PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]Protopic®

tacrolimus ointment

0.03% and 0.1% (w/w)

Topical Calcineurin Inhibitor

ATC Code: D11AH01

LEO Pharma Inc.
Thornhill, Ontario
L3T 7W8
www.leo-pharma.ca

Date of Revision:

August 13, 2021

Submission Control No: 243249

RECENT MAJOR LABEL CHANGES

3. SERIOUS WARNINGS AND PRECAUTIONS BOX	**08/2021**
7. WARNING AND PRECAUTIONS	**08/2021**

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

FOR DERMATOLOGIC USE ONLY, NOT FOR OPHTHALMIC USE.

Acute Treatment

Protopic, both 0.03% and 0.1% for adults and only 0.03% for children aged 2 to 15 years is indicated as a second-line therapy for short and long-term intermittent-treatment of moderate to severe atopic dermatitis in non-immunocompromised patients, in whom the use of conventional therapies are deemed inadvisable because of potential risks, or who are not adequately responsive to or intolerant of conventional therapies.

Maintenance Therapy

Protopic is also indicated for maintenance therapy to prevent flares and prolong flare-free intervals in patients with moderate to severe atopic dermatitis experiencing a high frequency of flares (i.e., occurring 5 or more times per year) who have had an initial response (i.e., lesions cleared, almost cleared or mildly affected) with up to 6 weeks of treatment with twice daily Protopic.

For additional safety information, please refer to the WARNINGS AND PRECAUTIONS Section.

1.1 Pediatrics

Pediatrics (2 to 15 years): Protopic, 0.03% strength only, is indicated for use in children aged 2 to 15 years. The safety and efficacy of Protopic have not been established in pediatric patients below 2 years of age, and its use in this age group is not recommended.

Geriatrics (≥ 65 years of age): In Phase 3 studies, 405 patients ≥ 65 years old received Protopic. The adverse event profile for these patients was consistent with that for other adult patients.

2 CONTRAINDICATIONS

- Protopic (tacrolimus ointment) is contraindicated in patients with a history of hypersensitivity to tacrolimus or to any other component of the preparation. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

- Cutaneous bacterial or viral infections should be resolved before commencing Protopic ointment treatment.
- Minimise or avoid natural or artificial sunlight exposure during Protopic ointment treatment.
- Limit application of Protopic ointment only to areas affected by atopic dermatitis and avoid long-term continuous use of topical calcineurin inhibitors, including Protopic ointment (see

Administration).The safety of Protopic ointment has not been established beyond one year of non-continuous use.

Please refer to WARNINGS AND PRECAUTIONS section.

3.2 Recommended Dose and Dosage Adjustment

Adults (age 16 and over): Protopic (tacrolimus ointment) 0.03% and 0.1%.
Pediatrics (2-15 years of age): Protopic (tacrolimus ointment) 0.03% only.

3.3 Administration

Protopic can be used for short-term and intermittent long-term treatment.

Each affected region of the skin should be treated with Protopic until lesions are cleared, almost cleared or mildly affected. Thereafter, patients who have a high frequency of flares (≥ 5 times per year) are considered suitable for maintenance treatment. At the first signs of recurrence (flares) of the disease symptoms, twice daily treatment should be re-initiated.

The use of Protopic under occlusion has not been studied; therefore occlusive dressings are not recommended.

Acute Treatment
Protopic 0.03% and 0.1% should be applied topically morning and evening twice daily as a thin layer to affected areas of skin, including the face, neck and eyelids. If no improvement occurs after 6 weeks of therapy or in case of disease exacerbation, Protopic therapy should be discontinued and patients should consult their physicians.

Maintenance Therapy
Patients who have a high frequency of flares (≥ 5 times per year) and are responding to up to 6 weeks of acute treatment with tacrolimus ointment twice daily are suitable for maintenance therapy. Protopic 0.03% or 0.1% should be applied once daily twice a week. There should be 2 to 3 days between applications (e.g., Monday and Thursday). Protopic should be applied as a thin layer to the areas of the skin normally affected by atopic dermatitis (including the face, neck and eyelids).

If signs of flares reoccur, twice daily treatment should be reinitiated (see Acute Treatment).

After 12 months, a review of the patient`s condition should be conducted by the physician and a decision taken whether to continue maintenance therapy in the absence of safety data for maintenance therapy beyond 12 months. In children, this review should include suspension of treatment to assess the need to continue this regimen and to evaluate the course of the disease.

3.4 Missed Dose

If you forget to use Protopic as directed, apply it as soon as possible, then go back to your regular schedule.

4 OVERDOSAGE

Protopic is not for oral use. Oral ingestion of Protopic may lead to adverse effects associated with systemic administration of tacrolimus. If oral ingestion occurs, medical advice should be sought.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Topical	Ointment / 0.03% and 0.1% (w/w)	White petrolatum, mineral oil, propylene carbonate, white wax and paraffin

Protopic is a white to slightly yellowish ointment for topical use. Each gram of Protopic contains (w/w) either 0.03% or 0.1% of tacrolimus.
Protopic 0.03% and 0.1% (w/w) are available in laminate tubes of 30, 60 and 100 grams.

6 WARNINGS AND PRECAUTIONS

General
Prolonged systemic exposure to calcineurin inhibitors has been associated with an increased risk of infections, lymphomas and skin malignancies. These risks are associated with the intensity and duration of immunosuppression. Therefore, Protopic should not be used in immunocompromised adults and children.

While a causal relationship has not been established, cases of skin malignancy and lymphoma have been reported in patients treated with topical calcineurin inhibitors, including Protopic. The use of Protopic should be avoided on pre-malignant and malignant skin conditions. Some malignant skin conditions, such as cutaneous T-cell lymphoma (CTCL), may mimic atopic dermatitis.

If signs and symptoms of atopic dermatitis do not improve within 6 weeks of twice daily treatment, Protopic treatment should be discontinued and patients should be re-examined by their healthcare provider and their diagnosis be confirmed.

Patients should minimize or avoid natural or artificial sunlight exposure during the course of treatment, even while Protopic is not on the skin. It is not known whether Protopic interferes with skin response to ultraviolet damage.
The safety of Protopic ointment has not been established beyond one year of non-continuous use.

Bacterial and Viral Skin Infections
Before commencing treatment with Protopic ointment, cutaneous bacterial or viral infections at treatment sites should be resolved.

Carcinogenesis and Mutagenesis
Prolonged use of calcineurin inhibitors for sustained immunosuppression in animal studies and systemic administration in transplant patients has been associated with an increased risk of lymphomas and skin malignancies. Although a causal relationship has not been established, cases of skin malignancy and lymphoma have been reported in patients treated with topical calcineurin inhibitors, including Protopic, during post-marketing surveillance (see Post-Market Adverse Drug Reactions, Clinical Trials and PART II, Toxicology).

Immune
In clinical studies, cases of lymphadenopathy were reported and were usually related to infections and noted to resolve upon appropriate antibiotic therapy. The majority of these cases had either a clear etiology or were known to resolve. Transplant patients receiving immunosuppressive regimens (e.g. systemic tacrolimus) are at increased risk for developing lymphoma; therefore, patients who receive Protopic and who develop lymphadenopathy should have the etiology of their lymphadenopathy investigated. In the absence of a clear etiology for the lymphadenopathy or in the presence of acute infectious mononucleosis, discontinuation of Protopic should be considered. Patients who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves.

Immunocompromised Patients
The safety and efficacy of Protopic in immunocompromised patients have not been studied.

Renal Insufficiency
Post-marketing cases of acute renal failure have been reported in patients treated with Protopic. Systemic absorption is more likely to occur in patients with epidermal barrier defects especially when Protopic is applied to large body surface areas. Caution should also be exercised in patients predisposed to renal impairment.

Sexual Health
Reproduction
Reproductive toxicology studies were not performed with tacrolimus ointment. In studies of oral tacrolimus no impairment of fertility was seen in male and female rats. Tacrolimus, given orally at 1.0 mg/kg to male and female rats, prior to and during mating, as well as to dams during gestation and lactation, was associated with embryolethality and with adverse effects on female reproduction. Effects on female reproductive function (parturition) and embryolethal effects were indicated by a higher rate of pre-implantation loss and increased numbers of undelivered and nonviable pups. When given at 3.2 mg/kg, tacrolimus was associated with maternal and paternal toxicity as well as reproductive toxicity including marked adverse effects on estrus cycles, parturition, pup viability, and pup malformations.

Skin
The use of Protopic may cause local symptoms of short duration, such as skin burning (burning sensation, stinging, soreness) or pruritus. Localized symptoms are most common during the first few days of Protopic application and typically resolve as the lesions of atopic dermatitis heal.

Protopic has not been studied for its efficacy and safety in the treatment of clinically infected atopic dermatitis. Patients with atopic dermatitis are predisposed to superficial skin infections. Treatment with Protopic may be associated with an increased risk of varicella zoster virus infection (chickenpox or shingles), herpes simplex virus infection, or eczema herpeticum. In the presence of infections, the balance of risks and benefits associated with Protopic use should be evaluated.

The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Despite the absence of observed phototoxicity in humans, Protopic shortened the time to skin tumour formation in an animal photocarcinogenicity study (see Carcinogenesis, and Mutagenesis. Therefore, it is prudent for patients to minimize or avoid natural or artificial sunlight exposure.

The use of tacrolimus ointment is not recommended in patients with a skin barrier defect such as Netherton's syndrome, lamellar ichthyosis, generalized erythroderma or cutaneous Graft Versus Host Disease. These skin conditions may increase systemic absorption of tacrolimus. Post-marketing cases of increased tacrolimus blood level have been reported in these conditions. Oral use of tacrolimus is also not recommended to treat these skin conditions. The safety of Protopic has not been established in patients with generalized erythroderma.

6.1 Special Populations

6.1.1 Pregnant Women

There are no studies on the use of Protopic in pregnant women. Reproduction studies were carried out with systemically administered tacrolimus in rats and rabbits. Adverse effects on the fetus were observed mainly at oral dose levels that were toxic to dams. Tacrolimus at oral doses of 0.32 and 1.0 mg/kg during organogenesis in rabbits was associated with maternal toxicity as well as an increase in incidence of abortions. At the higher dose only, an increased incidence of malformations and developmental variations was also seen. Tacrolimus, at oral doses of 3.2 mg/kg during organogenesis in rats, was associated with maternal toxicity and caused an increase in late resorptions, decreased numbers of live births, and decreased pup weight and viability. Tacrolimus, given orally at 1.0 and 3.2 mg/kg to pregnant rats after organogenesis and during lactation, was associated with reduced pup weights. No reduction in male or female fertility was evident.

There are no adequate and well-controlled studies of systemically administered tacrolimus in pregnant women. Tacrolimus is transferred across the placenta. The use of systemically administered tacrolimus during pregnancy has been associated with neonatal hyperkalemia and renal dysfunction. Protopic should be used during pregnancy only if the potential benefit to the mother justifies a potential risk to the fetus.

6.1.2 Breast-feeding

Although systemic absorption of tacrolimus following topical applications of Protopic is minimal relative to systemic administration, it is known that tacrolimus is excreted in milk. Therefore, breast feeding should be avoided during use of Protopic.

6.1.3 Pediatrics

Protopic 0.03% may be used in pediatric patients 2 years of age and older.

The safety and efficacy of Protopic have not been established in pediatric patients below 2 years of age, and its use in this age group is not recommended.

6.1.4 Geriatrics (≥ 65 years of age)

Four hundred and five (405) patients ≥ 65 years old received Protopic in Phase 3 studies. The adverse event profile for these patients was consistent with that for other adult patients.

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

In normal volunteer dermal safety studies, Protopic was neither phototoxic, nor photoallergenic, nor a contact sensitizer.

Overall, 14,828 patients treated with Protopic were evaluated in phase 3 studies and the cumulative topical exposure from the market experience is estimated to be 24 million patient years.

Spontaneous cases of T cell lymphomas, other types of lymphoma, and skin cancers have been reported in patients using tacrolimus ointment. However, overall experience from clinical trials, data from large post-authorization safety studies and post-marketing surveillance has failed to establish a causal relationship between topical use of tacrolimus and malignancies.

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Treatment

Clinical Trials with Protopic Compared to Active Comparators
In three active comparator studies using topical corticosteroids with Protopic, the duration of treatment was 3 weeks. In the adult study, the most common adverse events experienced were skin burning and pruritus, which were primarily application-site events caused by the medication. In total, 35.5% of patients in the 0.1% hydrocortisone butyrate group, 63.7% of patients in the 0.03% Protopic group and 68.6% of patients in the 0.1% Protopic group experienced an application-site adverse event. Both skin burning and pruritus tended to be brief; the occurrence of which decreased with time, lasting approximately 4-7 days.

Other adverse events reported in this clinical trial included flu-like symptoms, folliculitis, headache, allergic reaction, skin erythema, maculopapular rash, nausea, diarrhea and paresthesia. None of these adverse events showed a significant difference in incidence among the treatment groups. Herpes simplex, a less common adverse reaction (<5%), was more frequent in patients treated with Protopic compared to 0.1% hydrocortisone butyrate group.

As in the adult study, skin burning and pruritus comprised the most common application site adverse events and tended to occur only during the first few days of treatment in this pediatric comparator study. In this study population, 21.1% of patients in the 1% hydrocortisone acetate group, 38.1% of patients in the 0.03% Protopic group, and 36.6% of patients in the 0.1% Protopic group experienced an application site adverse event. There was a marked decrease in the

prevalence of skin burning over time, particularly in the Protopic treatment groups. Pruritus also decreased over time in the Protopic treatment groups but not in the hydrocortisone acetate group.

The incidence of other adverse events that may be associated with treatment was similar among all study groups and included flu-like symptoms, fever, abdominal pain, increased cough, rhinitis, diarrhea and headache.

Clinical Trials with Protopic Compared to Vehicle Ointment

Table 1 describes the adjusted incidence of adverse events (≥3%) pooled across the 3 identically designed 12-week, vehicle-controlled Phase 3 studies (two adult studies, one pediatric study).

Table 1: Incidence of Treatment Emergent Adverse Events (≥3% in Any Treatment Group)

COSTART Term	Adult			Pediatric	
	Vehicle (N=212) %	Tacrolimus 0.03% (N=210) %	Tacrolimus 0.1% (N=209) %	Vehicle (N=116) %	Tacrolimus 0.03% (N=118) %
Skin burning*	26	46	58	29	43
Pruritus*	37	46	46	27	41
Flu-like symptoms*	19	23	31	25	28
Allergic reaction	8	12	6	8	4
Skin erythema	20	25	28	13	12
Headache*	11	20	19	8	5
Skin infection	11	12	5	14	10
Fever	4	4	1	13	21
Infection	1	1	2	9	7
Cough increased	2	1	1	14	18
Asthma	4	6	4	6	6
Herpes simplex	4	4	4	2	0
Pharyngitis	3	3	4	11	6
Accidental injury	4	3	6	3	6
Pustular rash	2	3	4	3	2
Folliculitis*	1	6	4	0	2
Rhinitis	4	3	2	2	6
Otitis media	4	0	1	6	12
Sinusitis*	1	4	2	8	3
Diarrhea	3	3	4	2	5
Urticaria	3	3	6	1	1
Bronchitis	0	2	2	3	3
Vomiting	0	1	1	7	6
Maculopapular rash	2	2	2	3	0
Rash*	1	5	2	4	2
Abdominal pain	3	1	1	2	3
Fungal dermatitis	0	2	1	3	0
Gastroenteritis	1	2	2	3	0
Alcohol intolerance*	0	3	7	0	0
Acne*	2	4	7	1	0
Skin disorder	2	2	1	1	4
Vesiculobullous rash*	3	3	2	0	4

Table 1: Incidence of Treatment Emergent Adverse Events (≥3% in Any Treatment Group) – *Continued*

COSTART Term	Adult			Pediatric	
	Vehicle (N=212) %	Tacrolimus 0.03% (N=210) %	Tacrolimus 0.1% (N=209) %	Vehicle (N=212) %	Tacrolimus 0.03% (N=210) %
Lymphadenopathy	2	2	1	0	3
Nausea	4	3	2	0	1
Skin tingling*	2	3	8	1	2
Dyspepsia*	1	1	4	0	0
Dry skin	7	3	3	0	1
Hyperesthesia*	1	3	7	0	0
Peripheral edema	2	4	3	0	0
Varicella zoster/Herpes zoster*, **	0	1	0	0	5
Contact dermatitis	1	3	3	3	4
Asthenia	1	2	3	0	0
Insomnia	3	4	3	1	1
Exfoliative dermatitis	3	3	1	0	0
Dysmenorrhea	2	4	4	0	0
Myalgia*	0	3	2	0	0
Cyst*	0	1	3	0	0
Arthralgia	1	1	3	2	0
Paresthesia	1	3	3	0	0

* May be reasonably associated with the use of Protopic

** All the herpes zoster cases in the pediatric 12-week study were reported as chicken pox

In open-label, long-term safety studies of up to 4 years' duration, the adverse event profile of Protopic was similar to the adverse event profile seen in pivotal Phase 3 studies.

Maintenance

In the two Phase 3, multi-centre, double-blind, vehicle-controlled 12-month studies the nature and incidence of adverse events were consistent with the established safety profile of Protopic.

Table 2 describes the most frequently reported adverse events (≥3%) that occurred in the Phase 3 study in adults.

Table 2: Incidence of Most Frequently Reported Adverse Events (≥ 3%) Regardless of Relationship to Study Drug in the Double-Blind Maintenance Treatment Phase of Study FG-506-06-40 (Adults)

MedDRA preferred term	Number of Patients Experiencing an Adverse Event (%) at a Frequency of ≥ 3%	
	Protopic 0.1%	Vehicle
	N=80	N=73
Application-site		
Application-site pruritus	14 (17.5)	11 (15.1)
Application-site folliculitis	6 (7.5)	8 (11.0)
Application-site irritation	4 (5.0)	6 (8.2)
Application-site infection	6 (7.5)	3 (4.1)
Herpes simplex	3 (3.8)	4 (5.5)
Impetigo	3 (3.8)	4 (5.5)
Non-application-site		
Nasopharyngitis *	11 (13.8)	6 (8.2)
Headache	9 (11.3)	3 (4.1)
Pruritus	4 (5.0)	4 (5.5)
Influenza	3 (3.8)	4 (5.5)
Herpes simplex	1 (1.3)	2 (2.7)
Pharyngolaryngeal pain	0	4 (5.5)
Pyrexia	1 (1.3)	2 (2.7)
Respiratory tract infection viral	3 (3.8)	0

* The MedDRA preferred term “Nasopharyngitis” includes the lowest level terms “cold” and “cold symptoms”.

Table 3 describes the most frequently reported adverse events (≥3%) that occurred in the Phase 3 study in pediatrics.

Table 3. Incidence of Most Frequently Reported Adverse Events (≥ 3%) Regardless of Relationship to Study Drug in the Double-Blind Maintenance Treatment Phase of Study FG-506-06-41 (Pediatrics)

MedDRA preferred term	Number of Patients Experiencing an Adverse Event (%) at a Frequency of ≥ 3%	
	Protopic 0.03%	Vehicle
	N=78	N=75
Application-site		
Application-site pruritus	12 (15.4)	8 (10.7)
Impetigo	9 (11.5)	5 (6.7)
Application-site infection	7 (9.0)	4 (5.3)
Herpes simplex	3 (3.8)	1 (1.3)
Skin papilloma	3 (3.8)	4 (4.0)
Non-application-site		
Nasopharyngitis *	30 (38.5)	21 (28.0)
Influenza	9 (11.5)	1 (1.3)
Pyrexia	8 (10.3)	6 (8.0)
Respiratory tract infection viral	2 (2.6)	2 (2.7)
Cough	3 (3.8)	5 (6.7)
Pruritus	8 (10.3)	3 (4.0)
Rhinitis	2 (2.6)	4 (5.3)
Gastroenteritis viral	5 (6.4)	3 (4.0)
Headache	4 (5.1)	4 (5.3)
Asthma	6 (7.7)	3 (4.0)
Gastroenteritis	2 (2.6)	1 (1.3)
Tonsillitis	5 (6.4)	4 (5.3)
Bronchitis bacterial	3 (3.8)	0
Varicella	3 (3.8)	3 (4.0)
Upper respiratory tract infection	5 (6.4)	3 (4.0)
Vomiting	4 (5.1)	4 (5.3)
Molluscum contagiosum	4 (5.1)	2 (2.7)
Eczema infected	2 (2.6)	4 (5.3)
Pharyngitis	1 (1.3)	3 (4.0)
Abdominal pain	1 (1.3)	4 (5.3)
Gastrointestinal infection	2 (2.6)	4 (5.3)
Lice infestation	1 (1.3)	3 (4.0)
Skin bacterial infection	1 (1.3)	4 (5.3)
Diarrhea	4 (5.1)	0

* The MedDRA preferred term “Nasopharyngitis” includes the lowest level terms “cold” and “cold symptoms”.

7.3 Less Common Clinical Trial Adverse Reactions

Less common events occurring in 1% - 5% of patients in order of decreasing frequency include skin tingling, acne, folliculitis, hyperesthesia (sensitive skin, increased sensitivity to hot/cold temperature), alcohol intolerance (skin/facial flushing, redness, heat sensation), dyspepsia, myalgia, and cyst.

The incidence of herpes zoster (chickenpox) occurred less frequently in patients treated with vehicle (0 cases) and Protopic 0.1% (1 case) than in patients treated with Protopic 0.03% (4 cases).

7.4 Post-Market Adverse Reactions

The following adverse reactions have been reported from post-marketing surveillance for Protopic ointment 0.1% and 0.03%. Since these events are reported voluntarily from a population of uncertain size it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Central Nervous System: seizures

Metabolism: alcohol intolerance

Neoplasms: lymphomas, skin neoplasms (basal cell carcinoma, squamous cell carcinoma and melanoma)

Infections: bullous impetigo, osteomyelitis, septicemia, local skin infection regardless of specific etiology

Investigations: Drug level increased (See WARNINGS AND PRECAUTIONS, Skin)

Renal: Acute renal failure in patients with or without Nertherton's syndrome, renal impairment

Skin: application site edema, rosacea

8 DRUG INTERACTIONS

8.1 Overview

Formal topical drug interaction studies with Protopic have not been conducted. Based on its minimal extent of absorption, interactions of Protopic with systemically administered drugs cannot be ruled out, but are unlikely to occur.

8.2 Drug-Drug Interactions

Interactions with other drug products have not been established.

8.3 Drug-Food Interactions

There are no known interactions with food.

8.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

8.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

8.6 Drug-Lifestyle Interactions

Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using Protopic.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action/Pharmacodynamics

The exact mechanism of action of tacrolimus in atopic dermatitis is not known. However, It has been demonstrated that tacrolimus inhibits T-lymphocyte activation by first binding, an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin is inhibited. This effect has been shown to prevent the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (such as interleukin-2, gamma interferon). Tacrolimus also inhibits the transcription for genes which encode for IL-3, IL-4, IL-5, GM-CSF, and TNF-α, all of which are involved in the early stages of T-cell activation and have been postulated to play significant roles in the pathogenesis of atopic dermatitis. Additionally, tacrolimus has been shown to inhibit the release of pre-formed mediators from skin mast cells and basophils, and to downregulate the expression of FcεRI on Langerhans cells.

Application of tacrolimus ointment (0.03% - 0.3%) did not affect cutaneous pigmentation in micropigs. Tacrolimus ointment does not affect collagen synthesis, reduce skin thickness or cause skin atrophy in humans.

In the pharmacodynamic Study 97-0-030, immunohistochemical changes in skin biopsy specimens from patients with acute atopic dermatitis lesions treated with 0.1% Protopic or 0.1% triamcinolone acetonide ointment for 3 weeks were evaluated. Treatment with triamcinolone acetonide statistically significantly reduced expression of several cell surface markers (CD11a, CD1a, CD54, and CD8) with a trend toward reduced expression of CD11b, CD4, and ePOD. In contrast, treatment with Protopic significantly reduced expression of only IL-13 in the dermis, with a trend toward reduced expression of CD11b in the epidermis. This would suggest that triamcinolone acetonide may act less specifically than Protopic with respect to local immunomodulation. At the end of the 2-week posttreatment period, a number of patients in both treatment groups demonstrated an apparent recovery of the expression of those markers affected by treatment, suggesting that the local immunomodulation was reversible upon drug discontinuation.

In pharmacodynamic Study FG-06-17, the effects of 0.1% and 0.3% Protopic, vehicle, and 0.1% betamethasone valerate ointment (a known atrophogenic corticosteroid) on collagen synthesis were evaluated in unaffected skin of atopic dermatitis patients and in healthy volunteers. Exposure to 0.1% or 0.3% Protopic under occlusion over 7 days did not result in reduced collagen synthesis or skin thickness relative to vehicle control, demonstrating that Protopic does not produce skin atrophy. In contrast, similar exposure to the steroid ointment significantly reduced both parameters relative to Protopic and vehicle.

Protopic at concentrations ranging from 0.03% - 0.3% was evaluated in six patch test studies. The studies compared Protopic with vehicle, other marketed formulations used to treat inflammatory dermatoses (calcipotriene, hydrocortisone, and betamethasone valerate ointments) or with another control substance (sodium lauryl sulfate). Ointment (0.12 g) was applied to 3 cm^2 areas of intact skin on the back of each healthy volunteer. Irritation was graded by the investigator using a 5-point scale (0=No sign of irritation to 4=erythema with edema and blistering). Taken collectively, these studies demonstrated that Protopic, relative to these other products, was not inherently irritating, sensitizing, phototoxic, nor photoallergenic when applied as ointment to intact skin.

9.2 Pharmacokinetics

Tacrolimus blood concentrations following the topical application of Protopic were determined for both healthy volunteers and patients in 13 clinical studies.

A pharmacokinetic study in 21 adult patients with atopic dermatitis demonstrated that tacrolimus is absorbed into the systemic circulation following single or repeated application of tacrolimus ointment in 0.1% concentration. Peak tacrolimus blood concentrations ranged from undetectable to 20 ng/mL. A blood concentration of 20 ng/mL was detected in two patients in both the single dosing group and the multiple dosing group, both of whom had severe disease and were applying ointment to almost the entire body. These concentrations were transient and decreased to 2.9 ng/mL (72 hour) and 3.9 ng/mL (day 7), respectively. Eight pediatric patients (5 to 12 years of age), with moderate atopic dermatitis, received 0.3% tacrolimus ointment. Peak tacrolimus blood concentrations ranged from 0.14 to 3.28 ng/mL. Similarly to the adult results, these peak concentrations were transient. There was no systemic accumulation of tacrolimus in both adult and pediatric patients.

Although a direct determination of bioavailability was not performed, a comparison of area under the curve (AUC) data following topical administration to historical AUC data after oral and intravenous administration indicates that the bioavailability of tacrolimus ointment applied to damaged skin (atopic dermatitis) relative to oral administration is <3%; the absolute bioavailability is <0.5%. This limited systemic exposure diminished with repeated application, concurrent with improvement of skin condition. Despite prolonged and repeated topical application for periods of up to 1 year, there is no evidence based on blood concentrations that tacrolimus accumulates systemically.

In pharmacokinetic Study 94-0-008 in adult and pediatric atopic dermatitis patients, tacrolimus was absorbed into the systemic circulation following single or repeated application for 8 days of 0.3% Protopic to affected skin. (Note: this concentration is 3 to 10 times that of the commercial product). Although a direct determination of bioavailability has not been made for Protopic, a comparison of $AUC_{0\text{-}24}$ data from this study with historical data after oral and intravenous administration of Prograf® (tacrolimus capsules, tacrolimus injection) to healthy volunteers indicated a relative bioavailability of <3% and an absolute bioavailability of <0.5%. This limited systemic exposure diminished with repeated application, concurrent with improvement of skin condition. There was no evidence of systemic accumulation. One adult patient in this study had a blood concentration ≥5 ng/mL (9.42 ng/mL at 6 hours postapplication on Day 1); the tacrolimus blood concentration for this patient decreased over time and was 0.45 ng/mL on Day 11 (3 days after last ointment application). The highest individual tacrolimus blood concentration in a pediatric patient was 3.28 ng/mL 4 hours postapplication on Day 1; the blood concentration for this patient was 0.54 ng/mL at 8 hours postapplication on Day 1.

In the pharmacokinetic/safety Study FJ-106 and the 10 clinical studies in which blood samples were collected, tacrolimus blood concentrations above 0.5 ng/mL were isolated events and tended to decline with repeated application, concurrent with the clinical improvement of atopic dermatitis lesions. In these 11 studies, the highest individual tacrolimus blood concentration was ≥5 ng/mL in less than 2% (29/1681) of patients. For these few patients, it is important to note that these concentrations following topical application were isolated values representing the highest individual concentration. In contrast, the targeted range (5-20 ng/mL) in transplant patients represents recommended trough concentrations to be maintained for the patient's lifetime.

Special Populations and Conditions

Not applicable.

10 STORAGE AND STABILITY

Store between 15°C and 30°C.

11 SPECIAL HANDLING INSTRUCTIONS

None required.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

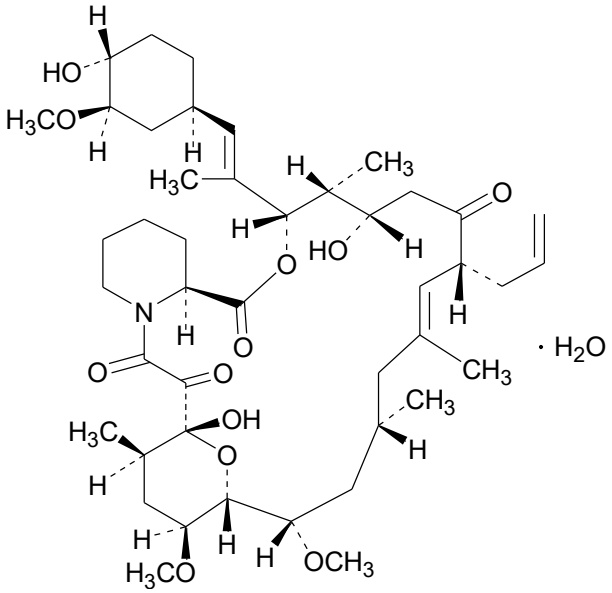
Drug Substance

Proper name: Tacrolimus

Chemical name: [3*S*-[3*R**[*E*(1*S**,3*S**,4*S**)],4*S**,5*R**,8*S**,9*E*,12*R**,14*R**,15*S**,16*R**,18*S**,19*S**, 26a*R**]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate.

Molecular formula and molecular mass: $C_{44}H_{69}NO_{12}\bullet H_2O$, 822.03

Structural formula:



Physicochemical properties: Tacrolimus appears as white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform. The melting point as determined by thermal analysis is 124.9 - 126.8 °C and the partition coefficient is > 1000 (in n-octanol/water).

Description: Protopic (tacrolimus) ointment contains tacrolimus, a macrolide immunosuppressant produced by Streptomyces tsukubaensis. It is for topical dermatologic use only.

13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

Acute Treatment

Table 4: Summary of Pivotal Protopic Phase 3 Atopic Dermatitis Trials.

Study #	Trial design	Dosage, route of administration and duration	Number of Subjects (N)	Mean age (Range)	Gender	Race (%) Black/ Caucasian/ Other
FG-506-06-018	Randomized, double-blind, active comparative	0.03% tacrolimus, topical administration twice daily for 3 weeks	N= 193	31.1 ± 11.5	M = 44% F= 57%	0.5/94.8/4.2
		0.1% tacrolimus, topical administration twice daily for 3 weeks	N= 191	32.4 ± 11.4	M = 43% F= 57%	0.0/96.3/3.7
		or 0.1% hydrocortisone butyrate topical administration twice daily for 3 weeks	N= 186	30.8 ± 10.3	M = 47% F= 53%	0.5/97.8/1.6
FG-506-06-019	Randomized, double-blind, active comparative	0.03% tacrolimus, topical administration twice daily for 3 weeks	N= 189	2-15 years	M = 40% F= 60%	7.4/74.1/18.5
		0.1% tacrolimus, topical administration twice daily for 3 weeks	N= 186	2-15 years	M = 52% F= 48%	5.4/77.4/17.2
		or 0.1% hydrocortisone acetate topical administration twice daily for 3 weeks	N= 185	2-15 years	M = 51% F= 49%	4.9/81.1/14.1
FJ-108*	Randomized, parallel group, active comparative	0.1% tacrolimus, twice daily for 3 weeks	N= 89	25.9 ± 5.7	M = 44% F= 56%	0.0/0.0/100.0
		or 12% betamethasone valerate, twice daily for 3 weeks	N= 92	26.3 ± 7.6	M = 64% F= 36%	0.0/0.0/100.0
FJ-109*	Randomized, parallel group, active comparative	0.1% tacrolimus, alclometasone dipropionate twice daily for 3 weeks	N= 75	25.6 ± 7.8	M = 51% F= 49%	0.0/0.0/100.0
		or 0.1% alclometasone dipropionate twice daily for 3 weeks	N= 76	25.9 ± 8.0	M = 41% F= 59%	0.0/0.0/100.0

Table 4: Summary of Pivotal Protopic Phase 3 Atopic Dermatitis Trials.

Study #	Trial design	Dosage, route of administration and duration	Number of Subjects (N)	Mean age (Range)	Gender	Race (%) Black/ Caucasian/ Other
97-0-037	Randomized, double-blind, vehicle controlled	Vehicle, topical, 12 weeks	N= 116	5.9 ± 3.4 (2 - 15)	M = 48% F= 53%	20/71/9
		0.03%, topical, 12 weeks	N= 117	6.2±3.8 (2 - 15)	M = 48% F= 52%	26/66/9
		0.1% topical, 12 weeks	N= 118	6.4 ± 3.7 (2 - 15)	M = 46% F= 54%	30/64/7
97-0-035	Randomized, double-blind, vehicle controlled	Vehicle, topical, 12 weeks	N= 102	38.5 ± 14.0 (16-72)	M = 49% F= 51%	30/65/4
		0.03%, topical, 12 weeks	N= 103	37.8 ± 13.3 (16-72)	M = 38% F= 63%	28/66/6
		0.1% topical, 12 weeks	N= 99	40.0 ± 12.8 (17-77)	M = 42% F= 58%	24/69/8
97-0-036	Randomized, double-blind, vehicle controlled	Vehicle, topical, 12 weeks	N= 110	38.8 ± 14.8 (16-73)	M = 39% F= 61%	27/66/8
		0.03%, topical, 12 weeks	N= 108	37.6 ± 13.9 (16-76)	M = 48% F= 52%	26/70/3
		0.1% topical, 12 weeks	N= 110	39.6 ± 16.1 (16-79)	M = 42% F= 58%	24/68/8

* All patients participating in studies FJ-108 and FJ109 were Asian ethnicity.

Maintenance Therapy

Table 5: Summary of Pivotal Phase 3 Atopic Dermatitis Trials

Study #	Trial design	Dosage, route of administration and duration	Number of Subjects (N)	Mean age (Range)	Gender	Race (%) Black/ Caucasian/ Oriental/ Other
FG-506-06-40 (Adult)	Randomized, double-blind, multi-centre, vehicle controlled.	0.1% tacrolimus ointment, topical; Acute Treatment: up to 6 weeks; Maintenance Treatment: 12 months	80	31.0 ± 11.8 (17-65)	M = 45% F= 55%	1.3/ 92.5/ 5.0/ 1.3
		Vehicle, topical; Acute Treatment: up to 6 weeks; Maintenance Treatment: 12 months	73	31.8 ± 11.1 (17-74)	M = 39.7% F= 60.3%	1.4/ 98.6/ 0.0/ 0.0

Table 5: Summary of Pivotal Phase 3 Atopic Dermatitis Trials

Study #	Trial design	Dosage, route of administration and duration	Number of Subjects (N)	Mean age (Range)	Gender	Race (%) Black/ Caucasian/ Oriental/ Other
FG-506-06-41 (Pediatric)	Randomized, double-blind, multi-centre, vehicle controlled.	0.03% tacrolimus ointment, topical; Acute Treatment: up to 6 weeks Maintenance Treatment: 12 months	78	6.8 ± 3.9 (2-15)	M= 47.4% F= 52.6	5.1/ 83.3/ 9.0/ 2.6
		Vehicle, topical; Acute Treatment: up to 6 weeks Maintenance Treatment: 12 months	75	6.9 ± 4.6 (2-15)	M= 46.7 F= 53.3	8.0/ 78.7/ 5.3/ 8.0

13.2 Study Results

Acute Treatment

Active Comparator-Controlled Phase 3 Studies

The active comparator studies (FG-506-06-018; FG-506-06-019; FJ-108; FJ-109) were 3 week multi-centre randomized, double-blind, studies to evaluate the effect of 0.03% and 0.1% Protopic (tacrolimus ointment) concentrations with 0.1% hydrocortisone butyrate in adults and 1% hydrocortisone acetate in children with moderate to severe atopic dermatitis. The effectiveness (decrease of the modified Eczema Area and Severity Index mEASI) of Protopic was evidenced within the first week of treatment. By the end of the study, the mean mEASI decreased from baseline by 63% to 75% in both the adult and pediatric patients treated with Protopic.

In the adult study, FG-506-06-018, 384 patients were treated with Protopic. The primary endpoint of evaluation, the mEASI, a composite score including the physician assessment of individual signs and symptoms, affected body surface area (BSA) and the patients' assessment of itch, demonstrated a substantial improvement during the treatment period for all 3 treatment groups. No significant difference in the improvement of symptoms was observed in patients treated with either 0.1% hydrocortisone butyrate or 0.1% Protopic, upon completion of the three-week study duration.

In the pediatric study, FG-506-06-019, 367 patients between the ages of 2-16 were treated with Protopic. As in the adult study, mEASI was the primary endpoint evaluated. Patients treated with Protopic (0.03% and 0.1%) demonstrated a two-fold decrease in mEASI compared to patients treated with 1% hydrocortisone acetate, which proved to be statistically significant. Approximately 50% more patients in the Protopic group experienced more than a moderate improvement in the severity of their eczema and completed the study as compared to patients in the hydrocortisone group. A greater improvement was also observed for the Protopic treatment groups compared to the hydrocortisone acetate group for all symptoms experienced by the patients excluding lichenification, which was similar for all treatment groups upon completion of this 3-week study.

Vehicle-Controlled Phase 3 Studies

Three randomized, double-blind, vehicle-controlled, multi-centre, phase 3 studies (97-0-037; 97-0-036; 97-0-035) were conducted to evaluate Protopic for the treatment of patients with moderate to severe atopic dermatitis. One study included 351 patients 2-15 years of age, and the other two studies included a total of 632 adult patients.

In these studies, patients applied either Protopic 0.03%, Protopic 0.1% or vehicle ointment twice daily to 10% - 100% of their BSA for up to 12 weeks.

In all three studies, a significantly greater ($p < 0.001$) percentage of patients achieved success ($\geq$ 90% improvement) based on the Physician's Global Evaluation of clinical response (the pre-defined primary efficacy end point) in both Protopic treatment groups compared to the vehicle treatment group. Overall, Protopic 0.1% was more effective than Protopic 0.03% in adult patients (97-0-035, 97-0-036). This difference was particularly evident in patients with severe disease at baseline, patients with extensive BSA involvement, and black patients. However, all the analyses demonstrated that there was no significant difference in efficacy between the 0.1% and 0.03% Protopic in pediatric patients (97-0-037). Improvement was usually observed within the first week of therapy.

As a result of the significant impact atopic dermatitis can have on a patient's life, hindering social interaction, lowering self-esteem, leading to work/school absenteeism, negatively affecting family interactions, and producing sleep disturbances and emotional distress, a quality of life questionnaire was completed by patients/ parents/guardians in five pivotal studies. The pediatric patients in these studies treated with 0.03% or 0.1% Protopic had statistically significant improvement in their quality of life compared with vehicle treated patients or those treated with hydrocortisone acetate. In adults, statistically significant improvements in the quality of life were observed in patients treated with 0.1% Protopic compared with those treated with the 0.03% Protopic concentration.

Table 6: Physician's Global Evaluation at the End of Treatment- Pediatric Study 97-0-037

Primary Endpoints	Treatment Group		
	Vehicle, n=105	Protopic 0.03%, n= 112	Protopic 0.1%, n=113
Cleared	4 (3.8%)	14 (12.5%)	13 (11.5%)
Excellent Improvement	4 (3.8%)	28 (25.0%)	35 (31.0%)
Marked Improvement	10 (9.5%)	23 (20.5%)	19 (16.8%)
Moderate Improvement	13 (12.4%)	20 (17.9%)	25 (22.1%)
Slight Improvement	19 (18.1%)	15 (13.4%)	12 (10.6%)
No Improvement	27 (25.7%)	10 (8.9%)	7 (6.2%)
Worse	28 (26.7%)	2 (1.8%)	2 (1.8%)

Table 7: Physician's Global Evaluation at the End of Treatment Adult Studies 97-0-035 & 97-0-036

Primary Endpoints	Treatment Group		
	Vehicle, n=187	Protopic 0.03%, n=202	Protopic 0.1%, n=198
Cleared	2 (1.1%)	21 (10.4%)	20 (10.1%)
Excellent Improvement	12 (6.4%)	37 (18.3%)	57 (28.8%)
Marked Improvement	16 (8.6%)	39 (19.3%)	40 (20.2%)
Moderate Improvement	12 (6.4%)	33 (16.3%)	35 (17.7%)
Slight Improvement	26 (13.9%)	29 (14.4%)	19 (9.6%)
No Improvement	50 (26.7%)	30 (14.9%)	15 (7.6%)
Worse	69 (36.9%)	13 (6.4%)	12 (6.1%)

Maintenance Therapy

Pivotal Phase 3 Atopic Dermatitis Trials FG-506-06-40 (Adult) and FG-506-06-41 (Pediatric)

The efficacy and safety of tacrolimus ointment in maintenance treatment of moderate to severe atopic dermatitis was assessed in 306 patients in two Phase 3 multicentre clinical trials of similar design, one in adult patients (≥ 16 years) and one in pediatric patients (2–15 years). In both studies, patients with active disease entered an open-label period (OLP) during which their affected lesions were treated with tacrolimus ointment twice daily for up to 6 weeks until improvement had reached a predefined score (Investigator's Global Assessment [IGA] ≤ 2, i.e., clear, almost clear or mild disease). If patients did not respond to treatment, they were discontinued from the studies. Thereafter, patients entered a double-blind disease control period (DCP) for up to 12 months. Patients were randomised to receive either tacrolimus ointment (0.1% adults; 0.03% children) or vehicle, once a day twice weekly on Mondays and Thursdays.

During the DCP, if a disease exacerbation occurred, patients were treated with open-label tacrolimus ointment twice daily for up to 6 weeks until the IGA score returned to ≤ 2. Those patients who did not achieve an IGA score of ≤ 2 were withdrawn from the study. The patients that achieved an IGA score of ≤ 2 returned to double-blind treatment in the DCP.

The primary endpoint in both studies was the number of disease exacerbations (DE) requiring a "substantial therapeutic intervention" during the DCP, defined as an exacerbation with an IGA of 3–5 (i.e., moderate, severe and very severe disease) on the first day of the flare, and requiring more than 7 days of twice daily treatment. Both studies showed significant benefit with twice weekly treatment with tacrolimus ointment with regard to the primary endpoint over a period of 12 months (Table 7). The median number of disease exacerbations requiring a substantial intervention (adjusted for length of time at risk) was 1.0 in the tacrolimus arm versus 5.3 in the vehicle arm ($p < 0.001$) in the adult study and 1.0 in the tacrolimus arm versus 2.9 in the vehicle arm ($p < 0.001$) in the pediatric study.

Table 8. Frequency of Disease Exacerbations (DE): Studies FG-506-06-40 (Adult) and FG-506-06-41 (Pediatric)

Frequency of Disease Exacerbations (DE)*	Number of Patients (%)			
	Adult, ≥ 16 years		Pediatric, 2-15 years	
	Tacrolimus 0.1% N = 80	Vehicle N = 73	Tacrolimus 0.03% N = 78	Vehicle N = 75
0	39 (48.8)	13 (17.8)	36 (46.2)	16 (21.3)
1 (0.5 - <1.5)	9 (11.3)	7 (9.6)	8 (10.3)	10 (13.3)
2 (1.5 - <2.5)	10 (12.5)	5 (6.8)	10 (12.8)	11 (14.7)
3 (2.5 - <3.5)	5 (6.3)	3 (4.1)	10 (12.8)	8 (10.7)

Table 8. Frequency of Disease Exacerbations (DE): Studies FG-506-06-40 (Adult) and FG-506-06-41 (Pediatric)

Frequency of Disease Exacerbations (DE)*	Number of Patients (%)			
	Adult, ≥ 16 years		Pediatric, 2-15 years	
	Tacrolimus 0.1% N = 80	Vehicle N = 73	Tacrolimus 0.03% N = 78	Vehicle N = 75
4 (3.5 - <4.5)	3 (3.8)	2 (2.7)	6 (7.7)	3 (4.0)
5 (4.5 - <5.5)	4 (5.0)	7 (9.6)	1 (1.3)	9 (12.0)
6 (5.5 - <6.5)	3 (3.8)	11 (15.1)	3 (3.8)	6 (8.0)
7 (6.5 - <7.5)	2 (2.5)	4 (5.5)	4 (5.1)	5 (6.7)
8 (7.5 - <8.5)	3 (3.8)	7 (9.6)	0 (0.0)	3 (4.0)
9 (8.5 - <9.5)	1 (1.3)	5 (6.8)	0 (0.0)	1 (1.3)
10 (9.5 - <10.5)	0 (0.0)	3 (4.1)	0 (0.0)	2 (2.7)
≥10.5	1 (1.3)	6 (8.2)	0 (0.0)	1 (1.3)

* Requiring a substantial intervention adjusted for length of time at risk; $p < 0.001$

In the adult study, the median time to the first disease exacerbation requiring a substantial intervention was 142 days in the tacrolimus arm versus 15 days in the vehicle arm ($p < 0.001$). The mean percentage of days of disease exacerbation treatment was 16.1% (±23.6%) in the tacrolimus arm versus 39.0% (±27.8%) in the vehicle arm ($p < 0.001$).

In the pediatric study, the median time to the first disease exacerbation requiring a substantial intervention was 217 days in the tacrolimus arm versus 36 days in the vehicle arm ($p < 0.001$). The mean percentage of days of disease exacerbation treatment was 16.9% (±22.1%) in the tacrolimus arm versus 29.9% (±26.8%) in the vehicle arm ($p < 0.001$).

The application of tacrolimus ointment once daily, twice per week as a maintenance treatment did not lead to an increase in the total average per day tacrolimus ointment use compared with vehicle group when both maintenance and disease exacerbation treatment use were combine.

Non-Interventional Post-Authorisation Long-Term Observational Safety Studies

Two large, long-term, non-interventional, post-authorization safety studies of tacrolimus ointment have been conducted with focus on the risk of cancer: APPLES™ (**A P**rospective **P**ediatric **L**ongitudinal **E**valuation to Assess the Long-Term **S**afety of Tacrolimus Ointment for the Treatment of Atopic Dermatitis) and JOELLE JOELLE (**JO**int **E**uropean **L**ongitudinal **L**ymphoma and skin cancer **E**valuation). These two, long-term, observational safety studies in real-world settings were very different in design. JOELLE analyzed the risk of lymphoma and skin cancer in both children and adults and covered a very large, unselected population. APPLES™ focused on 'all cancer' in children and covered a smaller but more well-defined population.

The JOELLE study was based on existing data in Denmark, Sweden (national databases), the Netherlands (PHARMO database network) and the United Kingdom (Clinical Practice Research Datalink (CPRD)), combining datasets within each country to gain information about demography, dispensing or prescription of medications, and diagnoses. The primary objective was to estimate the incidence rate ratios (IRRs) for skin cancer as malignant melanoma (MM) and non-melanoma skin cancer (NMSC) and for any type of lymphoma as Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL) except cutaneous T-cell lymphoma (CTCL), and CTCL

comparing new users of topical tacrolimus with users of moderate-to high potency topical corticosteroids (TCS).
The study included 32,605 children (age below 18 years) and 126,908 adults initiating treatment with topical tacrolimus matched to 117,592 children and 452,996 adults treated with topical corticosteroids. A total of 168,674 person-years of observation (PYRS) after first prescription of tacrolimus ointment were observed in children, 597,916 PYRS in adults. The median follow-up period in tacrolimus treated children was 5.7 years, in adults 5.0 years, and a total of 5,918 children and 17,410 adults were followed for 10 years or more. Half of the children and half of the adults had only one prescription, while around 20% of the children and 20% of the adults had 3 or more prescriptions.
For skin cancer, the IRR was 0.77 (95% CI 0.29-2.04) in children (5 cases) and 1.04 (95% CI 0.99-1.08) in adults (2,741 cases). For any lymphoma, the IRR was 2.49 (95% CI 1.32-4.70) in children (16 cases) and 1.04 (95% CI 0.90-1.20) in adults (227 cases). In children, when analyzed by lymphoma subtype, the IRR was 2.19 (95% CI 0.81-5.97) for NHL, 2.37 (95% CI 0.99-5.68) for HL, and 7.77 (95% CI 0.50-121.45) for CTCL. The IRR for each individual type of lymphoma in children was based on a low number of events, and no significant association or exposure-outcome relation was identified. For adults, the IRR was below 1 for HL and for NHL not including CTCL. The overall IRR for CTCL in adults was 1.80 (95% CI 1.25-2.58). The Incidence Rate Difference (IRD) is the number of extra cases per 100,000 years of observation occurring in the tacrolimus cohort. For adults the IRD for CTCL was 3 cases per 100,000 PYRS (95% CI 1-6 cases). In adults, an increase with dose level was observed for CTCL but the IRR decreased to below 1 after 4 years of follow-up. . When evaluating the Joelle study results, study limitations such as few events in children, low number of prescriptions, confounding by indication, surveillance bias, reverse causation (e.g. the possibility of CTCL being initially misdiagnosed and treated as atopic dermatitis), and multiple testing should be considered.

The APPLES™ study was a 10-year observational cohort study of children, adolescents and young adults who initiated treatment with tacrolimus ointment for atopic dermatitis before the age of 16 years. Over 8,000 patients were enrolled in North America and Europe between 2005 and 2012, and 7,954 patients were eligible for analysis. Enrolment criteria were very liberal, and treatment during enrolment was unrestricted, to represent real-life use conditions. The study focused on detection and documentation of any malignancy or potential malignancy which would then be reviewed by an independent expert committee. The calculated incidence rate for malignancy observed in the study was compared to the incidence rate in the background population in the country of residence of the same age, sex and in the United States, also race. At time of study termination 1,176 subjects had completed 10 years of follow-up and a total of 44,629 PYRS had accumulated. Half of the participants were observed for 6.4 years or longer. The median total exposure to tacrolimus ointment before and during enrolment was 330 grams. A total of 6 malignancies were observed, giving a point estimate of 1.01 for the Standardised Incidence Ratio with a 95% confidence interval of 0.37 to 2.20. The events were one chronic myeloid leukaemia, one alveolar rhabdomyosarcoma, one carcinoid tumour appendix, one spinal cord neoplasm, one malignant paraganglioma, and one spitzoid melanoma. No lymphomas or NMSC were observed. The APPLES™ study results did not show any association between treatment of atopic dermatitis with topical tacrolimus during childhood and risk of cancer.

14 NON-CLINICAL TOXICOLOGY

The pharmacokinetics of tacrolimus following ointment application was investigated in eight studies. In these studies, tacrolimus was absorbed into the systemic circulation following topical

administration, with more absorption occurring when tacrolimus ointment was applied to damaged compared with intact skin. The fraction of the dose that was absorbed varied with animal species, with pigs providing the most appropriate nonprimate absorption model for human skin. In a tissue distribution study in rats, tacrolimus did not accumulate in tissues.

In the micropig, a single topical application of ^{14}C-tacrolimus (0.1% under occlusion for 24 hours) was found to have approximately 1% of the bioavailability of a single IV dose (1 mg/kg).

Acute and Long-Term Toxicity

Single application of tacrolimus ointment, with or without occlusion, to intact or abraded skin did not produce skin abnormalities. Dermal findings in tacrolimus ointment-treated animals (0.03% to 1% administered daily; to rats, up to 26 weeks; to rabbits up to 28 days; or to micropigs, up to 13 weeks) were observed at the microscopic level (hyperplasia, epidermal vacuolation, acanthosis, superficial inflammation). Because these dermal effects were unrelated to tacrolimus concentration and were observed in vehicle-treated animals but rarely in sham controls, they were considered to be related to vehicle and not tacrolimus. Signs of systemic toxicity were observed with higher-concentration ointment (primarily ≥0.3%) in rodents and were similar to those observed after oral and intravenous doses of tacrolimus.

In the 52-week topical study with Yucatan micropigs, no macroscopic or microscopic changes were considered to be related to the application of tacrolimus ointment (0.03%–3%); all changes noted were also associated with application of the vehicle.

Tacrolimus ointment (0.03% to 3%) did not induce contact hypersensitivity or photosensitization in guinea pigs, or cutaneous phototoxicity in albino hairless mice. It also did not elicit skin depigmentation in Dark Yucatan miniature swine.

Photocarcinogenicity/Carcinogenicity

Two photocarcinogenicity/carcinogenicity studies were performed. In a 2-year dermal carcinogenicity study in B6C3F$_1$ mice, no important macroscopic or microscopic changes occurred at the site of tacrolimus ointment application (0.03% - 3%). Only five animals had skin tumors as follows: one male, vehicle control; two females, 0.03%; one male and one female 0.1%. Lymphoma was observed in this study. In all treatment groups, the incidence of lymphoma was higher in females than in males. The incidence of lymphoma for males and females was within published ranges for control mice of this strain for the vehicle and 0.03% tacrolimus ointment groups. In the 0.1% tacrolimus ointment group, the incidence of lymphoma was significantly increased compared with study controls for males (Peto analysis, $p<0.001$) and numerically higher for females. The lymphoma result is likely related to high systemic exposure resulting from a high cutaneous absorption. Rodents are known to have a much more permeable skin than man and other animal species and these animals were also shaved which damages the skin barrier (stratum corneum). High systemic exposure in the higher concentration tacrolimus ointment groups is supported by the dose-related mortality with classic signs of systemic toxicity (decreased body weight, decreased food consumption, tremors, etc.) and pharmacokinetic parameters (e.g., AUC,) evaluated in parallel toxicokinetic groups.

In a 52-week photocarcinogenicity study, albino hairless Crl:SKH1-*hr*BR mice (36/sex/group) were treated with tacrolimus ointment (0.03%, 0.1%, 0.3%, and 1%) or vehicle ointment and exposed to simulated solar ultraviolet radiation (low and high UVR) in a model designed to produce skin tumors in all animals. When the combined male and female tumor data were evaluated, the indication was that the 1.0% concentration enhanced the development of UVR-induced skin tumors as compared with vehicle-treated mice; however, enhancement was not

evident at the 0.03%, 0.1% (the clinically relevant concentrations) or the 0.3% concentrations. When tumor data were evaluated based on sex, administration of the 0.03% concentration had no influence on the development of UVR-induced skin tumors in either male or female mice, as compared with vehicle-treated mice. In male mice, administration of the 0.1%, 0.3%, and 1.0% concentrations shortened the time to skin tumor production as compared to vehicle-treated males. The relevance of these findings to humans is not known; however, potential similarities exist between human and animal mechanisms of photocarcinogenicity. Therefore, even though the biologic significance of these results to humans is not clear, patients will be advised to minimize or avoid exposure to natural or artificial sunlight.

Genotoxicity

No evidence of genotoxicity was seen in bacterial (*Salmonella* and *E. coli*) or mammalian (Chinese hamster, lung-derived cells) *in vitro* assays of mutagenicity, the *in-vitro* CHO/HGPRT assay of mutagenicity, the *in-vivo* clastogenicity assays performed in mice, or the unscheduled DNA synthesis assay in rodent hepatocytes.

Reproduction and Teratology

No reproductive studies were performed with tacrolimus ointment. Reproductive studies have been completed with oral tacrolimus formulations.

The reproductive toxicity of tacrolimus was evaluated in Segment I (rats), Segment II (rats and rabbits) and Segment III (rats) studies. Orally (gavage) administered tacrolimus altered reproductive function in female animals and reduced offspring viability during reproductive toxicity studies with rats (Segment I, fertility; Segment II teratology; and Segment III perinatal and postnatal toxicity) and rabbits (Segment II teratology). Male reproductive behaviour was only slightly altered. The changes in reproductive parameters observed during these studies included increased copulatory intervals, decreased implantation, increased loss of fetuses, fewer births, and smaller litter sizes. No reduction in male or female fertility was evident. Adverse effects in offspring whose mothers received tacrolimus during pregnancy included markedly reduced viability and slightly increased incidence of malformation.

Carcinogenesis and Mutagenesis

No evidence of genotoxicity was seen in bacterial (*Salmonella* and *E. coli*) or mammalian (Chinese hamster lung-derived cells) in-vitro assays of mutagenicity, the in-vitro CHO/HGPRT assay of mutagenicity, or in-vivo clastogenicity assays performed in mice; tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes.

Carcinogenicity studies have been carried out with systemically administered tacrolimus in male and female rats and mice. In the 80-week mouse study and in the 104-week rat study no relationship of tumour incidence to tacrolimus dosage was found.

A 104-week dermal carcinogenicity study was performed in mice with tacrolimus ointment (0.03% - 3.0%), equivalent to tacrolimus doses of 1.1-118 mg/kg or 3.3-354 mg/m^2/day. Mortality for animals dosed with 0.3, 1.0, and 3.0% tacrolimus ointment exceeded 60% prior to the end of 104 weeks of treatment. Consequently, only tissues from untreated and vehicle-treated animals and animals dosed at 0.03% and 0.1% tacrolimus ointment were evaluated microscopically. In the study, the incidence of skin tumor formation was minimal, similar to historic controls, and not associated with the topical application of tacrolimus ointment. However, in males and females treated with 0.1% ointment, the incidence of pleomorphic lymphoma in males (25/50) and females (27/50) and the incidence of undifferentiated lymphoma in females (13/50) was elevated. Peto mortality-prevalence test indicated that the increased incidence of lymphomas in males and

females treated with 0.1% ointment was statistically significant. The daily dose (0.1%) at which the elevated incidence of lymphomas was observed, was equivalent to 3.5 mg/kg/day or 26X Maximum Recommended Human Dose based on AUC comparison. The daily dose (0.03%) at which the incidence of lymphomas was not elevated, was equivalent to 1.6 mg/kg or 10X Maximum Recommended Human Dose based on AUC comparison.

In a 52-week photocarcinogenicity study, the median time to onset of tumor formation was decreased in hairless mice following chronic topical dosing with concurrent exposure to UV radiation (40 weeks of treatment followed by 12 weeks of observation) at a tacrolimus ointment concentration of ≥ 0.1% (equivalent to tacrolimus doses of ≥ 1.9 mg/kg or ≥ 24.5 mg/m^2). Even though the biological significance of this finding to humans is not clear, patients should minimize or avoid exposure to natural or artificial sunlight.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

PrPROTOPIC®
tacrolimus ointment

Read this carefully before you start taking **Protopic®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Protopic®**.

What is Protopic® used for?
Only use Protopic® on your skin. Do NOT use in the eyes.

Acute (Flare) Treatment: Protopic® is used to treat eczema flares in adults and children age 2 years and older. These patients must not have a weakened immune system.

Prevention (Maintenance Therapy): If you have a high frequency of eczema flares (5 or more times per year), Protopic® can be used to prevent these flares from coming back. It may also be used to increase the length of time between flares.

Only use Protopic® to treat eczema that has been diagnosed by a doctor. Do not use Protopic® to treat any other skin condition for which it was not prescribed.

How does Protopic® work?
The exact way that Protopic® works is not known. When the active ingredient in Protopic®, tacrolimus, is applied on the skin, it has been shown to control inflammation, itch or redness associated with eczema.

What are the ingredients in Protopic®?
Medicinal ingredient: tacrolimus
Non-medicinal ingredients: mineral oil, paraffin, propylene carbonate, white petrolatum, and white wax

Protopic® comes in the following dosage forms:
Ointment, 0.03% and 0.1% (w/w).

Do not use Protopic® if you:
- are allergic to tacrolimus, or any of the other ingredients in this medicine (See "What the nonmedicinal ingredients are"). Speak with your healthcare professional if you have had allergic reactions in the past.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Protopic®. Talk about any health conditions or problems you may have, including if you:
- Have a weakened immune system
- Are using any other type of skin product
- Have any skin infections that have not healed on the areas to be treated with Protopic®
- Are pregnant or planning to become pregnant or breast-feeding

- Have kidney problems
- Have an inherited skin barrier disease such as:
    - Netherton's syndrome,
    - lamellar ichthyosis, or
    - generalized erythrodema, this is a condition that causes inflammatory reddening and scaling of the entire skin
- Have an immune system reaction of the skin such as a cutaneous Graft Versus Host Disease. This is a common problem in patients who have had a bone marrow transplant.

Other warnings you should know about:

Lymphadenopathy: Patients treated with Protopic® may develop lymphadenopathy. This is when the lymph nodes (located on the sides of the neck, in the armpits and groin area) become enlarged. If you find that your lymph nodes are swollen while using Protopic®, talk to your healthcare professional.

Skin infections: Patients treated with Protopic® may experience skin infections. These patients may also be more likely to develop chicken pox, shingles, or cold sores. If your skin becomes infected, see your doctor.

Sunlight: Avoid sunlight and sun lamps, tanning salons, and treatment with UVA or UVB light. If you need to be outdoors after applying Protopic®, wear clothing that protects the treated area from the sun. In addition, ask your doctor what other type of protection from the sun you should use.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Be sure to check with your doctor or pharmacist before you:
- Take any new medicines.
- Use any other ointments, lotions, or creams on your skin.

How to take Protopic®:
- Wash your hands before applying Protopic®.
- If you are not treating your hands, wash your hands with soap and water after applying Protopic®. This should remove any ointment left on the hands.
- If you apply Protopic® after a bath or shower, be sure your skin is completely dry
- Protopic® must ONLY be used on your skin. It can be applied to all affected areas including on the face, neck and eyelids.
- Avoid getting Protopic® in your eyes.
- Do not swallow Protopic®.
- Apply a thin layer of Protopic® to all areas on the skin that your doctor has diagnosed as eczema. The layer should completely cover the affected areas.
- Do not cover the skin being treated with bandages, dressings, or wraps. However, you can wear normal clothing.
- Do not bathe, shower or swim right after applying Protopic®. This could wash off the ointment.

Usual dose:

Your doctor will tell you how to use Protopic® based on your medical condition and response to the drug. Do not use any more or any less of the drug than your doctor says.

Most people find that a pea-sized amount squeezed from the tube covers an area about the size of a 5-centimeter circle.

Treating eczema:
Apply Protopic® to the affected areas of the skin twice a day, in the morning and evening (about 12 hours apart).

Protopic® usually begins to provide relief from the symptoms of eczema within a few weeks.
If you do not notice an improvement in your eczema within the first 6 weeks of treatment or if your eczema gets worse, tell your doctor.

Preventing eczema flares from coming back:
This is only for patients who experience eczema flares 5 or more times per year.
Apply Protopic® to the affected areas once a day, two times a week. Between applications, there should be 2 to 3 days without treatment (e.g., apply Monday and Thursday). If your eczema comes back (flares), talk to your doctor.

After 12 months of treatment, see your doctor so that they can assess your eczema and determine if you should keep using Protopic®.

Overdose:
Do not swallow Protopic®. If you do, call your doctor immediately. Oral ingestion of Protopic® may lead to adverse effects not associated with the use of tacrolimus on the skin.

In case of drug overdose, particularly accidental oral ingestion, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to use Protopic® as directed, apply it as soon as possible, then go back to your regular schedule. If you forget to use Protopic®, do not apply twice as much Protopic® the next time you use it.

What are possible side effects from using Protopic®?

These are not all the possible side effects you may feel when taking Protopic®. If you experience any side effects not listed here, contact your healthcare professional.

- Reactions at the application site (stinging, a burning feeling, or itching) for the first few days of application, which typically resolve as the skin heals
- Increased sensitivity of the skin to hot or cold temperatures
- Skin tingling
- Fever, headache, or muscle pain
- Flu-like symptoms (common cold, congestion, upper respiratory infection)
- Acne
- Swollen or infected hair follicles
- Upset stomach

- Diarrhea

While you are using Protopic®, drinking alcohol may cause the skin or face to become flushed or red and feel hot.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Allergic Reaction: difficulty swallowing or breathing, wheezing; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat.			✓
Herpes Zoster (Chickenpox or Shingles): a painful skin rash of fluid-filled blisters, blisters appear along a strip of skin, itching			✓
Cyst			✓
Impetigo (bacterial infection of the skin): red fluid-filled blisters that break			✓
UNKNOWN			
Renal Problems (kidney problems): nausea, vomiting, fever, swelling of extremities, fatigue, thirst, dry skin, irritability, dark urine, increased or decreased urine output, blood in the urine, rash, weight gain (from retaining fluid), loss of appetite, abnormal blood test results, mental status changes (drowsiness, confusion, coma)			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store between 15°C and 30°C. Keep out of the reach and sight of children. Do not use after the expiry date.

If you want more information about Protopic®:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website www.leo-pharma.ca, or by contacting the sponsor, LEO Pharma Inc., calling 1-800-668-7234.

This leaflet was prepared by LEO Pharma Inc.

Last Revised: AUG-13-2021