F.P.O.

45698

PROFESSIONAL SAMPLES–NOT FOR SALE

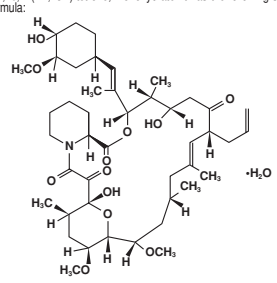
Fujisawa

45698/Revised: July 2003

Protopic®
(tacrolimus)
Ointment 0.03%
Ointment 0.1%

FOR DERMATOLOGIC USE ONLY
NOT FOR OPHTHALMIC USE

DESCRIPTION:
PROTOPIC (tacrolimus) Ointment contains tacrolimus, a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. It is for topical dermatologic use only. Chemically, tacrolimus is designated as [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. It has the following structural formula:



Tacrolimus has an empirical formula of $C_{44}H_{69}NO_{12}•H_2O$ and a formula weight of 822.03. Each gram of PROTOPIC Ointment contains (w/w) either 0.03% or 0.1% of tacrolimus in a base of mineral oil, paraffin, propylene carbonate, white petrolatum and white wax.

CLINICAL PHARMACOLOGY:
Mechanism of Action
The mechanism of action of tacrolimus in atopic dermatitis is not known. While the following have been observed, the clinical significance of these observations in atopic dermatitis is not known. It has been demonstrated that tacrolimus inhibits T-lymphocyte activation by first binding to 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 IL-3, IL-4, IL-5, GM-CSF, and TNF-α, all of which are involved in the early stages of T-cell activation. 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.

Pharmacokinetics
The pooled results from two pharmacokinetic studies in 49 adult atopic dermatitis patients indicate that tacrolimus is absorbed after the topical application of 0.1% PROTOPIC Ointment. Peak tacrolimus blood concentrations ranged from undetectable to 20 ng/mL after single or multiple doses of 0.1% PROTOPIC Ointment, with 45 of the 49 patients having peak blood concentrations less than 5 ng/mL. The results from a pharmacokinetic study of 0.1% PROTOPIC Ointment in 20 pediatric atopic dermatitis patients (ages 6-13 years), show peak tacrolimus blood concentrations below 1.6 ng/mL in all patients.

There was no evidence based on blood concentrations that tacrolimus accumulates systemically upon intermittent topical application for periods of up to 1 year. The absolute bioavailability of topical tacrolimus is unknown. Using IV historical data for comparison, the bioavailability of tacrolimus from PROTOPIC in atopic dermatitis patients is less than 0.5%. In adults with an average of 53% BSA treated, exposure (i.e., AUC) of tacrolimus from PROTOPIC is approximately 30-fold less than that seen with oral immunosuppressive doses in kidney and liver transplant patients. The lowest tacrolimus blood level at which systemic effects can be observed is not known.

CLINICAL STUDIES:
Three randomized, double-blind, vehicle-controlled, multi-center, phase 3 studies were conducted to evaluate PROTOPIC Ointment for the treatment of patients with moderate to severe atopic dermatitis. One (Pediatric) study included 351 patients 2-15 years of age, and the other two (Adult) studies included a total of 632 patients 15-79 years of age. Fifty-five percent (55%) of the patients were women and 27% were black. At baseline, 58% of the patients had severe disease and the mean body surface area (BSA) affected was 46%. Over 80% of patients had atopic dermatitis affecting the face and/or neck region. In these studies, patients applied either PROTOPIC Ointment 0.03%, PROTOPIC Ointment 0.1%, or vehicle ointment twice daily to 10% - 100% of their BSA for up to 12 weeks.

In the pediatric study, a significantly greater ($p < 0.001$) percentage of patients achieved at least 90% improvement based on the physician's global evaluation of clinical response (the pre-defined primary efficacy end point) in the PROTOPIC Ointment 0.03% treatment group compared to the vehicle treatment group, but there was insufficient evidence that PROTOPIC Ointment 0.1% provided more efficacy than PROTOPIC Ointment 0.03%.

In both adult studies, a significantly greater ($p < 0.001$) percentage of patients achieved at least 90% improvement based on the physician's global evaluation of clinical response in the PROTOPIC Ointment 0.03% and PROTOPIC Ointment 0.1% treatment groups compared to the vehicle treatment group. There was evidence that PROTOPIC Ointment 0.1% may provide more efficacy than PROTOPIC Ointment 0.03%. The difference in efficacy between PROTOPIC Ointment 0.1% and 0.03% was particularly evident in adult patients with severe disease at baseline, adults with extensive BSA involvement, and black adults. Response rates for each treatment group are shown below by age groups. Because the two adult studies were identically designed, the results from these studies were pooled in this table.

Global Improvement over Baseline at the End-Of-Treatment in Three Phase 3 Studies

Physician's Global Evaluation of Clinical Response (% Improvement)	Pediatric Study (2-15 Years of Age)		Adult Studies		
	Vehicle Ointment	PROTOPIC Ointment 0.03%	Vehicle Ointment	PROTOPIC Ointment 0.03%	PROTOPIC Ointment 0.1%
	N = 116	N = 117	N = 212	N = 211	N = 209
100%	4 (3%)	14 (12%)	2 (1%)	21 (10%)	20 (10%)
≥ 90%	8 (7%)	42 (36%)	14 (7%)	58 (28%)	77 (37%)
≥ 75%	18 (16%)	65 (56%)	30 (14%)	97 (46%)	117 (56%)
≥ 50%	31 (27%)	85 (73%)	42 (20%)	130 (62%)	152 (73%)

A statistically significant difference in the percentage of adult patients with ≥ 90% improvement was achieved by week 1 for those treated with PROTOPIC Ointment 0.1%, and by week 3 for those treated with PROTOPIC Ointment 0.03%. A statistically significant difference in the percentage of pediatric patients with ≥ 90% improvement was achieved by week 2 for those treated with PROTOPIC Ointment 0.03%.

In adult patients who had achieved ≥ 90% improvement at the end of treatment, 35% of those treated with PROTOPIC Ointment 0.03% and 41% of those treated with PROTOPIC Ointment 0.1%, regressed from this state of improvement at 2 weeks after end-of-treatment. In pediatric patients who had achieved ≥ 90% improvement, 54% of those treated with PROTOPIC Ointment 0.03% regressed from this state of improvement at 2 weeks after end-of-treatment. Because patients were not followed for longer than 2 weeks after end-of-treatment, it is not known how many additional patients regressed at periods longer than 2 weeks after cessation of therapy.

In both PROTOPIC Ointment treatment groups in adults and in the PROTOPIC Ointment 0.03% treatment group in pediatric patients, a significantly greater improvement compared to vehicle ($p < 0.001$) was observed in the secondary efficacy endpoints of percent body surface area involved, patient evaluation of pruritus, erythema, edema, excoriation, oozing, scaling, and lichenification. The following two graphs depict the time course of improvement in the percent body surface area affected in adult and in pediatric patients as a result of treatment.

Figure 1 – Adult Patients Body Surface Area Over Time

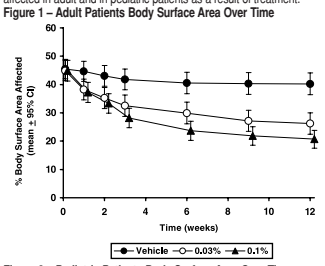
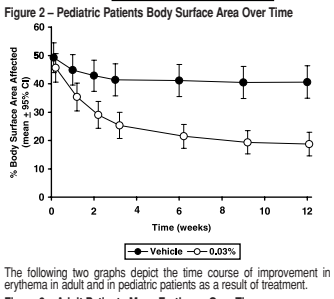


Figure 2 – Pediatric Patients Body Surface Area Over Time



The following two graphs depict the time course of improvement in erythema in adult and in pediatric patients as a result of treatment.

Figure 3 – Adult Patients Mean Erythema Over Time

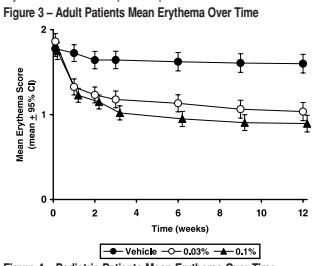
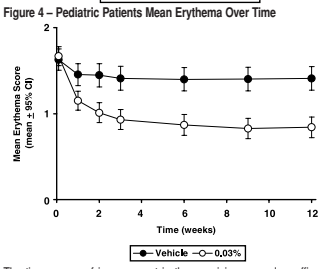


Figure 4 – Pediatric Patients Mean Erythema Over Time



The time course of improvement in the remaining secondary efficacy variables was similar to that of erythema, with improvement in lichenification slightly slower.

A total of 571 patients applied PROTOPIC Ointment 0.1% in long-term adult and pediatric safety studies for up to one year. In the adult study, 246 patients were evaluated for at least 6 months and 68 patients for 12 months. In the pediatric study, 219 patients were evaluated for at least 6 months and 180 patients for 12 months. On average, patients received treatment for 87% of study days.

INDICATIONS AND USAGE:
PROTOPIC Ointment, both 0.03% and 0.1% for adults, and only 0.03% for children aged 2 to 15 years, is indicated for short-term and intermittent long-term therapy in the treatment of patients with moderate to severe atopic dermatitis in whom the use of alternative, conventional therapies are deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or are intolerant of alternative, conventional therapies.

CONTRAINDICATIONS:
PROTOPIC Ointment is contraindicated in patients with a history of hypersensitivity to tacrolimus or any other component of the preparation.

PRECAUTIONS:
General
Studies have not evaluated the safety and efficacy of PROTOPIC Ointment in the treatment of clinically infected atopic dermatitis. Before commencing treatment with PROTOPIC Ointment, clinical infections at treatment sites should be cleared.

While patients with atopic dermatitis are predisposed to superficial skin infections including eczema herpeticum (Kaposi's varicelliform eruption), treatment with PROTOPIC Ointment may be associated with an increased risk of varicella zoster virus infection (chicken pox or shingles), herpes simplex virus infection, or eczema herpeticum. In the presence of these infections, the balance of risks and benefits associated with PROTOPIC Ointment use should be evaluated.

In clinical studies, 33 cases of lymphadenopathy (0.8%) were reported and were usually related to infections (particularly of the skin) and noted to resolve upon appropriate antibiotic therapy. Of these 33 cases, the majority 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 Ointment 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 Ointment should be considered. Patients who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves.

The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Despite the absence of observed phototoxicity in humans (see **ADVERSE REACTIONS**), PROTOPIC Ointment shortened the time to skin tumor formation in an animal photocarcinogenicity study (see **Carcinogenesis, Mutagenesis, Impairment of Fertility**). Therefore, it is prudent for patients to minimize or avoid natural or artificial sunlight exposure.

The use of PROTOPIC Ointment may cause local symptoms such as skin burning (burning sensation, stinging, soreness) or pruritus. Localized symptoms are most common during the first few days of

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PATIENT INFORMATION ABOUT

Protopic®
(tacrolimus)
Ointment

Read this important information before you start using PROTOPIC [pro-TOP-ik] Ointment and each time you refill your prescription.There may be new information. This summary is not meant to take the place of your doctor's advice.

What Is PROTOPIC?
PROTOPIC Ointment is a prescription medicine that is used to treat eczema (atopic dermatitis). It is for adults and children age 2 years and older. You can use PROTOPIC for short or intermittent long periods of treatment. Intermittent means starting and stopping repeatedly, as directed by your doctor. You can use it on all affected areas of your skin, including your face and neck.

Who should not use PROTOPIC?
Do not use PROTOPIC if you are
- breastfeeding
- allergic to PROTOPIC Ointment or any of its ingredients. The active ingredient is tacrolimus. Ask your doctor or pharmacist about the inactive ingredients.

Before you start using PROTOPIC, tell your doctor if you are:
- using **any** other prescription medicines, non-prescription (over-the-counter) medicines, or supplements
- receiving any form of light therapy (phototherapy, UVA or UVB) on your skin
- using any other type of skin product
- pregnant or planning to become pregnant

How Do I Use PROTOPIC?
Use PROTOPIC only to treat eczema that has been diagnosed by a doctor.
- Wash your hands before using PROTOPIC.
- 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 two-inch circle (approximately the size of a silver dollar).
- Apply the ointment twice a day, about 12 hours apart.
- Before applying PROTOPIC Ointment after a bath or shower, be sure your skin is completely dry.
- Do not cover the skin being treated with bandages, dressings or wraps. Unless otherwise instructed by your doctor, do not apply another type of skin product on top of PROTOPIC Ointment. However, you can wear normal clothing.
- Do not bathe, shower or swim right after applying PROTOPIC. This could wash off the ointment.
- If you are a caregiver applying PROTOPIC Ointment to a patient, or if you are a patient who is **not** treating your hands, wash your hands with soap and water after applying PROTOPIC. This should remove any ointment left on the hands.
- Use PROTOPIC only on your skin. Do **not** swallow PROTOPIC.

CrossTech–G41471–Proof A3
Form M01–PS:G1
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Fonts: Helvetica (A)
Typesmiths Pi Font
Gill Sans (Job)

CrossTech COMMUNICATIONS INC
312 382-0111 FAX 382-0004

Because 2 strengths of PROTOPIC are available for adult patients, your doctor will decide what strength of PROTOPIC Ointment is best for you.

Many people notice that their skin starts to improve after the first few weeks of treatment. Even though your skin looks and feels better, it is important to keep using PROTOPIC as instructed by your doctor.

If you do not notice an improvement in your eczema or if your eczema gets worse within the first few weeks of treatment, tell your doctor.

What Should I Avoid While Using PROTOPIC?

- Avoid sunlight and sun lamps, tanning beds, and treatment with UVA or UVB light. If you need to be outdoors after applying PROTOPIC, wear loose fitting 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.
- Check with your doctor or pharmacist before you
  - start taking any new medicines while using PROTOPIC.
  - Start using any other ointment, lotions, or creams on your skin.

What Are The Possible Side Effects of PROTOPIC?

The most common side effects of PROTOPIC are stinging, soreness, a burning feeling, or itching of the skin treated with PROTOPIC. These side effects are usually mild to moderate, are most common during the first few days of treatment, and typically lessen if your skin heals.

Less common side effects include acne, swollen or infected hair follicles, headache, increased sensitivity of the skin to hot or cold temperatures, or flu-like symptoms [common cold and congestion (stuffy nose)]. Some people may get skin tingling, upset stomach, herpes zoster (chicken pox or shingles), or muscle pain. While you are using PROTOPIC, drinking alcohol may cause the skin or face to become flushed or red and feel hot. Call your doctor if side effects continue or become a problem.

How Should I Store PROTOPIC?

Store PROTOPIC at room temperature (59° to 86°F). For instance, never leave PROTOPIC in your car in cold or hot weather. Make sure the cap on the tube is tightly closed. Keep PROTOPIC out of the reach of children.

General Advice about Prescription Medicines

Do not use PROTOPIC for a condition for which it was not prescribed. If you have any concerns about PROTOPIC, ask your doctor. Your doctor or pharmacist can give you information about PROTOPIC that was written for health care professionals. For more information, you can also visit the Fujisawa Internet site at www.protopic.com or call the PROTOPIC Help Line at 1-800-727-7003.

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PROTOPIC Ointment application and typically improve as the lesions of atopic dermatitis heal. With PROTOPIC Ointment 0.1%, 90% of the skin burning events had a duration between 2 minutes and 3 hours (median 15 minutes). Ninety percent of the pruritus events had a duration between 3 minutes and 10 hours (median 20 minutes).

The use of PROTOPIC Ointment in patients with Netherton's Syndrome is not recommended due to the potential for increased systemic absorption of tacrolimus. The safety of PROTOPIC Ointment has not been established in patients with generalized erythroderma.

Information for Patients

(See patient package insert)

Patients using PROTOPIC Ointment should receive the following information and instructions:

1. Patients should use PROTOPIC Ointment as directed by the physician. PROTOPIC Ointment is for external use only. As with any topical medication, patients or caregivers should wash hands after application if hands are not an area for treatment.
2. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using PROTOPIC Ointment.
3. Patients should not use this medication for any disorder other than that for which it was prescribed.
4. Patients should report any signs of adverse reactions to their physician.
5. Before applying PROTOPIC Ointment after a bath or shower, be sure your skin is completely dry.

Drug Interactions

Formal topical drug interaction studies with PROTOPIC Ointment have not been conducted. Based on its minimal extent of absorption, interactions of PROTOPIC Ointment with systemically administered drugs are unlikely to occur but cannot be ruled out. The concomitant administration of known CYP3A4 inhibitors in patients with widespread and/or erythrodermic disease should be done with caution. Some examples of such drugs are erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers and cimetidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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.

Oral (feed) 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 tumor incidence to tacrolimus dosage was found at daily doses up to 3 mg/kg [9X the Maximum Recommended Human Dose (MRHD) based on AUC comparisons] and 5 mg/kg (3X the MRHD based on AUC comparisons), respectively.

A 104-week dermal carcinogenicity study was performed in mice with tacrolimus ointment (0.03% - 3%), equivalent to tacrolimus doses of 1.1-118 mg/kg/day or 3.3-354 mg/m^2/day. In the study, the incidence of skin tumors was minimal and the topical application of tacrolimus was not associated with skin tumor formation under ambient room lighting. However, a statistically significant elevation in the incidence of pleomorphic lymphoma in high dose male (25/50) and female animals (27/50) and in the incidence of undifferentiated lymphoma in high dose female animals (13/50) was noted in the mouse dermal carcinogenicity study. Lymphomas were noted in the mouse dermal carcinogenicity study at a daily dose of 3.5 mg/kg (0.1% tacrolimus ointment) (26X MRHD based on AUC comparisons). No drug-related tumors were noted in the mouse dermal carcinogenicity study at a daily dose of 1.1 mg/kg (0.03% tacrolimus ointment) (10X MRHD based on AUC comparisons).

In a 52-week photocarcinogenicity study, the median time to onset of skin 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) with tacrolimus ointment at ≥0.1% tacrolimus.

Reproductive toxicology studies were not performed with topical tacrolimus. In studies of oral tacrolimus no impairment of fertility was seen in male and female rats. Tacrolimus, given orally at 1.0 mg/kg (0.12X MRHD based on body surface area [BSA]) 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 (0.43X MRHD based on BSA), 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.

Pregnancy:

Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies of topically administered tacrolimus in pregnant women. The experience with PROTOPIC Ointment when used by pregnant women is too limited to permit assessment of the safety of its use during pregnancy.

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 (0.04X - 0.12X MRHD based on BSA) 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 (0.04X - 0.12X MRHD based on BSA) 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 Ointment should be used during pregnancy only if the potential benefit to the mother justifies a potential risk to the fetus.

Nursing Mothers

Although systemic absorption of tacrolimus following topical applications of PROTOPIC Ointment is minimal relative to systemic administration, it is known that tacrolimus is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from tacrolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

PROTOPIC Ointment 0.03% may be used in pediatric patients 2 years of age and older. Two phase 3 pediatric studies were conducted involving 606 patients 2-15 years of age: one 12-week randomized vehicle-controlled study and one open-label, 1 year, long-term safety study. Three hundred and thirty (330) of these patients were 2 to 6 years of age.

The most common adverse events associated with PROTOPIC Ointment application in pediatric patients were skin burning and pruritus (see **ADVERSE REACTIONS**). In addition to skin burning and pruritus, the less common events (< 5%) of varicella zoster (mostly chicken pox), and vesiculobullous rash were more frequent in patients treated with PROTOPIC Ointment 0.03% compared to vehicle. In the long-term 1 year safety study involving 255 pediatric patients using PROTOPIC Ointment, the incidence of adverse events, including infections, did not increase with increased duration of study drug exposure or amount of ointment used. In 491 pediatric patients treated with PROTOPIC Ointment, 3(0.6%) developed eczema herpeticum. Since the safety and efficacy of PROTOPIC Ointment have not been established in pediatric patients below 2 years of age, its use in this age group is not recommended.

Geriatric Use

Twenty-five (25) patients ≥ 65 years old received PROTOPIC Ointment in phase 3 studies. The adverse event profile for these patients was consistent with that for other adult patients.

ADVERSE REACTIONS:

No phototoxicity and no photoallergenicity was detected in clinical studies of 12 and 216 normal volunteers, respectively. One out of 198 normal volunteers showed evidence of sensitization in a contact sensitization study.

In three randomized vehicle-controlled studies and two long-term safety studies, 655 and 571 patients respectively, were treated with PROTOPIC Ointment.

The following table depicts the adjusted incidence of adverse events pooled across the 3 identically designed 12-week studies for patients in vehicle, PROTOPIC Ointment 0.03%, and PROTOPIC Ointment 0.1% treatment groups, and the unadjusted incidence of adverse events in two one year long-term safety studies, regardless of relationship to study drug.

Incidence of Treatment Emergent Adverse Events

	12-Week, Randomized, Double-Blind, Phase 3 Studies 12-Week Adjusted Incidence Rate (%)					Open-Label Studies (up to 1 year) 0.1% Tacrolimus Ointment Incidence(%)	
	Adult			Pediatric		Adult	Pediatric
	Vehicle n=212	0.03% Tacrolimus Ointment n=210	0.1% Tacrolimus Ointment n=289	Vehicle n=116	0.03% Tacrolimus Ointment n=118	n=316	n=255
Skin Burning†	26	46	58	29	43	47	26
Pruritus†	37	46	46	27	41	25	25
Flu-like symptoms†	19	23	31	25	28	22	35
Allergic Reaction	8	12	6	8	4	22	15
Skin Erythema	20	25	28	13	12	12	9
Headache†	11	20	19	8	5	10	18
Skin Infection	11	12	5	14	10	11	11
Fever	4	4	1	13	21	2	18
Infection	1	1	2	9	7	14	8
Cough Increased	2	1	1	14	18	3	15
Asthma	4	6	4	6	6	5	16
Herpes Simplex	4	4	4	2	0	12	5
Eczema Herpeticum	0	1	1	0	2	2	0
Pharyngitis	3	3	4	11	6	5	10
Accidental Injury	4	3	6	3	6	4	12
Pustular Rash	2	3	4	3	2	6	8
Folliculitis†	1	6	4	0	2	11	2
Rhinitis	4	3	2	2	6	5	5
Otitis Media	4	0	1	6	12	1	7
Sinusitis†	1	4	2	8	3	3	7
Diarrhea	3	3	4	2	5	4	6
Urticaria	3	3	6	1	1	5	5
Lack of Drug Effect	1	1	0	1	1	10	2
Bronchitis	0	2	2	3	3	3	6
Vomiting	0	1	1	7	6	1	5
Maculopapular Rash	2	2	2	3	0	4	3
Rash†	1	5	2	4	2	2	5
Abdominal Pain	3	1	1	2	3	1	5
Fungal Dermatitis	0	2	1	3	0	2	6
Gastroenteritis	1	2	2	3	0	4	2
Alcohol Intolerance†	0	3	7	0	0	6	0
Acne†	2	4	7	1	0	2	4
Sunburn	1	2	1	0	0	4	4
Skin Disorder	2	2	1	1	4	1	4
Conjunctivitis	0	2	2	2	1	4	2
Pain	1	2	1	0	1	4	3
Vesiculobullous Rash†	3	3	2	0	4	2	2
Lymphadenopathy	2	2	1	0	3	2	3
Nausea	4	3	2	0	1	1	2
Skin Tingling†	2	3	8	1	2	2	1
Face Edema	2	2	1	2	1	3	1
Dyspepsia†	1	1	4	0	0	1	4
Dry Skin	7	3	3	0	1	0	1
Hyperesthesia†	1	3	7	0	0	3	0
Skin Neoplasm Benign‡‡	1	1	1	0	0	2	3
Back Pain†	0	2	2	1	1	3	1
Peripheral Edema	2	4	3	0	0	2	1
Varicella Zoster/ Herpes Zoster†‡	0	1	0	0	5	1	3
Contact Dermatitis	1	3	3	3	4	1	1
Asthenia	1	2	3	0	0	2	1
Pneumonia	0	1	1	2	0	1	2
Eczema	2	2	2	0	0	3	0
Insomnia	3	4	3	1	1	1	0
Exfoliative Dermatitis	3	3	1	0	0	0	2
Dysmenorrhea	2	4	4	0	0	0	2
Periodontal Abscess	1	0	1	0	0	3	0
Myalgia†	0	3	2	0	0	1	0
Cyst†	0	1	3	0	0	0	0

† May be reasonably associated with the use of this drug product.

‡ Four cases of chicken pox in the pediatric 12-week study; 1 case of "zoster of the lip" in the adult 12-week study; 7 cases of chicken pox and 1 case of shingles in the open-label pediatric study; 2 cases of herpes zoster in the open-label adult study.

‡‡ Generally "warts".

Other adverse events which occurred at an incidence greater than or equal to 1% in any clinical study include: alopecia, ALT or AST increased, anaphylactoid reaction, angina pectoris, angioedema, anorexia, anxiety, arrhythmia, arthralgia, arthritis, bilirubinemia, breast pain, cellulitis, cerebrovascular accident, cheilitis, chills, constipation, creatinine increased, dehydration, depression, dizziness, dyspnea, ear pain, ecchymosis, edema, epistaxis, exacerbation of untreated area, eye disorder, eye pain, furunculosis, gastritis, hernia, hyperglycemia, hypertension, hypoglycemia, hypoxia, laryngitis, leukocytosis, leukopenia, liver function tests abnormal, lung disorder, malaise, migraine, neck pain, neuritis, palpitations, paresthesia, peripheral vascular disorder, photosensitivity reaction, procedural complication, routine procedure, skin discoloration, sweating, taste perversion, tooth disorder, unintended pregnancy, vaginal moniliasis, vasodilatation, and vertigo.

OVERDOSAGE:

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

DOSAGE AND ADMINISTRATION:

ADULT

PROTOPIC Ointment 0.03% and 0.1%

Apply a thin layer of PROTOPIC Ointment 0.03% or 0.1% to the affected skin areas twice daily and rub in gently and completely. Treatment should be continued for one week after clearing of signs and symptoms of atopic dermatitis.

The safety of PROTOPIC Ointment under occlusion which may promote systemic exposure, has not been evaluated. **PROTOPIC Ointment 0.03% and 0.1% should not be used with occlusive dressings.**

PEDIATRIC

PROTOPIC Ointment 0.03%

Apply a thin layer of PROTOPIC Ointment 0.03% to the affected skin areas twice daily and rub in gently and completely. Treatment should be continued for one week after clearing of signs and symptoms of atopic dermatitis. The safety of PROTOPIC Ointment under occlusion, which may promote systemic exposure, has not been evaluated. **PROTOPIC Ointment 0.03% should not be used with occlusive dressings.**

HOW SUPPLIED:

Professional Samples:

PROTOPIC® (tacrolimus) Ointment

0.03% NDC 0469-5201-02 Product Code 520102
approx. 2 gram laminate tube

0.1% NDC 0469-5202-02 Product Code 520202
approx. 2 gram laminate tube

Commercially Available as:

PROTOPIC® (tacrolimus) Ointment 0.03%

NDC 0469-5201-30 Product Code 520130
30 gram laminate tube

NDC 0469-5201-60 Product Code 520160
60 gram laminate tube

NDC 0469-5201-11 Product Code 520111
100 gram laminate tube

PROTOPIC® (tacrolimus) Ointment 0.1%

NDC 0469-5202-30 Product Code 520230
30 gram laminate tube

NDC 0469-5202-60 Product Code 520260
60 gram laminate tube

NDC 0469-5202-11 Product Code 520211
100 gram laminate tube

Store at room temperature 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

Rx only

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