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SUBJECT: ODS Postmarketing Safety Review (PID 040754, PID 040752)
Update - Update on Malignancy Related Events in all Age Groups
Drug: Pimecrolimus (Elidel®, NDA 21-302), Topical Tacrolimus (Protopic®, NDA 50-777)

EXECUTIVE SUMMARY

This document summarizes all reports of malignancy-related adverse events in all age groups associated with pimecrolimus and topical tacrolimus use, and is a companion document to previous ODS reviews.^{1,2,3,4} Some of the information in this review was orally presented on November 29, 2004 at the FDA meeting between DDDDP/HFD-540, OCTAP/DPDD/HFD-960, ODS/HFD-430 and Sandy Kweder, M.D., Deputy Office Director, Office of New Drugs. The meeting was convened to discuss the malignancy signal suggested by biological plausibility, updated animal data and post-marketing adverse event reports, as well as to discuss the proposed box warnings for the topical calcineurin inhibitors.

Since approval of both agents we have found ten malignancy adverse event cases related to pimecrolimus, and 19 cases related to topical tacrolimus (t. tacrolimus) use, with one case⁵ common to both series. The majority of cases were of US origin (pimecrolimus – 7, t. tacrolimus – 8), and involved male patients (pimecrolimus – 5, t. tacrolimus – 15). Malignancy related adverse events were reported for adults and children, and are listed in Appendices 1 and 2. Seven of the cases were reported in children (pimecrolimus – 4, t. tacrolimus – 3),⁶ with three of the children less than six years old. There were no cases in children less than two years old reported in either series. The most serious outcomes reported were death (t. tacrolimus – 2, pimecrolimus – 0) and hospitalization (t. tacrolimus – 8,

¹ Pitts MR. ODS Safety Review – Pimecrolimus NDA 21-302, All Adverse Events, PID # 0303434, September 24, 2003

² Pitts MR. ODS Safety Review – Pimecrolimus NDA 21-302, All Adverse Events in Children < 2 years, and Update on Malignancy Related Events in all Age Groups, PID # 040609, September 28, 2004

³ Bonnel RA. ODS Safety Review – Topical Tacrolimus, NDA 50-777, All Adverse Drug Reactions, PID # 030433, September 24, 2003

⁴ Pitts MR. ODS Safety Review – Topical Tacrolimus, NDA 50-777, All Adverse Events in Children < 2 years, and Update on Malignancy Related Events in all Age Groups, PID # 040608, October 5, 2004

⁵ The patient used both topical tacrolimus, and pimecrolimus prior to development of T-cell lymphoma

⁶ The children ranged in age from 2 years to 16 years old

pimecrolimus - 1). The death cases occurred in adults, and two of the topical tacrolimus hospitalization cases occurred in children.^{7,8}

The topical calcineurin inhibitors were used primarily to treat atopic dermatitis, with a small number (7) used for non-approved indications. The cases reported a variety of malignancy-related events with a median onset of symptoms occurring in 150 days⁹ for topical tacrolimus patients, and 90 days¹⁰ for pimecrolimus. One case reported an Epstein Barr virus-associated malignancy. Eight malignancies occurred at the site of application of the calcineurin inhibitor and were reported as squamous cell carcinoma (4), t-cell lymphoma (2), Kaposi's sarcoma (1), and lymphoma nos (1).¹¹ One adult case reported a serum tacrolimus level less than 0.50 ng/ml, however, the case did not provide further information to assess the meaning of the level. There were no serum levels reported in any of the pimecrolimus cases. Two cases reported pre-existing serious underlying conditions that could have contributed to the reported events.

In response to DDDDP's request to determine causality in the malignancy cases, spontaneous surveillance systems such as AERS may not be the best tools to determine causality. Spontaneous surveillance systems are subject to many limitations, one of which is that drug/event causality may not definitely be derived from its data. Consequently, an active surveillance system such as provided through a registry, may be more useful in determining causality between topical calcineurin inhibitors and malignancy related events. Although, the role of topical calcineurin inhibitors in the development of malignancy related events in the individual reports in our case series is unknown, collectively the AERS cases provide a signal for a possible association between the use of topical calcineurin inhibitors and the development of malignancies. The malignancy occurrences reported with the topical calcineurin inhibitors are not inconsistent with the known increased risk of lymphoma development reported with the use of Prograf®, a systemic calcineurin inhibitor.

Background

During the October 2003 Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee Meeting, the Office of Drug Safety (ODS) presented two cases of tumor growth associated with pimecrolimus, and five cases of malignancies associated with topical tacrolimus use.¹² Subsequently, DDDDP requested that ODS update malignancy related information for both pimecrolimus and topical tacrolimus. In response, on September 28, 2004, and October 5, 2004, ODS reviewed six new pimecrolimus, and 12 new topical tacrolimus cases, for a total of eight and 17 cases respectively. ODS conducted additional searches of the AERS database and found three additional cases (pimecrolimus – 1, t. tacrolimus – 1, pimecrolimus + t. tacrolimus – 1). At the time of this report, ODS has analyzed ten malignancy cases associated with pimecrolimus use, and 19 malignancy cases associated with the use of topical tacrolimus. Since the September and October 2004 analyses, and in preparation for the November 29,

⁷ Pitts MR. ODS Safety Review – Pimecrolimus NDA 21-302, All Adverse Events, PID # 0303434, September 24, 2003

⁸ Bonnel RA. ODS Safety Review – Topical Tacrolimus, NDA 50-777, All Adverse Drug Reactions, PID # 030433, September 24, 2003

⁹ Range = 21 days to 790 days, n = 13

¹⁰ Range = 1 – 2 weeks to 10 months, n = 9

¹¹ Pimecrolimus (1), topical tacrolimus (6), pimecrolimus + topical tacrolimus (1)

2004 DDDDP/OCTAP/ODS meeting, DDDDP requested that ODS provide a breakdown of malignancy related events as being related, probably related or definitely not related to pimecrolimus or topical tacrolimus.

This document is organized into three parts:

- Part I briefly reviews limitations and strengths of spontaneous surveillance systems such as AERS
- Part II analyzes new malignancy cases associated with pimecrolimus reports
- Part III analyzes new malignancy cases associated with topical tacrolimus reports

Part I: Spontaneous Surveillance Systems – Limitations and Strengths¹³

The AERS database is a collection of spontaneous adverse event reports submitted by consumers, health care professionals, manufacturers and others. Submission of reports to the AERS database occurs on a voluntary basis, except for manufacturers and distributors, who have mandatory reporting requirements. Based on the spontaneous nature of reporting, there are limitations, as well as strengths to the AERS database. The limitations and strengths of AERS, as well as other spontaneous adverse event reporting systems are as follows:

Limitations

- The recognition of an adverse event associated with a drug product is subjective and imprecise. Failure to recognize the association between a drug and event may be further complicated in cases where there is a latency period between exposure to the drug product and occurrence of the observed event.
- Under-reporting is a limitation of spontaneous reporting systems. It has been estimated that the FDA receives approximately 1 to 10% of suspected serious adverse event reports.
- Report quality varies.
- Reporting is subject to biases. Unlike clinical trial data, which are obtained under strictly controlled conditions, spontaneously submitted report information is uncontrolled and subjected to a number of biases, including the length of time a product has been on the market. In addition to these biases, it is possible that reported cases might differ from non-reported cases in characteristics such as time to onset or severity.
- Spontaneous reporting systems lack denominator data, such as user population and drug exposure patterns, and therefore cannot be used to derive incidence data.

Strengths

Despite the acknowledged limitations to spontaneous reporting systems, these systems do have strengths, which include the following:

- Spontaneous systems allow for large-scale ongoing surveillance of all patients.
- Spontaneous systems are relatively inexpensive. In fact, spontaneous systems are probably the most cost effective way to detect rare, serious adverse events undiscovered during clinical trials.

¹² Pediatric Subcommittee of the Anti-Infectives Drugs Advisory Committee, October 30, 2003

¹³ Kennedy DL, Goldman SA, Lillie RB. Pharmacoepidemiology, 3rd Edition, Edited by BL Strom, 2000, pg 165 – 169.

- Spontaneous systems greatest strength lies in the ability to generate hypotheses. Spontaneous surveillance programs can be used to generate signals of potential problems that warrant further investigation.

Part II: Pimecrolimus (Elidel®) Malignancy Related Reports found in the AERS database:

On November 29, 2004 we searched the AERS database for all reports of pimecrolimus-associated malignancies in all patient age groups. We used the following search terms and levels:

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

We found ten cases reporting malignancy related adverse events. Eight of the ten cases had been previously analyzed in the September 2003¹⁴ and September 2004¹⁵ ODS reviews. Consequently we provide information only on the two new cases. The new cases involved a 53-year old male (US), and 71-year old female (foreign). The male patient used pimecrolimus to treat atopic dermatitis of the trunk and limbs. The female patient used pimecrolimus on the vulva to treat lichen sclerosis thought to be related to Zocor use. The reported malignancies were paniculitis-like T-cell lymphoma, and squamous cell carcinoma. Both malignancies occurred at the site of pimecrolimus application and occurred five and three months, respectively, after pimecrolimus was started. The atopic dermatitis case reported concomitant use of topical corticosteroids, as well as a nine-day overlap where pimecrolimus and topical tacrolimus were both used. The lichen sclerosis case reported using topical corticosteroids just prior to starting pimecrolimus. Neither case reported serum pimecrolimus levels. One case reported hospitalization, and the other reported a non-serious outcome. A brief narrative of each case, as well as a table of all pimecrolimus related malignancies is provided in Appendix 1.

Part III: Topical Tacrolimus (Protopic®) Malignancy Related Reports found in the AERS database:

On November 29, 2004 we searched the AERS database for all reports of topical tacrolimus-associated malignancies in all patient age groups. We used the following search terms and levels:

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

We found 20 cases reporting malignancy related adverse events. One case was previously excluded because the teratoma occurred prior to drug exposure to topical tacrolimus, and 17 cases had been previously analyzed in the September 2003¹⁶ and October 2004¹⁷ ODS reviews. There were two new cases, of which one is a duplicate to FDA case # 4472779-4 described in the pimecrolimus section of this document. The patient had used both pimecrolimus

¹⁴ Pitts MR. ODS Safety Review – Pimecrolimus NDA 21-302, All Adverse Events, PID # 0303434, Sept 24, 2003

¹⁵ Pitts MR. ODS Safety Review – Pimecrolimus NDA 21-302, All Adverse Events in Children < 2 years, and Update on Malignancy Related Events in all Age Groups, PID # 040609, Sept 28, 2004

¹⁶ Bonnel RA. ODS Safety Review – Topical Tacrolimus, NDA 50-777, All Adverse Drug Reactions, PID # 030433, September 24, 2003

¹⁷ Pitts MR. ODS Safety Review – Topical Tacrolimus, NDA 50-777, All Adverse Events in Children < 2 years, and Update on Malignancy Related Events in all Age Groups, PID # 040608, October 5, 2004

and topical tacrolimus prior to the development of the T-cell lymphoma. Consequently, we provide information for only one new case. The new case was of a 49-year old male (foreign) who used Protopic 0.1% ointment to the face for 26 months to treat atopic dermatitis. Approximately 24 months into treatment the patient was diagnosed with senile Epstein Barr Virus-associated large B-cell lymphoma of the left kidney. The lymphoma was treated with chemotherapy. Two months after developing the lymphoma, the patient was diagnosed with primary lung cancer, which was treated with a pneumonectomy. The patient continued using topical tacrolimus up to the point the primary lung cancer was diagnosed. The patient worked in a chemical plant and had a history of acute hepatitis and a gallbladder polyp. These events occurred 16 and 14 years, respectively, prior to the onset of the reported malignancies. The patient had previously used topical corticosteroids to treat atopic dermatitis. A brief narrative of this case, as well as a table of all topical tacrolimus related malignancies is provided in Appendix 2.

Discussion/Conclusion

This review is an update to the 2003 and Sept/Oct 2004 analyses of malignancy related adverse events associated with the topical calcineurin inhibitors. We summarize the findings from the 2003, Sept/Oct 2004 and updated information in this Discussion section.

Since approval of both agents we have found ten malignancy adverse event cases related to pimecrolimus, and 19 cases related to topical tacrolimus use. One case is common to both case series since the patient used both products prior to the diagnosis of T-cell lymphoma. The majority of cases were of US origin (pimecrolimus – 7, t. tacrolimus – 8), and involved male patients (pimecrolimus – 5, t. tacrolimus – 15). Overall, there were seven cases reported in children (pimecrolimus – 4, t. tacrolimus – 3), ranging in age from two years to 16 years old. There were no cases reported in children less than two years old. The most serious outcomes reported were death (t. tacrolimus – 2, pimecrolimus – 0) and hospitalization (t. tacrolimus – 8, pimecrolimus - 1), with two hospitalizations associated with topical tacrolimus occurring in children. There were no new death cases, and one new foreign hospitalization case reported for pimecrolimus since the Sept/Oct 2004 analysis. The topical calcineurin inhibitors were used primarily to treat atopic dermatitis, with a small number (7) used for non-approved indications. Although no specific pattern could be identified at this time, the cases reported a variety of malignancy-related events with a median onset of symptoms occurring in 150 days for topical tacrolimus patients, and 90 days for pimecrolimus patients. A listing of the reported malignancies is in Appendix 1 and 2. Although the significance is unknown, eight adult cases reported malignancies at the site of application of the topical calcineurin inhibitor. One case reported a serum tacrolimus level of less than 0.5 ng/ml, however, the case did not provide further information to assess the meaning of the level. No pimecrolimus case reported serum levels, as well it is unknown the concentration of the topical calcineurin inhibitor at the application site.

In response to DDDDP's request to determine causality in the malignancy cases, spontaneous surveillance systems such as AERS may not be the best tools to determine causality. Spontaneous surveillance systems are subject to many limitations, one of which is that drug/event causality may not definitively be derived from its data.

Consequently, an active surveillance system such as provided through a registry, may be more useful in determining causality between topical calcineurin inhibitors and malignancy related events. Although, the role of topical calcineurin inhibitors in the development of malignancy related events in the individual reports in our case series is unknown, collectively the AERS cases provide a signal for a possible association between the use of topical calcineurin inhibitors and the development of malignancies. The malignancy occurrences reported with the topical calcineurin inhibitors are not inconsistent with the known increased risk of lymphoma development reported with the use of Prograf®, a systemic calcineurin inhibitor.

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NDA: 21-302, 50-777

Electronic only cc:

HFD-400/Seligman

HFD-430/Avigan/Karwoski/Nguyen/Pimecrolimus (Drug File)

HFD-540/Nikhar/Luke/Wright/Kozma-Fornaro

Appendix 1

Pimecrolimus (Elidel®) Narratives (New cases since last review – last two cases in table below):

FDA 4472779-4, MCN PHEH2004US10204, US, 2004, T-Cell Lymphoma, Paniculitis-like. A 53-year old male with a history of atopic dermatitis intermittently used Elidel (187 days) and Protopic (274 days) over 60% BSA.¹⁸ Elidel and Protopic use overlapped by approximately nine days. The patient used Elidel ± Protopic to the trunk and limbs. Approximately 5 months after starting Elidel, and 8 months after starting Protopic the patient developed tender swollen masses on his finger, popliteal fossa, thigh and foot. Since the masses were suggestive of cellulitis, or possibly a herpetic infection, the patient was treated with a variety of antibiotics, as well as an antiviral agent. The patient developed additional masses, as well as scaly patches on the trunk, limbs and fingers. A CT scan of the chest, abdomen and pelvis showed mild axillary lymphadenopathy. Additional lab data showed dermis and subcutaneous adipose tissue extensively infiltrated by lymphoma. The report stated that “morphologic and immunophenotypic features are most consistent with subcutaneous paniculitis-like T-Cell lymphoma.” T-cell gene rearrangement studies were conducted and were found negative. The patient did not have a family or personal history of cancer, and did not have a history of smoking. The patient concomitantly used topical corticosteroids, doxepin cream, metronidazole topical, klaron lotion, lida-mantle, hydrocortisone lotion and dicloxacillin.

Reviewer’s Comment: The development of the lymphoma occurred five to six months after starting Elidel. The initial presentation of the T-cell lymphoma occurred at sites where both topical calcineurin inhibitors had been applied. This is one of two cases associated with lymphoma development at the site of Elidel application. It is unclear the role of Elidel in the development of lymphoma in this patient.

FDA 4478512-4, MCN PHNR2004AU01498, Foreign, 2004, Squamous Cell Carcinoma – Vulva, Hospitalization. A 71-year old female developed a low grade squamous cell carcinoma (SCC) approximately 3 months after using Elidel to treat lichen sclerosus. The lichen sclerosus was thought to be related to Zocor administration, and was initially treated with topical corticosteroids, and then changed to Elidel. The patient was hospitalized and the squamous cell carcinoma was excised.

Reviewer’s Comment: The development of the lymphoma occurred three months after starting Elidel. This is one of two cases associated with lymphoma development at the site of Elidel application. It is unclear the role of Elidel in the development of SCC in this patient.

Pimecrolimus (Elidel®) Related Malignancies – Accumulative from Marketing to November 2004¹⁹

Malignancy	Age (years)	Application Site	Occurrence Site	Onset from Exposure (Days)
Non-hodgkin’s lymphoma	2	----	----	300
“Tumor”	2	----	Chin	90
Granulomatous lymphadenitis with hyperplasia	2	Face, arms	Scalp	49
Tumor	Child	----	Face	----
Lymphoma	61	Arms	----	----
Intraductal papilloma of the nipple	58	Palms	Nipple	60
Lymphoma	----	----	----	150
Basal Cell Carcinoma	53	----	Nose	7 to 14
T-Cell lymphoma, paniculitis like²⁰	53	Trunk, limbs	Trunk, limbs	150
Squamous Cell Carcinoma	71	Vulva	Vulva	90

¹⁸ BSA = Body Surface Area

¹⁹ For information on previously analyzed cases see Pitts MR. ODS Safety Review – Pimecrolimus NDA 21-302, All Adverse Events, PID # 0303434, September 24, 2003 and Pitts MR. ODS Safety Review – Pimecrolimus NDA 21-302, All Adverse Events in Children < 2 years, and Update on Malignancy Related Events in all Age Groups, PID # 040609, September 28, 2004

²⁰ This patient used both Elidel and Tacrolimus and appears in both tables.

Appendix 2

Topical Tacrolimus (Protopic®) Narrative (New case since last review – last case in table below):

FDA 4492567-2, MCN 2004JP001620, Foreign, 2004, Hospitalization. Malignant B-Cell Lymphoma + Primary Lung Cancer. A 49 year old male used Protopic 0.1% ointment to the face for 26 months to treat atopic dermatitis. Approximately 24 months into Protopic treatment the patient developed Epstein Barr Virus-associated malignant large B-Cell lymphoma of the left kidney, and two months later primary lung cancer. It was the patient’s decision to continue Protopic after the diagnosis of the kidney lymphoma. The kidney lymphoma was treated with chemotherapy, and the lung tumor was treated with a pneumonectomy. The patient had previously used corticosteroids. The patient worked at a chemical plant. The patient has a history of acute hepatitis 16 years previous and gallbladder polyp 14 years prior to the latest adverse event.

Reviewer’s Comment: The development of the lymphoma occurred 24 months after starting Protopic, and the development of the primary lung cancer occurred 26 months after exposure to Protopic. The patient has a past history of acute hepatitis and a gallbladder polyp, as well as a history of working in a chemical plant. It is unclear the role of Protopic in the development of this patient’s malignancies.

Topical Tacrolimus (Protopic®) Related Malignancies - Accumulative from Marketing to November 2004²¹

Malignancy	Age (years)	Application Site	Occurrence Site	Onset from Exposure (Days)
Hepatoblastoma	5	----	Liver	455
Angiosarcoma, metastatic	16	Face, neck	Clavicle	105
Lymphoma malignant or Sezary Syndrome	16	Face	Lymph nodes	730
Lymphoma	22	“whole body”	NR	790
Esophageal cancer with metastasis	49	----	Esophagus	122
Tumor	43	----	Sweat Gland	----
Squamous Cell Carcinoma	34 or 35	Face	Face	----
T-Cell lymphoma, panniculitis like²²	53	Trunk, limbs	Trunk, limbs	240
Squamous Cell Carcinoma, recurrence	75	Vulva	Vulva	42
Melanoma, metastatic - new onset	39	----	Generalized	21 - 28
Squamous Cell carcinoma ²³	51	----	Mouth	----
Lymphoma – possible, lymphadenopathy	40	“application site”	“application site”	----
T-cell type lymphoma, anaplastic large cell lymphoma	50	Right hip	Right hip	----
Cutaneous Kaposi’s Sarcoma²⁴	28	Axilla, groin	Axilla, groin	30
Non-Hodgkin’s lymphoma	52	----	----	365
Non-Hodgkin’s lymphoma	54	----	----	----
Nodular follicular lymphoma	50	Lower limbs, face	----	~ 504
Squamous cell carcinoma	57	Penis	Penis	56
B-cell lymphoma, Epstein Barr associated	49	Face	Kidney	730

²¹ For previously analyzed cases see Bonnel RA. ODS Safety Review – Topical Tacrolimus, NDA 50-777, All Adverse Drug Reactions, PID # 030433, September 24, 2003 and Pitts MR. ODS Safety Review – Topical Tacrolimus, NDA 50-777, All Adverse Events in Children < 2 years, and Update on Malignancy Related Events in all Age Groups, PID # 040608, October 5, 2004

²² Duplicate to pimecrolimus case

²³ Long history of pipe and cigarette smoking

²⁴ Also Pulmonary Kaposi’s despite having significantly improved on HAART with incr. CD4 counts, decreasing viral load