PRODUCT MONOGRAPH

# PrProtopic®

tacrolimus ointment

0.03% and 0.1% (w/w)

Topical Calcineurin Inhibitor

ATC Code: D11AH01

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# [Pr]Protopic®

tacrolimus ointment

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| Topical | Ointment / 0.03% and 0.1% (w/w) | *For a complete listing of nonmedicinal ingredients see Dosage Forms, Composition and Packaging section.* |

### INDICATIONS AND CLINICAL USE

**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**
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.

**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.

**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.

## 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.

## WARNINGS AND PRECAUTIONS

**Long-term safety of topical calcineurin inhibitors has not been established. Although a causal relationship has not been established, rare cases of skin malignancy and lymphoma have been reported in patients treated with topical calcineurin inhibitors, including Protopic ointment 0.1% and 0.03%.**

**Therefore:**

- **Continuous long-term use of topical calcineurin inhibitors including Protopic ointment 0.1% and 0.03% should be avoided, and application limited to areas of involvement with atopic dermatitis.**
- **Protopic ointment is not indicated in children less than 2 years of age. Only 0.03% Protopic ointment is indicated for use in children 2-15 years of age.**

### 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.

**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 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 Function/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.

**Special Populations**

**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.

**Nursing Women:** 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.

**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.

**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.

## ADVERSE REACTIONS

### Adverse Drug 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.

### Clinical Trial Adverse Drug 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 drug 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.

Less Common Clinical Trial Adverse Drug 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).

## ***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) |

**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) – *Continued***

| MedDRA preferred term | Number of Patients Experiencing an Adverse Event (%) at a Frequency of ≥ 3% | |
|---|---|---|
| | Protopic 0.03% | Vehicle |
| | N=78 | N=75 |
| **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".

## Post-Market Adverse Drug 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

## DRUG INTERACTIONS

### 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.

### Drug-Drug Interactions
Interactions with other drug products have not been established.

### Drug-Food Interactions
There are no known interactions with food.

### Drug-Herb Interactions
Interactions with herbal products have not been established.

### Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

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

## DOSAGE AND ADMINISTRATION

### Dosing Considerations
Not Applicable.

### 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.

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

### Administration

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.

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
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 treatment. 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 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 treatment in the absence of safety data for maintenance treatment 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.

## OVERDOSAGE

| For management of a suspected drug overdose, contact your regional Poison Control Centre. |
|---|

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.

## ACTION AND CLINICAL PHARMACOLOGY

### 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.

**Pharmacokinetics**

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.

**Special Populations and Conditions**

Not Applicable.

## STORAGE AND STABILITY

Store between 15°C and 30°C.

## SPECIAL HANDLING INSTRUCTIONS

None required.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

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 in a base of white petrolatum, mineral oil, propylene carbonate, white wax and paraffin.

Protopic 0.03% and 0.1% (w/w) are available in laminate tubes of 30, 60 and 100 grams.

## PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

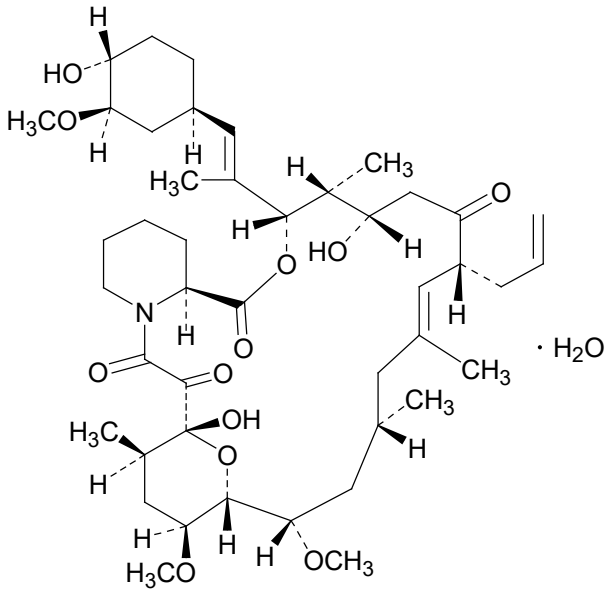
### Drug Substance

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: $C_{44}H_{69}NO_{12}\bullet H_2O$ Molecular mass: 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).

## CLINICAL TRIALS

## Treatment

## Study Demographics and Trial Design

**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%<br>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%<br>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%<br>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%<br>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%<br>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%<br>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%<br>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%<br>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%<br>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%<br>F= 59% | 0.0/0.0/100.0 |
| 97-0-037 | Randomized, double-blind, vehicle controlled | Vehicle, topical, 12 weeks | N= 116 | 5.9 ± 3.4<br>(2 - 15 ) | M = 48%<br>F= 53% | 20/71/9 |
| | | 0.03%, topical, 12 weeks | N= 117 | 6.2±3.8<br>(2 - 15 ) | M = 48%<br>F= 52% | 26/66/9 |
| | | 0.1% topical, 12 weeks | N= 118 | 6.4 ± 3.7<br>(2 - 15 ) | M = 46%<br>F= 54% | 30/64/7 |

**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 |
|---|---|---|---|---|---|---|
| 97-0-035 | 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 Oriental.

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-center, 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 5: 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 6: 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%) |

| Primary Endpoints | Treatment Group | | |
|---|---|---|---|
| | Vehicle, n=187 | Protopic 0.03%, n=202 | Protopic 0.1%, n=198 |
| 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

### Study Demographics and Trial Design

**Table 7: 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 |
| 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 |

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 6). 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: Studies FG-506-06-40 (Adult) and FG-506-06-41 (Pediatric)**

| Frequency of Disease Exacerbations* | 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) |
| 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 combined.

## DETAILED PHARMACOLOGY

### Clinical Studies

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.

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.

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

Tacrolimus blood concentration data from Study FG-06-04 indicated very little or no tacrolimus absorption into the systemic circulation following single or repeated application to intact skin of healthy volunteers.

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 $AUC_{0-24}$ 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.

**Animal Studies**

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).

## TOXICOLOGY

**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.

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# PART III: CONSUMER INFORMATION

**PrPROTOPIC®**
tacrolimus ointment

**This leaflet is part III of a three-part "Product Monograph" published when Protopic was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Protopic.**

**Read this important information before you start using Protopic and each time you refill your prescription. This summary is not meant to take the place of your doctor's instructions. If you have any questions or want more information about Protopic, talk with your doctor or pharmacist.**

## ABOUT THIS MEDICATION

**What the medication is used for:**
Protopic, a non-steroid prescription medicine, is in the class of medicines called topical calcineurin inhibitors. Protopic is used to treat eczema (atopic dermatitis) in adults and children age 2 years and older who do not have a weakened immune system. Protopic is for use on the skin only and should be used only after other therapies have been shown to be ineffective or unsuitable. Protopic should be used for short or intermittent long periods of treatment, as directed by your doctor. If you have a high frequency of flares (5 or more times per year) your doctor may advise you to use Protopic to prevent flares of your eczema from coming back or to prolong the time you are free from flares, once the affected areas of your skin have cleared.

Protopic can be applied to all affected areas of the skin including the face, neck and eyelids.

Protopic should be used only to treat eczema (atopic dermatitis) that has been diagnosed by a doctor. Do not use Protopic to treat any other skin condition for which it was not prescribed.

**What it does:**
The exact mechanism by which Protopic works is not known. However, tacrolimus applied topically has been shown to control inflammation, itch or redness associated with atopic dermatitis.

**When it should not be used:**
Do not use Protopic if you:

- are breast-feeding or pregnant, unless your doctor determines it is necessary to use Protopic.
- are allergic to any medicines including tacrolimus or any of the ingredients of Protopic (See "What the nonmedicinal ingredients are"). Speak with your doctor if you have had allergic reactions in the past.
- Have any skin infections at the site to be treated; or have a viral infection of your skin, such as chickenpox or herpes. If your skin becomes infected, see your doctor.
- Have been told you have a weakened immune system.

Contact your doctor or pharmacist if you have any questions.

**What the medicinal ingredient is:**
tacrolimus

**What the nonmedicinal ingredients are:**
mineral oil, paraffin, propylene carbonate, white petrolatum, and white wax

**What dosage forms it comes in:**
Protopic is a white to slightly yellowish ointment for topical use and comes in two strengths 0.03% and 0.1% (w/w).

## WARNINGS AND PRECAUTIONS

**Long-term safety of topical calcineurin inhibitors (a new class of eczema medication that includes Protopic) has not been established. Although a link has not been established, rare cases of skin cancer and lymphomas (cancer of certain white blood cells) have been reported in patients treated with topical calcineurin inhibitors, including Protopic ointment 0.1% and 0.03%.**

**Therefore:**

- **Continuous long-term use of Protopic ointment 0.1% and 0.03% should be avoided, and application limited to areas that have eczema.**
- **Protopic ointment is not indicated in children less than 2 years of age. Only 0.03% Protopic ointment is indicated for use in children 2-15 years of age.**

**BEFORE you start using Protopic be sure to tell your doctor if you:**

- are using **any** other prescription medicines.
- are receiving any form of light therapy (phototherapy or UV) to your skin.
- are using any over-the-counter medicines or any natural/herbal remedies.
- are using any other type of skin product.
- are pregnant or planning to become pregnant or breast-feeding.
- are suffering from any kidney problems or disease
- have an inherited skin barrier disease such as Netherton's syndrome, lamellar ichthyosis, or if you suffer from generalized erythrodema (inflammatory reddening and scaling of the entire skin).
- have a cutaneous Graft Versus Host Disease (a immune reaction of the skin which is a common complication in patients who have undergone a bone marrow transplant).

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, you should ask your doctor what other type of protection from the sun you should use.

## INTERACTIONS WITH THIS MEDICATION

No drug interaction studies have been done with Protopic.
Be sure to check with your doctor or pharmacist before you start taking any new medicines while using Protopic. Also, before you use any other ointments, lotions, or creams on your skin, discuss it with your doctor or pharmacist.

## PROPER USE OF THIS MEDICATION

- Wash your hands before applying Protopic.
- If your hands **are not** being treated, wash your hands with soap and water after applying Protopic. This should remove any ointment left on the hands.
- Apply a thin layer of Protopic to all skin areas that your doctor has diagnosed as eczema. Try to cover the affected areas completely. Most people find that a pea-sized amount squeezed from the tube covers an area about the size of a 5 centimeter (two-inch) circle.
- Protopic should be applied twice a day, about 12 hours apart for treating flares.
- Protopic should be applied once a day twice a week for preventing flares from coming back if you have a high frequency of flares (5 or more times per year).
- 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.
- Before applying Protopic after a bath or shower, be sure your skin is completely dry.
- Protopic must be used **only** on your skin. Protopic can also be safely used on your eyelids but it is recommended that you avoid direct contact with the eyes. Do not swallow Protopic.

**Usual dose:**
Protopic comes in two strengths (0.03% or 0.1%). The 0.1% strength is for use in patients age 16 and over. The 0.03% strength is for patients age 2 and over. 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.

**Treating eczema (atopic dermatitis):**Protopic 0.03% or 0.1% should be applied topically morning and evening twice daily as a thin layer to affected areas of skin.

Protopic usually begins to provide relief from the symptoms of eczema within a few weeks. It is important to use Protopic as instructed by your doctor.

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 (atopic dermatitis) from coming back:**
You may be told by your doctor to continue using Protopic once your eczema has cleared. Protopic 0.03% or 0.1% should be applied once a day twice per week (e.g., Monday and Thursday) to the areas normally affected by eczema. Between applications there should be 2 to 3 days without Protopic treatment. If your eczema comes back, you should call your doctor.

After 12 months of treatment you should see your doctor so that he or she can assess your atopic dermatitis 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 application 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.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medicines, Protopic can cause side effects. The most common side effects of Protopic are stinging, a burning feeling or itching of the skin that is being treated with Protopic. These side effects are usually mild to moderate and usually go away after the first few days of using Protopic.

Less common side effects include acne, allergic reaction, fever, diarrhea, swollen or infected hair follicles, headache, increased sensitivity of the skin to hot or cold temperature, or flu-like symptoms (common cold, congestion, upper respiratory infection). While you are using Protopic, drinking alcohol may cause the skin or face to become flushed or red and feel hot. Some people may develop skin tingling, upset stomach, herpes zoster (chickenpox or shingles), muscle pain, cyst, an infection on the skin where Protopic was applied or a bacterial infection of the skin called impetigo. Call your doctor if side effects persist or become bothersome.

Although a link has not been established, rare cases of skin cancer and lymphomas (cancer of certain white blood cells) have also been reported in postmarketing reports (reporting of adverse events by health care professionals and consumers after the launch of the product) for patients treated with topical calcineurin inhibitors, including Protopic ointment 0.1% and 0.03%.

Rare cases of renal (kidney) problems have also been reported in postmarketing use.

***For any unexpected effects while taking Protopic, contact your doctor or pharmacist.***

## HOW TO STORE IT

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

**REPORTING SUSPECTED SIDE EFFECTS**

**You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:**

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    **Health Canada**
    **Postal Locator 0701C**
    **Ottawa, ON K1A 0K9**

**Postage paid labels, the Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada web site at www.healthcanada.gc.ca/medeffect.**

**NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.**

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.leo-pharma.ca or by contacting the sponsor, LEO Pharma Inc., at: 1-800-668-7234.

This leaflet was prepared by LEO Pharma Inc.

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