dermatitis. The patient was admitted to the hospital for 10 days for meningitis and septicemia. The patient also experienced seizures. The patient is now out of the hospital and doing well. At the time of the report serum tacrolimus levels were pending.

Reviewers comment: Infection is a labeled adverse event; however, the role of tacrolimus in the development of meningitis is unknown. The seizure event was most likely due to the meningitis.

2004 Foreign, FDA 4267212-1, MCN 2003EU006714. A 6 week old male was exposed to tacrolimus through breast milk. The baby experienced two episodes of hematemesis and melena in a one month period while being breast fed while the mom was being treated for a generalized eczema. The mom was treated with Protopic® 0.1% over 95% of BSA (one tube per day), except on the breast. The mom stopped Protopic® after the first episode of hematemesis, but re-started Protopic due to recurrence of the eczema. The breast feeding was stopped. The hematemesis and the melena stopped. The baby was found to have a duodenal ulceration, and esophagitis. Esophagitis was a result of the regurgitations. Blood tacrolimus levels in the mother, baby and breast milk were negative. The baby recovered but he still had regurgitations. The reporter considered the role of tacrolimus as "definitely not".

Reviewers comment: The role of tacrolimus in the development of hematemesis and melena is unknown, although topical tacrolimus is labeled for vomiting. Although topical tacrolimus can be absorbed by the mother, and secreted into breast milk, it appears in this case that the breast milk was negative for tacrolimus.

2004 US, FDA 4244152-5, MCN 2003US005646. An 8 month of male was treated was treated for atopic dermatitis with topical tacrolimus 0.1% (mixed with petrolatum) over his entire body since the age of two months. The patient was hospitalized for eczema herpeticum. Tacrolimus was discontinued. The patient's condition continued to worsen. The patient developed an abscess at the IV access site, as well as a pseudomonas sepsis leading to cardiac arrest. Two weeks after tacrolimus was discontinued a serum tacrolimus level was 3.5 ng/ml. There was no level taken at the start of the admission. At the time of the report the patient was back in the ICU due to hyperthermia and hypernatremia, atopic dermatitis flare and altered neurological status.

Reviewers comment: Eczema herpeticum, skin infections and infection are labeled events for topical tacrolimus. Detectable serum levels from topical tacrolimus is labeled in the Pharmacokinetic section of the label.

Malignancy Related Adverse Events Reported with Topical Tacrolimus (Protopic®)

	AERS ISR Number	Manufacturer Case Number	Rpt Year	Age/ Gender	Location	Outcome	Tacrolimus Strength	Type of Malignancy	Narrative
1	4446523-0	2004EU000429	2004	5 M	France	Other – Medically significant	NR	Hepatoblastoma	A 5 year old female with a history of atopic dermatitis received an unreported strength of Protopic for 365 days. Less than 3 months after discontinuation of Protopic the patient experienced abdominal pain. A scan showed a liver anomaly. The patient was diagnosed with a hepatoblastoma. Approximately 2 months later a hepatectomy was performed. The reporter indicated that telephone follow-up with the reporting physician confirmed that the event was unrelated to Protopic, however, he would provide the patient's hospitalization report.
2	4317145-7	2003JP007511	2003	16 M	Japan	Hospitalization, Other	0.1%	Angiosarcoma, metastatic	A 16 year old used Protopic twice daily on face and neck for atopic dermatitis for approximately 3 months (~ 10 grams total). The medication was discontinued because dermatitis improved. Approximately 15 days after discontinuation the patient noticed a mass around his clavicle. The small (0.5 cm) tumor was present prior to start of protopic, but became suddenly large (8 x 6cm – doubled in size over an eleven day period, 15 days after discontinuation of protopic. The tumor was biopsy diagnosed as malignant angiosarcoma stage III, highly positive for anti-factor-VIII antibody staining. Prior to protopic the tumor had been present for ~ 1.5 years. The patient also had lymphadenopathy.
3	4251585-X 4243687-9 4421293-0	2003JP006781	2003	16 F	Foreign	Hospitalization Life-threatening	0.075% (Obtained by mixing tacrolimus 0.1% with Vaseline)	Lymphoma, malignant or Sezary Syndrome	A 16 year old female with a seven year history of atopic dermatitis was diagnosed with malignant lymphoma approximately 3 years after starting tacrolimus 0.1% + Vaseline combination. The patient's symptoms started 2 years after the start of tacrolimus. The patient presented with swollen lymph nodes, SOB, anemia, prolonged menstrual bleeding, HPA suppression. The patient was committantly using mometasone, prednisolone oral and nystatin oral. The patient used the tacrolimus + Vaseline combination for 3 years and 4 months applied to her face. The corticosteroid was applied to the lower body. The patient also used cyclosporine for 2 months. Further review of the document indicate that the initial diagnosis of atopic dermatitis may have been in error, and the symptoms that the patient presented with seven years ago may have been related to Sezary syndrome. Lymphocyte biopsy revealed rearrangement of T cell receptor beta 1, therefore, it was considered that the patient had

	AERS ISR Number	Manufacturer Case Number	Rpt Year	Age/ Gender	Location	Outcome	Tacrolimus Strength	Type of Malignancy	Narrative
									Sezary syndrome
4	4322347-X	2004JP000323	2004	22 M	Japan	Other	0.1%	Lymphoma	A 22 year old male used protopic for atopic dermatitis. He applied protopic to his whole body for about 2 years. Approximately 2 months after discontinuation the patient developed lymphadenopathy of his neck, axilla and groin, and weight loss. The reporter initially "diagnosed lymphoma", however, further in the report the physician "did not yet receive the results of histopathological examination". The reporter did not consider the patient's event malignant.
5	4264860-X	2003EU006920	2003	49 M	France	Other	0.1%, 0.03%	Esophageal cancer with metastasis	A 49 year old male used Protopic for severe large lichenified atopic dermatitis for approximately 154 days. 122 days after starting Protopic a large right cervical fixed adenopathy (equivalent in size to hen's egg) was discovered. A biopsy was performed which revealed a metastases of a malpighian poorly differentiated cancer. Esophageal cancer was discovered as the primary. The patient concomitantly used topical corticosteroids. The patient did not have a history of tobacco or alcohol use. The patient had atopic dermatitis over 95% of body since childhood. The patient had a history of hypertension, and was also suffering from severe chronic renal insufficiency.
6	4317147-0 4386942-4	2004JP000422	2004	43 M	Japan	Hospitalized (information in narrative – not coded) Life-Threatening	0.1%	Sweat gland tumor	A 43 year old male used Protopic 0.1% to treat atopic dermatitis for ~ 4 years (~ 735 to 835 grams prescribed). The patient developed a sweat gland carcinoma on his left axilla. Metastatic lymphadenopathy and infiltration to vasa were also observed. Blood tacrolimus levels were reported as below 0.50 ng/ml. The carcinoma was excised, and the patient underwent chemotherapy, The patient had an 18 year history of atopic dermatitis, and had used topical corticosteroids in the past. The patient had developed skin atrophy from corticosteroid use. Subsequently the patient was started on topical tacrolimus. The patient said that he did not apply tacrolimus over the left axilla.
7	4356448-7	PHNR2004AU00896	2004	34 – 35 M	Australia	Other	0.1%	Squamous Cell carcinoma on the face	A 34-35 year old male was diagnosed with squamous cell carcinoma on the face while using topical tacrolimus on the face. The patient used topical tacrolimus on the face for atopic dermatitis, and reportedly had a history of using corticosteroids on the face. The patient also had UV phototherapy to the body, but not the face. The patient had a prescription for pimecrolimus, but had not used it prior to the development of the squamous cell carcinoma on the face. The patient played sports and

	AERS ISR Number	Manufacturer Case Number	Rpt Year	Age/ Gender	Location	Outcome	Tacrolimus Strength	Type of Malignancy	Narrative
									had a reasonable level of sun exposure.
8	4300116-4	2003EU007301	2003	75 F	France	Hospitalization, Other	0.1%	Squamous Cell Carcinoma of the vulva	A 75 year old female used Protopic for approximately 3 months to treat vulval atrophic sclerosis lichen. The patient had previously used topical corticosteroids. Approximately 6 weeks after starting Protopic the patient developed granulation. Protopic was stopped. The patient was diagnosed with a recurrence of vulvar squamous cell carcinoma (T2, 1.5 cm) with sentinel lymph node metastases. A total vulvectomy with a lymphadenectomy was performed. In 1992 the patient had a partial vulvectomy due to in situ epithelioma. In 1995 the patient had a total vulvectomy with disappearance of the epithelioma. In 1999 and 2000 multiple biopsies were normal, although erosive lesions remained.
9	4230257-1	2003US005460	2003	39 M	US	Other	Unknown	Melanoma, recurrence	A 39 year old male experienced lymphadenopathy and new onset of melanoma 3 to 4 weeks after using topical tacrolimus (strength NR) for vitiligo. The melanoma was generalized metastatic, not at application site. The patient is being treated (at time of report) for stage IV malignant melanoma. The patient had a past history of melanoma 3 years before onset of vitiligo.
10	3824791-3	2001000869	2001	51 M	US	Hospitalization, Life-Threatening	0.1%	Squamous Cell Carcinoma of anterior floor of the mouth	This 51-year-old male was diagnosed with squamous cell carcinoma of anterior floor of the mouth some time after starting tacrolimus 0.1% topically for eczema. The patient has a history of smoking and is currently using nicotine gum to aid in the discontinuation of smoking. The patient also experienced mouth ulceration, pain, and erythema. The patient underwent surgical resection. The patient has a long history of eczema (50+ years), and corticosteroid use. The patient smoked a pipe for 30+ years and cigarettes for 5+ years. The patient does not have emphysema or COLD, and is otherwise considered healthy.
11	3758860	200200005	2002	40 F	US	Other	0.1%	Lymphadenopathy – possible lymphoma	This 40-year-old female with pre-existing lymphoma and severe atopic dermatitis developed two lumpy areas that looked like lymphoma at the site of tacrolimus 0.1% ointment application. The lumps spontaneously resolved. The patient was diagnosed with lymphadenopathy.
12	4035680-6	2002000048	2002	50 M	US	Other	0.1%	Anaplastic large cell lymphoma	This 50-year-old male with a life-long history of atopic dermatitis was diagnosed with large cell lymphoma an

	AERS ISR Number	Manufacturer Case Number	Rpt Year	Age/ Gender	Location	Outcome	Tacrolimus Strength	Type of Malignancy	Narrative
								cell lymphoma, t-cell type at application site, with progression to the lungs	unknown time after starting tacrolimus 0.1% ointment. The patient underwent chemotherapy and radiation treatment. The lymphoma was started on the flank (right hip) in the protopic application area, and progressed to the lungs. The patient's prognosis is not good. The patient did not have a history of lymphoma. However, the patient has a history of prior use of topical corticosteroids and systemic antipruritics to treat the atopic dermatitis.
13	4271491-4	2002US005059	2002	28 M	US	Death (9.12.2002) Hospitalization, Other	0.1%	Cutaneous & Pulmonary Kaposi's sarcoma	This 28 year old HIV+ patient was treated with tacrolimus topically 0.1% bid for "inverse psoriasis" in the axilla and the groin. One month after Protopic application the patient presented with cutaneous and pulmonary Kaposi's sarcoma despite having significantly improved on HAART ¹⁴ , with CD4 counts increasing and viral load decreasing two months before the development of KS lesions. The cutaneous KS developed on areas of the skin where the topical tacrolimus as applied. The patient reportedly died of KS of the lungs and the author thought its relationship to topical tacrolimus was unlikely. However, the relationship of cutaneous KS to topical tacrolimus was considered possible. Case report published: Cho M, Puma I, Nguyen D, et al. Development of Kaposi's sarcoma in an AIDS patient after treatment with topical tacrolimus. JAAD, Vol 50, 2004, 149-150.
14	4003967-9	Direct	2002 2003	52 M	US	Life-Threatening, Disability	0.1%	Non-Hodgkins Lymphoma nos	This 52-year-old male developed non-hodgkins lymphoma approximately one year after using tacrolimus 0.1% bid for eczema. Used tacrolimus approximately six months.
15	4128931-0	2002000316	2003	54 M	US	Death	0.03% and 0.1%	Non-Hodgkins Lymphoma	This 54 year old male lymphoma after starting tacrolimus topically for severe atopic dermatitis (100% BSA). The patient used tacrolimus 0.03% and 0.1% on 25 – 50% of his body intermittently for an unreported period. The patient concomitantly use oral corticosteroids, and previously used topical corticosteroids. The patient died of complications due to the lymphoma.
16	4334190-6 4354458-7	2004JP000625	2004	50 F	Japan	Hospitalization, Life-Threatening	0.1%	Nodular follicular Lymphoma	This 50 year old female used topical tacrolimus 0.1% to treat atopic dermatitis (60% BSA). She applied tacrolimus to lower limbs and face, starting Jan 15,

¹⁴ HAART – Highly active antiretroviral therapy

	AERS ISR Number	Manufacturer Case Number	Rpt Year	Age/ Gender	Location	Outcome	Tacrolimus Strength	Type of Malignancy	Narrative
									2002 and continuing until June 2003. Approximately 3 months after discontinuation of tacrolimus the patient developed a malignant lymphoma, biopsy diagnosed as follicular lymphoma stage IV (which might be unassociated with EB virus). The patient has a history of using multiple topical steroid products, and oral anti-histamines. The patient was concomitantly taking steroids.
17	4356599-7	2004EU000823	2004	57 M	Norway	Hospitalization, Life-threatening	0.1%	Squamous cell carcinoma – penis	This 57 year old male with a history of balanitis used topical tacrolimus 0.1% for 70 days. The patient had a 2 year history of inflammatory changes on his penis that was understood as lichen sclerosus et atrophicus. A biopsy showed nonspecific inflammation and epidermal hyperplasia, but no signs of malignancy. Eight weeks after treatment with topical tacrolimus a tumor developed on the glans penis. A biopsy diagnosed squamous cell carcinoma with infiltrate growth.

Deleted Case – Because teratoma (benign) actually occurred prior to the start of topical tacrolimus

3	4217389-9	2003JP006920	2002	29 M	Foreign	Hospitalization	0.1%	Teratoma, benign	A 29 year old male used protopic on his face and neck for atopic dermatitis. The report states that a teratoma (on chest) was observed Aug 2002. Protopic was started on Oct 5, 2002 or Oct 5, 2000. Surgical intervention occurred on Jan 8, 2003. It was unclear in this document based on how the dates were reported if the teratoma was present prior to starting protopic. Follow up information indicates that the Protopic was started after development of the teratoma.
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