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Committee for Medicinal Products for Human Use (CHMP)

Protopic

(tacrolimus)

Procedure No. EMEA/H/C/000374/P45/0038

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Protopic
INN (or common name) of the active substance:	tacrolimus
MAH:	Astellas Pharma Europe B.V.
Pharmaco-therapeutic group (ATC Code):	Dermatitis, Atopic D11AH01
Pharmaceutical form and strengths:	Ointment, 0.03% Ointment 0.1%

I. EXECUTIVE SUMMARY

Astellas has performed studies for investigational cream and gel formulations of tacrolimus for use in treatment of patients with atopic dermatitis. The results from these studies suggested minimal systemic absorption of tacrolimus and a safety profile similar to that seen with the currently registered tacrolimus ointment.

Astellas has also performed studies with investigational cream and gel formulations of tacrolimus for use in treatment of patients with psoriasis. Studies suggest minimal absorption, lower than levels seen with atopic dermatitis. The most common adverse events were application site reactions. There was a greater incidence of some application site reactions in the active group compared with the vehicle group, but the differences were small.
Cancer was diagnosed in 10 patients treated with tacrolimus cream 0.1%, of which 8 patients were from the long-term, open label study with the cream formulation, and 1 patient treated with cream vehicle. Of the patients in the tacrolimus cream 0.1% group, 4 of the patients had a history of cutaneous malignancies or precancerous lesions, 1 had evidence of the cutaneous tumour prior to starting study drug, and 1 patient had a history of lung cancer.
The seven of 658 patients, diagnosed with a malignancy during the long term study included 2 basal cell carcinomas (68 and 73 years), 1 basal cell carcinoma and squamous cell carcinoma (79 years), 1 lentigo maligna (65 years), 1 keratoacanthoma (53 years), 1 squamous cell carcinoma of the cervix (32 years), and 1 recurrence of lung cancer that had metastasised (57 years). The MAH notes that several studies have shown that psoriasis patients have an increased risk of developing cancer, overall as well as specific types such as non-melanoma skin cancer (NMSC) which primarily includes squamous cell carcinoma and basal cell carcinoma.

In this report there is also information from three long term (1 year) open label Canadian studies with topical applied tacrolimus in paediatric patients with atopic dermatitis where the safety profile was consistent with the known safety profile of the licensed product.

Overall the information provided is consistent with the known safety profile of tacrolimus ointment in the treatment of patients with atopic dermatitis. Protopic® 0.03 % is licensed for use in adults and children over the age of 2 years. Protopic® 0.1 % is licensed for use in adults and adolescents (16 years of age and above).

II. RECOMMENDATION

The Rapporteur agrees that no further action is required

III. INTRODUCTION

The MAH has submitted several completed paediatric studies with topical tacrolimus, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The safety profile for cream and gel formulations was consistent with the safety profile of tacrolimus ointment in adults and children. The most common adverse events for all topical applications were local application site reactions including burning or stinging.
Ongoing registry studies and signal detection programs continue to monitor the long-term safety of tacrolimus ointment and no additional safety concerns have been identified in the above described studies. Based on these data, the MAH believes that no changes to the current Protopic® Product Information are required.

The MAH states that the submitted paediatric studies do not influence the benefit risk for Protopic® and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical studies

Protopic® is licensed as an ointment. Many of the studies discussed relate to cream or gel formulations, with many, though not all, of the studies in indications other than atopic dermatitis.

IV.2 Non-clinical aspects

The MAH has not submitted any non-clinical reports.

IV.3 Clinical aspects

Introduction

The MAH has provided information relating to the following:

1. Tacrolimus Pharmacokinetics after Topical Administration of Tacrolimus Cream 0.01% and 0.03% to Paediatric Subjects with Atopic Dermatitis (02-0-150)
2. An Open-Label Study to Assess the Safety and Efficacy of 0.1% Tacrolimus Ointment in Subjects with Eyelid Dermatitis (00-0-081)
3. A phase 3, randomised, double-blind study comparing twice daily tacrolimus cream 0.03% versus cream vehicle in the treatment of atopic dermatitis in paediatric subjects (03-0-166)
4. A Phase 3, Randomised, Double-Blind Study Comparing Twice Daily FK506 Cream 0.03% Versus Cream Vehicle in the Treatment of Atopic Dermatitis in Paediatric Subjects (03-0-183)
5. An Open-Label, Long-term, Follow-up Study to Evaluate the Safety of Topically Applied Tacrolimus Ointment for the Treatment of Atopic Dermatitis in Paediatric Patients (PRO-002)
6. An Open-Label, Long-term, Follow-up Study to Evaluate the Safety of Topically Applied Tacrolimus Ointment for the Treatment of Atopic Dermatitis in Paediatric Patients (PRO-002b)
7. An open-label study to evaluate the safety of topically applied tacrolimus ointment for the treatment of atopic dermatitis (PRO-004)
8. A Phase 2, Randomised, Double-Blind Study To Evaluate the Dosing Concentration and Application Frequency of Tacrolimus Gel in the Treatment of Mild to Moderate Psoriasis in Paediatric and Adult subjects (01-0126)

9. A Phase 3, Randomised, Double-Blind Study to Evaluate the Efficacy and Safety of Once Daily 0.3% Tacrolimus Gel Versus Gel Vehicle in the Treatment of Psoriasis (03-0-169)
10. A Phase 3, Randomised, Double-Blind Study to Evaluate the Efficacy and Safety of Once Daily 0.3% FK506 Gel Versus Gel Vehicle in the Treatment of Psoriasis (03-0-170)
11. Tacrolimus ointment is effective for facial and intertriginous psoriasis (J Am Acad Dermatol 2004;51:723-30.) (20-02-001)
12. A Phase 3 Long-Term Open Label Study to Evaluate the Safety of Once Daily 0.3% Tacrolimus Gel in the Treatment of Psoriasis (03-0-171)
13. Study 04-0-205. Randomised, double-blind, vehicle-controlled efficacy and safety study; tacrolimus cream-B 0.1% vs cream-B vehicle; twice daily application for 12 weeks with 4-week follow-up.
14. Study 04-0-206. Randomised, double-blind, vehicle-controlled efficacy and safety study; tacrolimus cream-B 0.1% vs cream-B vehicle; twice daily application for 12 weeks with 4-week follow-up.
15 Study 04-0-207. Long-term, open-label safety study of tacrolimus cream-B 0.1%; twice daily application for up to 12-months.

Clinical studies

Astellas developed and evaluated several topical formulations with tacrolimus for the treatment of atopic dermatitis as well as for the treatment of psoriasis. Tacrolimus cream was developed to treat body surfaces that could benefit from treatment with a cream formulation. While ointments are best used on dry, scaly and fissured skin, creams are preferable on the face (also from a cosmetic point of view), hairy areas and intertriginous areas.
Tacrolimus cream as well as tacrolimus gel were also developed and evaluated in patients with psoriasis, another inflammatory skin disease.

Cream formulation for Atopic Dermatitis

In Study 03-0-166, the success rate at the end of treatment for the tacrolimus cream 0.03% treatment group (71/190; 37.4%) was statistically significant (P< 0.001) compared with cream vehicle (23/187; 12.3%). Success was defined as a score of 0 (clear) or 1 (almost clear) on a 6-point Physician's Static Global Assessment (PSGA).
In Study 03-0-183, the success rate at the end of treatment for the tacrolimus cream 0.03% treatment group was 28.6% (54/189) compared to 21.1% (41/194) for the cream vehicle treatment group; a statistical difference was not observed (P=0.070). After controlling for differences observed in baseline characteristics between treatment groups, tacrolimus cream 0.03% was statistically significantly more effective (P=0.032) than cream vehicle in treating atopic dermatitis.

The collective results of pharmacokinetic studies of tacrolimus cream suggest that systemic absorption of tacrolimus is minimal after twice-daily application of tacrolimus cream 0.03% in adults and paediatrics with atopic dermatitis affecting ≥ 35% body surface area (BSA).

Table 1: Clinical Studies Conducted During the Tacrolimus Cream, Atopic Dermatitis Development Program

Study	Description	Target Population	Number Enrolled/ Randomized
Efficacy and Safety Studies			
03-0-166†	Phase III, randomized, double-blind, vehicle-controlled study of tacrolimus cream 0.03% twice daily for 6 weeks (+2-week follow-up).	Children (2 to 15 years) with mild to very severe atopic dermatitis (PSGA score 2 to 5) affecting at least 5% BSA.	379§
03-0-183†	Phase 3, randomized, double-blind, vehicle-controlled study of tacrolimus cream 0.03% twice daily for 6 weeks (+2-week follow-up).	Children (2 to 15 years) with mild to very severe atopic dermatitis (PSGA score 2 to 5) affecting at least 5% BSA.	385§
01-0-115†	Phase 2, randomized, double-blind, vehicle-controlled study of tacrolimus cream (0.1% and 0.03%) twice daily for 4 weeks (+1-week follow-up).	Adults (≥18 years) with mild or moderate atopic dermatitis (Rajka and Langeland criteria) affecting 5% to 36% BSA.	133
Pharmacokinetic Studies			
01-0-127†	Phase 1, randomized, open-label pharmacokinetic and bioavailability study; tacrolimus cream 0.01% and 0.03% and Protopic ointment 0.03%; twice daily application for 28 days except once daily on days 1 and 28. Single 1 mg intravenous dose of tacrolimus 2 weeks after last topical application.	Adults (≥18 years) with moderate to severe atopic dermatitis affecting 35% to 75% total BSA.	31‡
02-0-150†	Phase 1, randomized, open-label pharmacokinetic study; tacrolimus cream 0.01% and 0.03%; twice daily application for 4 weeks except once daily on days 1 and 15.	Children (2 to 16 years) with atopic dermatitis affecting at least 35% BSA.	18
FG-506-06-100†	Phase 1, open-label pharmacokinetic study; tacrolimus cream 0.1%; twice daily application for 28 days except once daily on days 1 and 28.	Healthy adult (≥18 years) male volunteers	16

PSGA: Physician's Static Global Assessment; BSA: body surface area.

†Included analysis of tacrolimus whole blood levels.

‡In Study 01-0-127, the full analysis set comprised 30 subjects: 21 subjects received tacrolimus cream, 9 subjects received Protopic Ointment. 14 (8 cream, 6 ointment) subjects participated in the IV phase of the study.

Safety

The safety profile, in subjects with atopic dermatitis, observed with tacrolimus cream 0.03% was consistent with that of tacrolimus ointment.

Study 02-0-150

In Study 02-0-150, tacrolimus cream was well tolerated in both treatment groups (0.03% and 0.01%) regardless of age. There were no deaths or serious/unexpected adverse events during the study and all 18 of the paediatric patients who were enrolled, completed the study.
A commonly experienced application site treatment-emergent adverse event was a mild sensation of skin burning. However, all such cases were short in duration and resolved with continued use. No other application area adverse events were reported. There were no clinically significant changes from baseline for routine clinical laboratory tests, vital sign measurements, or physical examinations.

Study 03-0-166
In Study 03-0-166, the overall incidence of treatment-emergent adverse events was similar between the cream vehicle and tacrolimus cream 0.03% treatment groups (57.2% and 61.6%, respectively). The incidence of the most common treatment-emergent adverse event, application site burning, was similar in the cream vehicle and the tacrolimus cream treatment arms (33.7% vs. 29.5%, respectively). The incidence of treatment-emergent application site burning, application site pruritus, application site pain, and application site dryness was similar in subjects who received cream vehicle compared to subjects who received tacrolimus cream 0.03%.
The incidence of treatment-emergent adverse events that were considered by the investigators to be at least possibly related to study drug, serious adverse events, and adverse events that led to discontinuation from the study were similar in the cream vehicle and tacrolimus cream 0.03% treatment groups (42.8% and 41.1%; 0.5% and 0.5%; and 8.0% and 4.7%, respectively). There were no deaths reported during this study.
Lymphadenopathy was experienced by 3.7% of subjects in the cream vehicle group and 2.6% of subjects in the tacrolimus cream 0.03% treatment groups. No adverse events of lymphoma, skin cancer, or cancer were reported during the study.
The incidence of treatment-emergent adverse events of infection and infestation that occurred during the study was similar in subjects who received cream vehicle (15.5%) compared to subjects who received tacrolimus cream 0.03% (13.7%).
Overall, there were no clinically significant mean changes from baseline in laboratory values or vital signs measurements observed during the study. One subject discontinued from the study due to adverse events related to clinical laboratory findings.

Study 03-0-183
During Study 03-0-183, the overall incidence of treatment-emergent adverse events was similar in the cream vehicle and the tacrolimus cream 0.03% treatment groups (60.3% and 59.3%, respectively). The incidence of the most common treatment-emergent adverse event, application site burning, was also similar in the cream vehicle and tacrolimus cream 0.03% treatment groups (22.7% and 25.4%, respectively). The incidence of treatment-emergent application site burning, application site pruritus, application site pain, and application site dryness was similar in subjects who received cream vehicle compared to subjects who received tacrolimus cream 0.03%.
The incidence of treatment-emergent adverse events that were considered by the investigators to have at least a possible relationship to study drug, serious adverse events, and adverse events that led to discontinuation from the study were similar between the cream vehicle and the tacrolimus cream 0.03% treatment groups (38.7% and 37.0%; 1.0% and 0.5%; and 6.7% and 3.2%, respectively).
Lymphadenopathy was experienced by 2.1% of subjects in the cream vehicle treatment group and 3.2% of subjects in the tacrolimus cream 0.03% treatment group. Lymphadenopathy resolved with no residual effects in all but 2 subjects in the tacrolimus cream 0.03% treatment group. No adverse events of lymphoma, skin cancer, or cancer were reported during the study.
The incidence of treatment-emergent adverse events of infection and infestation that occurred during the study was similar in subjects who received cream vehicle (15.5%) compared to subjects who received tacrolimus cream 0.03% (16.4%).
Overall, there were no clinically significant mean changes from baseline in laboratory values or vital signs measurements observed during the study. No subjects discontinued from the study due to adverse events related to clinical laboratory findings or due to vital signs measurements.

Cream Formulation for the Treatment of Psoriasis

The clinical development program for tacrolimus cream for the treatment of patients with plaque psoriasis consisted of 3 studies pertinent to demonstrate efficacy for the claimed indication, 1

long-term safety study; 4 pharmacokinetic studies; 1 active-controlled study; and 13 local tolerance studies. Two phase III safety and efficacy studies, 1 long-term safety study, 2 pharmacokinetic studies, and 4 local tolerance studies were conducted with a tacrolimus cream formulation (this cream formulation B was dissimilar to the cream G used for the AD studies and displayed a longer shelf life), as described below. Studies in adults are also described here to provide a full overview of the development program. The paediatric study reports were 04-0-205, 04-0-206 and 04-0-207

Table 3: Overview of Efficacy/Safety and Pharmacokinetic Clinical Studies of Tacrolimus Cream

Study No.	Description	Target Population	Number Enrolled/ Randomized
Studies Pertinent to the Claimed Indication			
01-0-117	Randomized, double–blind, vehicle-controlled efficacy and safety study; tacrolimus cream-G 0.1% and 0.5% versus cream vehicle; twice-daily application for 8 weeks with 2-week follow-up	Patients ≥ 18 years old with mild to moderate plaque psoriasis affecting ≤ 15% BSA	129
04-0-205	Randomized, double-blind, vehicle-controlled efficacy and safety study; tacrolimus cream-B 0.1% vs cream-B vehicle; twice daily application for 12 weeks with 4-week follow-up	Patients ≥ 12 years old with plaque psoriasis and PSGA of 3, 4, or 5 excluding scalp; and at least 1 plaque of ≥ 2 cm^2 that was not on elbow or knee	645
04-0-206	Randomized, double-blind, vehicle-controlled efficacy and safety study; tacrolimus cream-B 0.1% vs cream-B vehicle; twice daily application for 12 weeks with 4-week follow-up	Patients ≥ 12 years old with plaque psoriasis and PSGA of 3, 4, or 5 excluding scalp; at least 1 plaque of ≥ 2 cm^2 that was not on elbow or knee	658
Long-term Safety Study			
04-0-207	Long-term, open-label safety study of tacrolimus cream-B 0.1%; twice daily application for up to 12-months	Patients ≥ 12 years old with plaque psoriasis and PSGA of 2, 3, 4, or 5	658

The systemic bioavailability of tacrolimus cream in patients with psoriasis is consistently low and has been shown to be lower than in patients with atopic dermatitis who have received other topical tacrolimus formulations.

Safety

Overall, the incidence of adverse events in patients with psoriasis treated with tacrolimus cream 0.1% was low and similar to that observed in vehicle-treated patients. There were no clinically significant differences between adverse events in the vehicle arm vs. the tacrolimus cream 0.1% arm. The most common adverse events were application site reactions. There was a greater incidence of some application site reactions in the active group compared with the vehicle group, but the differences were small. In the pooled data set of Studies 04-0-205 and 04-0-206, the adverse event profile between patients with extensive BSA involvement was similar to that in patients with minimal BSA involvement.

The adverse event profile for patients treated with tacrolimus cream 0.1% long-term was similar to that observed in the shorter-term, 12-week studies.

Cancer was diagnosed in 10 patients treated with tacrolimus cream 0.1%, of which 8 patients were from the long-term, open label study, and 1 patient treated with cream vehicle. Of the patients in the tacrolimus cream 0.1% group, 4 of the patients had a history of cutaneous malignancies or precancerous lesions, 1 had evidence of the cutaneous tumour prior to starting study drug, and 1 patient had a history of lung cancer.

Several studies have shown that psoriasis patients have an increased risk of developing cancer, overall as well as specific types such as non-melanoma skin cancer (NMSC) which primarily includes squamous cell carcinoma and basal cell carcinoma. Long-term follow-up studies conducted among psoriasis patients have shown an increased overall cancer risk, with standardised incidence ratios up to 4 for NMSC when comparing the observed to the expected incidence within the general population [Boffetta et al, 2001; Hannuksela-Svahn et al, 2000; Frentz & Olsen, 1999]. A previous NMSC diagnosis among psoriasis patients may be associated with developing a second NMSC, with 1 meta-analysis of 17 studies calculating a 3-year cumulative risk of 18% for squamous cell carcinoma and 44% for basal cell carcinoma [Marcil & Stern, 2000]. In addition, some of the earlier treatments for psoriasis such as psoralen plus ultraviolet A (PUVA) have been linked to an increase in the risk of initial and recurrent NMSC even after prolonged discontinuation of high cumulative dosed treatments [Katz et al, 2002, Nijsten & Stern, 2003].
The overall incidence of infections was low and in the vehicle-controlled studies the incidence was similar between treatment groups.

Gel Formulation for the Treatment of Psoriasis

Two formulations, original gel and gel-3, were evaluated during the development of tacrolimus gel. The formulation known as gel-3 was the planned to-be-marketed formulation and was utilised in the phase III studies.
The clinical development program for tacrolimus gel for the gel-3 formulation consisted of 4 efficacy and safety studies, 1 long-term safety study and 1 pharmacokinetic study, as described in Table 6. Additionally, local tolerance studies in healthy volunteers were conducted including 1 cumulative irritation study, 1 contact sensitisation study, 1 phototoxicity study, and 1 photocontact allergy study.

Efficacy
The end of treatment in four of the tacrolimus gel treatment groups (tacrolimus gel 0.1% qd, 0.3% qd, 0.1% bid, and 0.3% bid) compared with the gel vehicle group. Success was defined as a score of 0 (“clear”) or 1 (“almost clear”) based on the PSGA.
In Study 03-0-170, the success rate at the end of treatment, stratified by center, for the tacrolimus gel 0.3% treatment group was statistically significant (P=0.007) compared to gel vehicle. Success was defined as a score of 0 (“clear”) or 1 (“almost clear”) based on the PSGA.
In Study 03-0-169, the success rate at the end of treatment for the gel vehicle treatment group was 10.6% compared to 15.2% for the tacrolimus gel 0.3% treatment group (P=0.167); a statistical difference was not observed. Success was defined as a score of 0 (“clear”) or 1 (“almost clear”) based on the PSGA.

Pharmacokinetics and Bioavailability
The majority of subjects treated with tacrolimus gel 0.3% in vehicle-controlled studies who had blood samples collected during treatment had tacrolimus blood concentrations < 1.0 ng/mL; 95.1% of subjects in Study 01-0-126, 88.5% of subjects in Study 03-0-169 and 90.6% of subjects in Study 03-0-170. For those subjects with quantifiable levels, such concentrations were typically isolated events and decreased over treatment time. For most subjects, the concentrations were minimal compared with those following oral or intravenous administration.

Table 6: Clinical Studies Conducted During the Tacrolimus Gel, Psoriasis Development Program

Study	Description	Target Population	Number Enrolled/ Randomized
Efficacy and Safety Studies			
03-0-169†	Phase 3, randomized, double-blind, vehicle-controlled study of tacrolimus gel 0.3% once daily for 12 weeks (+4 week follow-up)	Adults and adolescents ≥ 12 years with moderate to very severe psoriasis (PSGA score 3 to 5)	431
03-0-170†	Phase 3, randomized, double-blind, vehicle-controlled study of tacrolimus gel 0.3% once daily for 12 weeks (+4 week follow-up)	Adults and adolescents ≥ 12 years with moderate to very severe psoriasis (PSGA score 3 to 5)	428
01-0-126†	Phase 2, randomized, double-blind, vehicle-controlled study of tacrolimus gel (0.03%, 0.1%, and 0.3%) once daily compared with twice daily vs gel vehicle for 12 weeks (+2 week follow-up)	Adults and adolescents ≥ 12 years with mild or moderate psoriasis (PSGA score 2 to 4, affecting ≤ 20% total BSA)	356
Phase 2 Supportive Study			
FG-506-08-07	Phase 2, randomized, open-label, observer-blinded study to assess efficacy and safety of tacrolimus gel 0.3% versus calcipotriol ointment 0.005% vs tacrolimus cream 0.5% twice daily for 12 weeks (+2 week follow-up)	Adults ≥ 18 years with mild to moderate plaque psoriasis affecting ≤ 10% total BSA	125
Long-term Safety Study			
03-0-171†	Phase 3, long-term, open-label study to assess safety of tacrolimus gel 0.3% once daily	Adults ≥ 12 years with mild to very severe plaque psoriasis (PSGA score 2 to 5)	591
Pharmacokinetic Study			
02-0-140	Phase 1, randomized, open-label pharmacokinetic study; tacrolimus gel 0.03%, 0.1%, and 0.3%; Twice daily application for 12 weeks except once daily on days 1, 28, and 84.	Adults ≥ 18 years with plaque psoriasis and a PSGA score of 2, 3, or 4 and 10% - 20% total BSA involvement, not including scalp.	34

PSGA: Physician's Static Global Assessment; BSA: body surface area.

Safety

The safety of tacrolimus gel was evaluated in 536 healthy volunteers and 1873 subjects with psoriasis, 1546 of who applied tacrolimus gel. Additionally, a total of 591 subjects were enrolled in a long-term safety study (03-0-171); the mean duration of treatment was approximately 7.5 months and the median duration of treatment was approximately 9.5 months.

In the vehicle-controlled studies, the most common adverse events were application site events of burning and pruritus. Application site burning was numerically greater in the tacrolimus gel 0.3% treatment group compared to gel vehicle in all three studies. The incidence of infections was comparable between treatment groups. The most common application site events reported from these studies include burning and itching. There were no significant differences in the adverse event rates between tacrolimus gel 0.3% and vehicle-control treated subjects. Overall, these adverse events rarely led to discontinuation or study drug interruption.

In the long-term Study 03-0-171, the most common adverse event was application site burning (47.5%). Application site burning generally occurred on the first day of application, and tended to be mild to moderate in intensity. Other more common application site reactions included pruritus, pain, warmth and dermatitis. Headache was the most common non-application site reaction. No deaths were reported. A total of 10 subjects (1.7%) experienced a serious adverse event. None of the serious adverse events were considered by the investigator to be related to study drug.

There were no clinically significant changes in laboratory values, including renal function, or physical examinations, including blood pressure, during treatment.
The adverse events that occurred in the long-term safety study were consistent with the adverse event profile in the 12-week vehicle-controlled studies. These data demonstrate that tacrolimus gel 0.3% was safe during the treatment of psoriasis for up to 6 months.

Long-term Safety Studies of Tacrolimus Ointment for the Treatment of Atopic Dermatitis
Three studies were conducted in Canada to evaluate the safety of longer-term (6 months or 1 year) treatment with topically applied tacrolimus ointment 0.1% in paediatric subjects (2 years of age or older) with atopic dermatitis. Studies PRO-002 and PRO-002b enrolled subjects that had participated previously in Astellas (formerly Fujisawa)-sponsored studies with tacrolimus ointment.

Study PRO-002 was a long-term (1-year), open-label, non-comparative study. A total of 43 subjects received at least one dose of study medication. The most frequently reported adverse events were application site reactions (25.0%), allergies (11.6%) and asthma (9.3%). Six subjects (14%) prematurely discontinued the study, 3 due to application site events, 2 due to lack of efficacy and 1 subject due to non-compliance. Three subjects required hospitalisation, one for pneumonia and two for asthma. None of the application site adverse events were considered to be serious.

Study PRO-002b was a long-term (1-year), open-label, non-comparative study. A total of 12 subjects received at least one dose of study medication. In Study PRO-002b, non application site adverse events were observed in 83% (10/12) of subjects; none of these events were considered related to study therapy. The most frequently reported events were respiratory system disorders (41.7%) and skin and appendages disorders (41.7%).
Application site adverse events were observed in 50% (6/12) of the study population; 4 subjects experienced itching and 2 subjects experienced burning. No subject was permanently discontinued from the study.

Study PRO-004 was a long-term (1-year), open-label, non-comparative study in patients at least 2 years of age with moderate to severe atopic dermatitis. A total of 236 subjects received at least one dose of study medication. Sixty-five percent (154/236) of subjects were older than 16 years of age and the rest of these subjects were between 2 and 16 years of age.
In Study PRO-004, the incidence of non-application site adverse events was 71.6% (169/236). The most frequently reported adverse events were nasopharyngitis (21.2%) and headache NOS (16.9%). The incidence of application site adverse events was 67.4% (159/236). The most frequently reported application site reactions included application site burning (38.1%) and application site pruritus (33.9%). Six serious adverse events were reported, 3 of these 6 were non-application site and 3 were associated with the application site. Of the 6 serious adverse events, only one was considered to have a possible relationship to study medication.

Other Studies of Tacrolimus Ointment

Patients with atopic dermatitis often develop involvement of the eyelids. The application of topical corticosteroids to areas of thin skin such as the eyelids has been associated with increased intraocular pressure as well as local skin thinning. To assess the ability of tacrolimus ointment to treat eyelid dermatitis, an open-label, single arm, single centre study was conducted (00-0-081) in 21 patients 12 years of age or older with active, moderate to severe, eyelid dermatitis. There were no notable changes in ocular pressure from baseline to any study visit or to the end of treatment. The most common adverse events were burning sensation (57.1%) and itching (23.8%). Three patients discontinued the study due to an application site adverse event (2 patients for itching and burning; 1 patient for pain and swelling). There was no skin atrophy,

telangiectasia or striae present on the eyelids of any patient at baseline or at any time during the study or at end of treatment.
The application of corticosteroids to the face and intertriginous areas is associated with local skin thinning, telangiectasia and striae. To assess the ability of tacrolimus ointment to treat psoriasis on thin-skinned areas, an investigator-initiated, randomized (2:1), double-blind, vehicle-controlled study (20-02-001) was conducted in 167 patients 16 years of age or older with facial and intertriginous psoriasis. Tacrolimus ointment 0.1% or vehicle was applied twice daily to all psoriatic lesions of the face or intertriginous areas for 8 weeks. There were no significant differences in the incidence of adverse events between treatment groups.
Adverse events considered by the investigator to be related to study drug treatment and observed in more than 2% of the population included burning or stinging (8.0% vs 7.3%), hyperaesthesia (4.5% vs. 0), and itching (7.1% vs. 1.8%) in the tacrolimus ointment 0.1% vs. vehicle groups, respectively. There were no reports of cutaneous infections or systemic adverse events [Lebwohl et al, 2004].

V. MAH CONCLUSIONS

Topically-applied tacrolimus has been extensively studied in atopic dermatitis (Protopic® ointment, tacrolimus cream formulation) and psoriasis development programs (cream and gel formulations). Other post-marketing studies with tacrolimus ointment, including studies in eyelid dermatitis and facial and intertriginous psoriasis have also been conducted.
Approximately 19,000 subjects have been studied in clinical trials using tacrolimus ointment. Astellas has studied over 2400 patients with psoriasis in the tacrolimus cream and gel programs. The safety profile for the cream and gel formulations was consistent with the safety profile of tacrolimus ointment in adults and children. The most common adverse events for all topical applications are local application site reactions including burning or stinging.
Ongoing registry studies with the approved tacrolimus ointment and signal detection programs continue to monitor the long-term safety of Protopic® and no additional safety concerns have been identified in the above described studies. Based on these data, the MAH believes that no changes to the current Protopic® Product Information are required.

VI. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

Astellas has performed studies for a tacrolimus cream formulation for use in treatment of patients with atopic dermatitis. Their studies suggested minimal absorption and a safety profile similar to that seen with the currently available ointment.
Astellas has also performed studies with both a tacrolimus cream and a tacrolimus gel for use in treatment of patients with psoriasis. Studies suggest minimal absorption, lower than levels seen with atopic dermatitis. The most common adverse events were application site reactions. There was a greater incidence of some application site reactions in the active group compared with the vehicle group, but the differences were small.
Cancer was diagnosed in 10 patients treated with tacrolimus cream 0.1%, of which 8 patients were from the long-term, open label study with the cream formulation, and 1 patient treated with cream vehicle. Of the patients in the tacrolimus cream 0.1% group, 4 of the patients had a history of cutaneous malignancies or precancerous lesions, 1 had evidence of the cutaneous tumour prior to starting study drug, and 1 patient had a history of lung cancer.

The seven of 658 patients, diagnosed with a malignancy during the long term study included 2 basal cell carcinomas (68 and 73 years), 1 basal cell carcinoma and squamous cell carcinoma (79 years), 1 lentigo maligna (65 years), 1 keratoacanthoma (53 years), 1 squamous cell carcinoma of the cervix (32 years), and 1 recurrence of lung cancer that had metastasised (57 years). The MAH notes that several studies have shown that psoriasis patients have an increased risk of developing cancer, overall as well as specific types such as non-melanoma skin cancer (NMSC) which primarily includes squamous cell carcinoma and basal cell carcinoma.

In this report there is also information from three long term (1 year) open label Canadian studies with topically applied tacrolimus ointment 0.1 % in paediatric patients with atopic dermatitis where the safety profile was consistent with the known safety profile of the licensed product.

Overall the information provided is consistent with the known safety profile of Protopic® in the treatment of patients with atopic dermatitis. Protopic® 0.03 % is licensed for use in adults and children over the age of 2 years. Protopic® 0.1 % is licensed for use in adults and adolescents (16 years of age and above).

- **Recommendation**

The Rapporteur agrees that no further action required

VII. REQUEST FOR SUPPLEMENTARY INFORMATION

Not applicable

VIII. LIST OF MEDICINCAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

The list can be taken from the spreadsheet compiled from the EMEA