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PROTOPIC[®]
(tacrolimus)

Ointment 0.03%
Ointment 0.1%

FOR DERMATOLOGIC USE ONLY
NOT FOR OPHTHALMIC USE

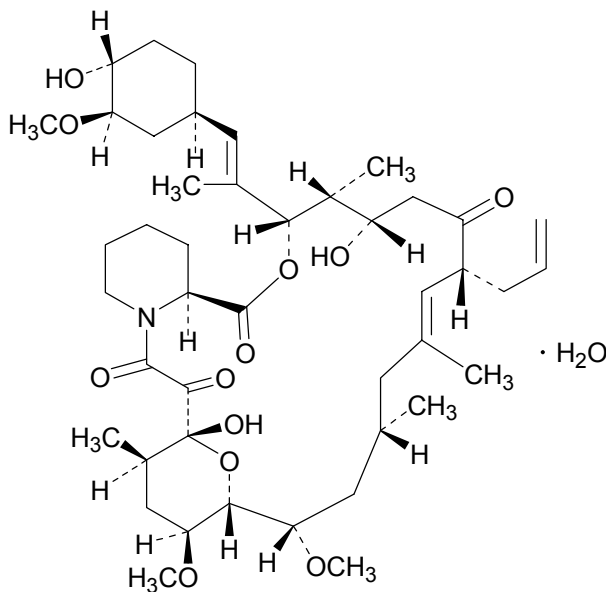
Rx Only

Prescribing Information

See boxed WARNING concerning long-term safety of topical calcineurin inhibitors

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 [3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-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:



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33 Tacrolimus has an empirical formula of $C_{44}H_{69}NO_{12} \cdot H_2O$ and a formula weight
34 of 822.03. Each gram of PROTOPIC Ointment contains (w/w) either 0.03% or
35 0.1% of tacrolimus in a base of mineral oil, paraffin, propylene carbonate, white
36 petrolatum and white wax.

37

38 **CLINICAL PHARMACOLOGY**

39 **Mechanism of Action**

40 The mechanism of action of tacrolimus in atopic dermatitis is not known. While
41 the following have been observed, the clinical significance of these
42 observations in atopic dermatitis is not known. It has been demonstrated that
43 tacrolimus inhibits T-lymphocyte activation by first binding to an intracellular
44 protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and
45 calcineurin is then formed and the phosphatase activity of calcineurin is
46 inhibited. This effect has been shown to prevent the dephosphorylation and
47 translocation of nuclear factor of activated T-cells (NF-AT), a nuclear
48 component thought to initiate gene transcription for the formation of
49 lymphokines (such as interleukin-2, gamma interferon). Tacrolimus also inhibits
50 the transcription for genes which encode IL-3, IL-4, IL-5, GM-CSF, and TNF- α ,
51 all of which are involved in the early stages of T-cell activation. Additionally,
52 tacrolimus has been shown to inhibit the release of pre-formed mediators from
53 skin mast cells and basophils, and to down regulate the expression of Fc ϵ RI on
54 Langerhans cells.

55

56 **Pharmacokinetics**

57 **Absorption**

58 The pooled results from three pharmacokinetic studies in 88 adult atopic
59 dermatitis patients indicate that tacrolimus is minimally absorbed after the
60 topical application of PROTOPIC Ointment. Peak tacrolimus blood
61 concentrations ranged from undetectable to 20 ng/mL after single or multiple
62 doses of 0.03% and 0.1% PROTOPIC Ointment, with 85% (75/88) of the
63 patients having peak blood concentrations less than 2 ng/mL. In general as
64 treatment continued, systemic exposure declined as the skin returned to
65 normal. In clinical studies with periodic blood sampling, a similar distribution of
66 tacrolimus blood levels was also observed in adult patients, with 90%
67 (1253/1391) of patients having a blood concentration less than 2 ng/mL.

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71 The absolute bioavailability of tacrolimus from PROTOPIC in atopic dermatitis
72 patients is approximately 0.5%. In adults with an average of 53% BSA treated,
73 exposure (AUC) of tacrolimus from PROTOPIC is approximately 30-fold less
74 than that seen with oral immunosuppressive doses in kidney and liver
75 transplant patients.

76

77 Mean peak tacrolimus blood concentrations following oral administration (0.3
78 mg/kg/day) in adult kidney transplant (n=26) and liver transplant (n=17) patients
79 are 24.2 ± 15.8 ng/mL and 68.5 ± 30.0 ng/mL, respectively. The lowest tacrolimus
80 blood level at which systemic effects (e.g., immunosuppression) can be
81 observed is not known.

82

83

84 Systemic levels of tacrolimus have also been measured in pediatric patients
85 (see **Special Populations: Pediatrics**).

86

87

88 **Distribution**

89 The plasma protein binding of tacrolimus is approximately 99% and is
90 independent of concentration over a range of 5-50 ng/mL. Tacrolimus is bound
91 mainly to albumin and alpha-1-acid glycoprotein, and has a high level of
92 association with erythrocytes. The distribution of tacrolimus between whole
93 blood and plasma depends on several factors, such as hematocrit, temperature
94 at the time of plasma separation, drug concentration, and plasma protein
95 concentration. In a US study, the ratio of whole blood concentration to plasma
96 concentration averaged 35 (range 12 to 67).

97

98 There was no evidence based on blood concentrations that tacrolimus
99 accumulates systemically upon intermittent topical application for periods of up
100 to 1 year. As with other topical calcineurin inhibitors, it is not known whether
101 tacrolimus is distributed into the lymphatic system.

102

103 **Metabolism**

104 Tacrolimus is extensively metabolized by the mixed-function oxidase system,
105 primarily the cytochrome P-450 system (CYP3A). A metabolic pathway leading
106 to the formation of 8 possible metabolites has been proposed. Demethylation
107 and hydroxylation were identified as the primary mechanisms of
108 biotransformation in vitro. The major metabolite identified in incubations with
109 human liver microsomes is 13-demethyl tacrolimus. In in vitro studies, a 31-
110 demethyl metabolite has been reported to have the same activity as tacrolimus.

111

112 **Excretion**

113 The mean clearance following IV administration of tacrolimus is 0.040, 0.083
114 and 0.053 L/hr/kg in healthy volunteers, adult kidney transplant patients and
115 adult liver transplant patients, respectively. In man, less than 1% of the dose
116 administered is excreted unchanged in urine.

117

118 In a mass balance study of IV administered radiolabeled tacrolimus to 6 healthy
119 volunteers, the mean recovery of radiolabel was $77.8 \pm 12.7\%$. Fecal
120 elimination accounted for $92.4 \pm 1.0\%$ and the elimination half-life based on
121 radioactivity was 48.1 ± 15.9 hours whereas it was 43.5 ± 11.6 hours based on

122 tacrolimus concentrations. The mean clearance of radiolabel was $0.029 \pm$
123 0.015 L/hr/kg and clearance of tacrolimus was 0.029 ± 0.009 L/hr/kg.

124

125 When administered PO, the mean recovery of the radiolabel was $94.9 \pm 30.7\%$.
126 Fecal elimination accounted for $92.6 \pm 30.7\%$, urinary elimination accounted for
127 $2.3 \pm 1.1\%$ and the elimination half-life based on radioactivity was 31.9 ± 10.5
128 hours whereas it was 48.4 ± 12.3 hours based on tacrolimus concentrations.
129 The mean clearance of radiolabel was 0.226 ± 0.116 L/hr/kg and clearance of
130 tacrolimus 0.172 ± 0.088 L/hr/kg.

131

132 ***Special Populations***

133 **Pediatrics**

134

135 In a pharmacokinetic study of 14 pediatric atopic dermatitis patients, between
136 the ages of 2-5 years, peak blood concentrations of tacrolimus ranged from
137 undetectable to 14.8 ng/mL after single or multiple doses of 0.03% PROTOPIC
138 Ointment, with 86% (12/14) of patients having peak blood concentrations below
139 2 ng/mL throughout the study.

140

141 The highest peak concentration was observed in one patient with 82% BSA
142 involvement on day 1 following application of 0.03% PROTOPIC Ointment. The
143 peak concentrations for this subject were 14.8 ng/mL on day 1 and 4.1 ng/mL
144 on day 14. Mean peak tacrolimus blood concentrations following oral
145 administration in pediatric liver transplant patients (n = 9) were 43.4 ± 27.9
146 ng/mL.

147

148

149 In a similar pharmacokinetic study with 61 enrolled pediatric patients (ages 6 -
150 12 years) with atopic dermatitis, peak tacrolimus blood concentrations ranged
151 from undetectable to 5.3 ng/mL after single or multiple doses of 0.1%
152 PROTOPIC Ointment, with 91% (52/57) of evaluable patients having peak
153 blood concentrations below 2 ng/mL throughout the study period. When
154 detected, systemic exposure generally declined as treatment continued.

155

156 In clinical studies with periodic blood sampling, a similar distribution of
157 tacrolimus blood levels was also observed, with 98% (509/522) of pediatric
158 patients having a blood concentration below 2 ng/mL.

159

160

161 **Renal Insufficiency**

162 The effect of renal insufficiency on the pharmacokinetics of topically
163 administered tacrolimus has not been evaluated. The mean clearance of IV
164 administered tacrolimus in patients with renal dysfunction was similar to that of
165 normal volunteers. On the basis of this information dose-adjustment is not
166 expected to be needed.

167

168 **Hepatic Insufficiency**

169 The effect of hepatic insufficiency on the pharmacokinetics of topically
170 administered tacrolimus has not been evaluated but dose-adjustment is not
171 expected to be needed.

172

173

174 **CLINICAL STUDIES**

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

186

187 In the pediatric study, a significantly greater ($p < 0.001$) percentage of patients
188 achieved at least 90% improvement based on the physician's global evaluation
189 of clinical response (the pre-defined primary efficacy endpoint) in the
190 PROTOPIC Ointment 0.03% treatment group compared to the vehicle
191 treatment group, but there was insufficient evidence that PROTOPIC Ointment
192 0.1% provided more efficacy than PROTOPIC Ointment 0.03%.

193

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

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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 N = 116	PROTOPIC Ointment 0.03% N = 117	Vehicle Ointment N = 212	PROTOPIC Ointment 0.03% N = 211	PROTOPIC Ointment 0.1% 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%)

212

213 A statistically significant difference in the percentage of adult patients with ≥
214 90% improvement was achieved by week 1 for those treated with PROTOPIC
215 Ointment 0.1%, and by week 3 for those treated with PROTOPIC Ointment
216 0.03%. A statistically significant difference in the percentage of pediatric
217 patients with ≥ 90% improvement was achieved by week 2 for those treated
218 with PROTOPIC Ointment 0.03%.

219

220 In adult patients who had achieved ≥ 90% improvement at the end of treatment,
221 35% of those treated with PROTOPIC Ointment 0.03% and 41% of those
222 treated with PROTOPIC Ointment 0.1%, regressed from this state of
223 improvement at 2 weeks after end-of-treatment. In pediatric patients who had
224 achieved ≥ 90% improvement, 54% of those treated with PROTOPIC Ointment
225 0.03% regressed from this state of improvement at 2 weeks after end-of-
226 treatment. Because patients were not followed for longer than 2 weeks after
227 end-of-treatment, it is not known how many additional patients regressed at
228 periods longer than 2 weeks after cessation of therapy.

229

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

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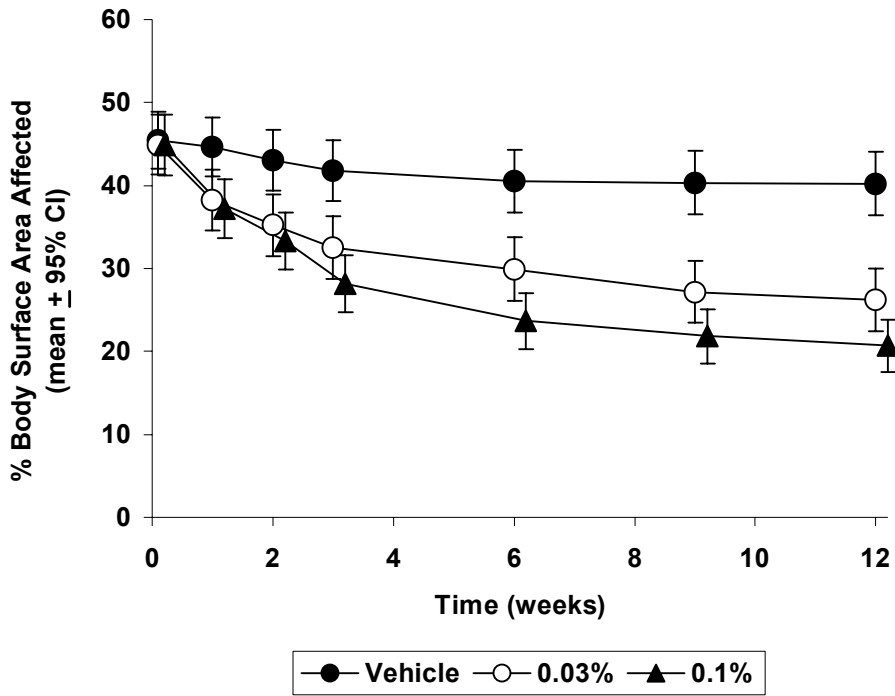
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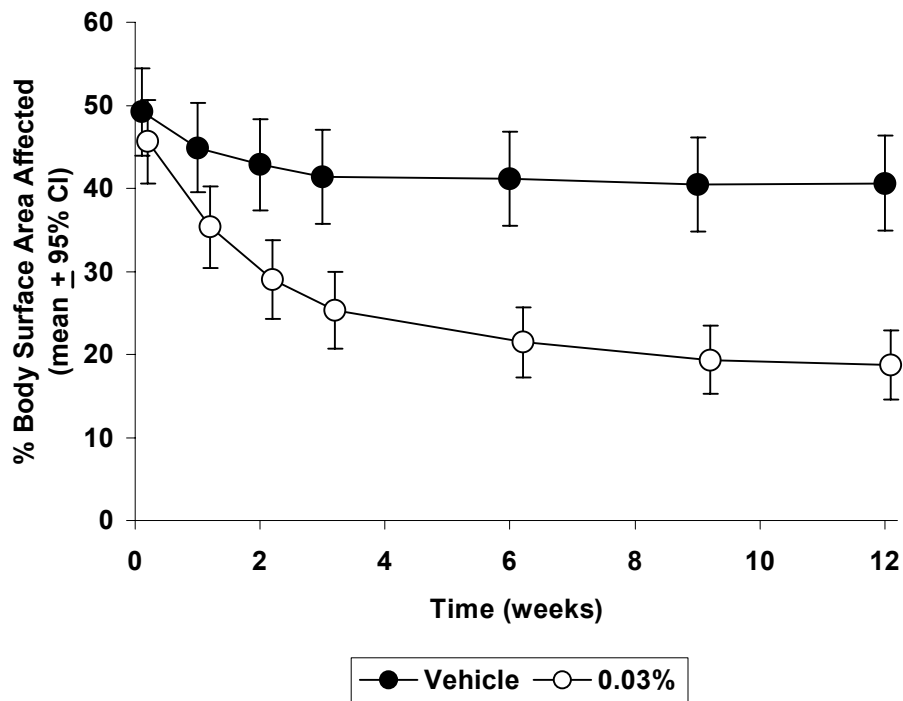
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247 **Figure 1 - Adult Patients Body Surface Area Over Time**



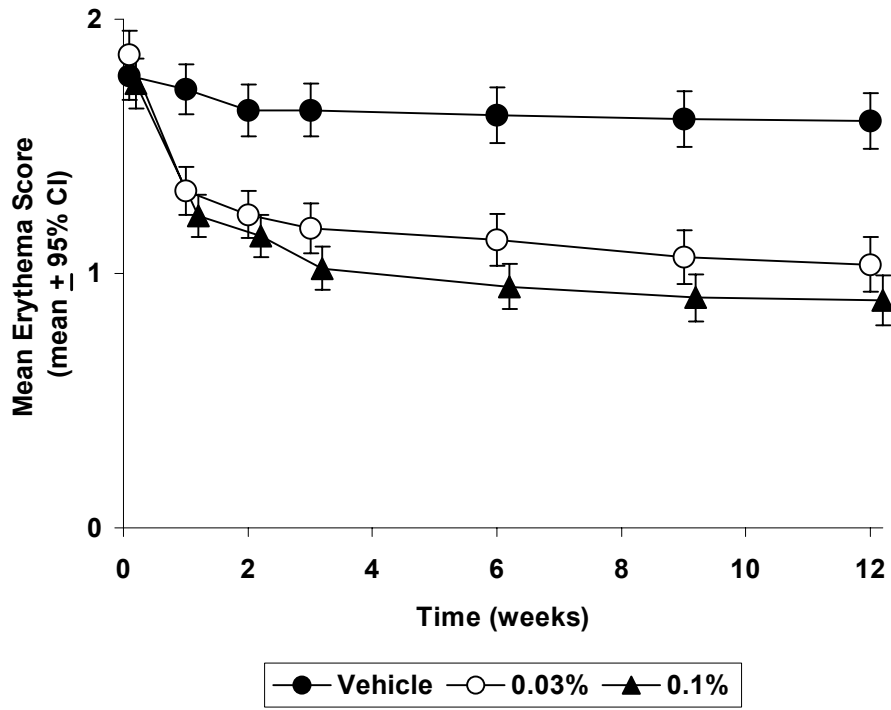
248 **Figure 2 – Pediatric Patients Body Surface Area Over Time**



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

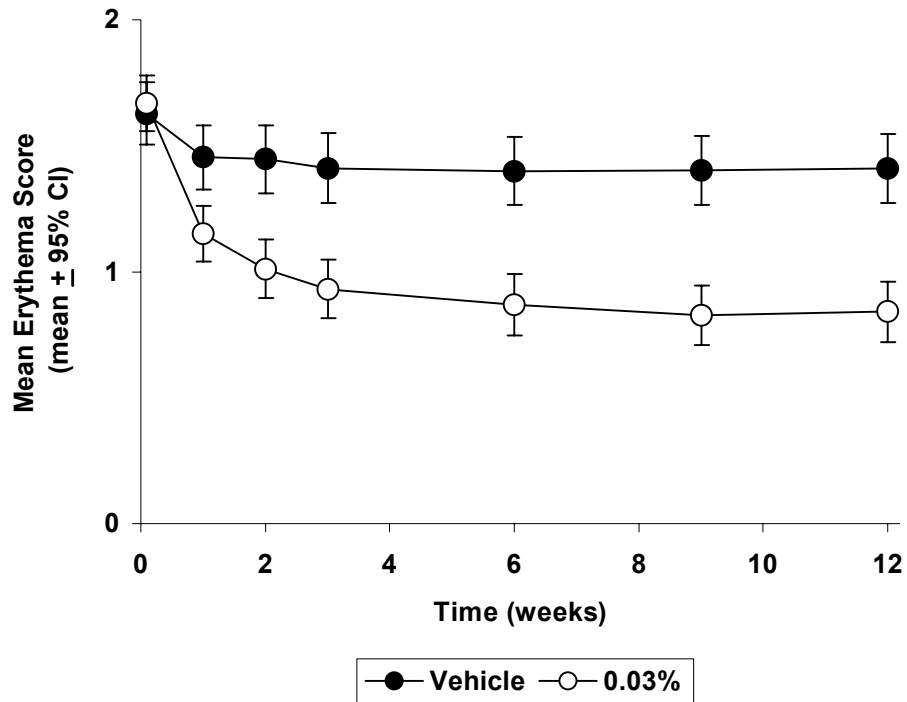
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Figure 3 - Adult Patients Mean Erythema Over Time



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Figure 4 - Pediatric Patients Mean Erythema Over Time



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

259

260 **INDICATIONS AND USAGE**

261 PROTOPIC Ointment, both 0.03% and 0.1% for adults, and only 0.03% for
262 children aged 2 to 15 years, is indicated as *second-line therapy* for the short-
263 term and non-continuous chronic treatment of moderate to severe atopic
264 dermatitis in non-immunocompromised adults and children who have failed to
265 respond adequately to other topical prescription treatments for atopic dermatitis,
266 or when those treatments are not advisable.

267

268 **PROTOPIC Ointment is not indicated for children younger than 2 years of**
269 **age (see boxed WARNING, WARNINGS and PRECAUTIONS: Pediatric**
270 **Use).**

271

272

273 **CONTRAINDICATIONS**

274 PROTOPIC (tacrolimus) Ointment is contraindicated in patients with a history of
275 hypersensitivity to tacrolimus or any other component of the ointment.

276

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279 **WARNINGS**

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WARNING

Long-term Safety of Topical Calcineurin Inhibitors Has Not Been Established

Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including PROTOPIC Ointment.

Therefore:

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

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Prolonged systemic use of calcineurin inhibitors for sustained immunosuppression in animal studies and transplant patients following systemic administration has been associated with an increased risk of infections, lymphomas, and skin malignancies. These risks are associated with the intensity and duration of immunosuppression.

Based on the information above and the mechanism of action, there is a concern about potential risk with the use of topical calcineurin inhibitors, including PROTOPIC Ointment. While 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. Therefore:

- PROTOPIC Ointment should not be used in immunocompromised adults and children.
- If signs and symptoms of atopic dermatitis do not improve within 6 weeks, patients should be re-examined by their healthcare provider and their diagnosis be confirmed (see PRECAUTIONS: General).
- The safety of PROTOPIC Ointment has not been established beyond one year of non-continuous use.

(See **CLINICAL PHARMACOLOGY**, boxed **WARNING**, **INDICATIONS AND USAGE**, and **DOSAGE AND ADMINISTRATION**).

PRECAUTIONS
General

The use of PROTOPIC Ointment 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.

The use of PROTOPIC Ointment in patients with Netherton’s Syndrome or other skin diseases where there is the potential for increased systemic absorption of tacrolimus is not recommended. The safety of PROTOPIC Ointment has not been established in patients with generalized erythroderma.

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

328

329

330 **Bacterial and Viral Skin Infections**

331 Before commencing treatment with PROTOPIC Ointment, cutaneous bacterial
332 or viral infections at treatment sites should be resolved. Studies have not
333 evaluated the safety and efficacy of PROTOPIC Ointment in the treatment of
334 clinically infected atopic dermatitis.

335

336 While patients with atopic dermatitis are predisposed to superficial skin
337 infections including eczema herpeticum (Kaposi's varicelliform eruption),
338 treatment with PROTOPIC Ointment may be independently associated with an
339 increased risk of varicella zoster virus infection (chicken pox or shingles),
340 herpes simplex virus infection, or eczema herpeticum.

341

342 **Patients with Lymphadenopathy**

343 In clinical studies, 112/13494 (0.8%) cases of lymphadenopathy were reported
344 and were usually related to infections (particularly of the skin) and noted to
345 resolve upon appropriate antibiotic therapy. Of these 112 cases, the majority
346 had either a clear etiology or were known to resolve. Transplant patients
347 receiving immunosuppressive regimens (e.g., systemic tacrolimus) are at
348 increased risk for developing lymphoma; therefore, patients who receive
349 PROTOPIC Ointment and who develop lymphadenopathy should have the
350 etiology of their lymphadenopathy investigated. In the absence of a clear
351 etiology for the lymphadenopathy, or in the presence of acute infectious
352 mononucleosis, PROTOPIC Ointment should be discontinued. Patients who
353 develop lymphadenopathy should be monitored to ensure that the
354 lymphadenopathy resolves.

355

356 **Sun Exposure**

357 During the course of treatment, patients should minimize or avoid natural or
358 artificial sunlight exposure, even while PROTOPIC is not on the skin. It is not
359 known whether PROTOPIC Ointment interferes with skin response to ultraviolet
360 damage.

361

362 **Immunocompromised Patients**

363 The safety and efficacy of PROTOPIC Ointment in immunocompromised
364 patients have not been studied.

365

366 **Renal Insufficiency**

367 Rare post-marketing cases of acute renal failure have been reported in patients
368 treated with PROTOPIC Ointment. Systemic absorption is more likely to occur
369 in patients with epidermal barrier defects especially when PROTOPIC is applied
370 to large body surface areas. Caution should also be exercised in patients
371 predisposed to renal impairment.

372

373 **Information for Patients**

374 **(See Medication Guide)**

375 Patients using PROTOPIC Ointment should receive and understand the
376 information in the Medication Guide. Please refer to the Medication Guide for
377 providing instruction and information to the patient.

378

379 **What is the most important information patients should know about**
380 **PROTOPIC Ointment?**

381 The safety of using PROTOPIC Ointment for a long period of time is not known.
382 A very small number of people who have used PROTOPIC Ointment have had
383 cancer (for example, skin or lymphoma). However, a link with PROTOPIC
384 Ointment has not been shown. Because of this concern, instruct patients:

- 385 • Do not use PROTOPIC Ointment continuously for a long time.
- 386 • Use PROTOPIC Ointment only on areas of skin that have eczema.
- 387 • Do not use PROTOPIC Ointment on a child under 2 years old.

388 **PROTOPIC Ointment comes in two strengths:**

- 389 • Only PROTOPIC Ointment 0.03% is for use on children aged 2 to 15
390 years.
- 391 • Either PROTOPIC Ointment 0.03% or 0.1% can be used by adults and
392 children 16 years and older.

393 Advise patients to talk to their prescriber for more information.

394

395 **How should PROTOPIC Ointment be used?**

396

397 Advise patients to:

- 398 • Use PROTOPIC Ointment exactly as prescribed.
- 399 • Use PROTOPIC Ointment only on areas of skin that have eczema.
- 400 • Use PROTOPIC Ointment for short periods, and if needed, treatment
401 may be repeated with breaks in between.
- 402 • Stop PROTOPIC Ointment when the signs and symptoms of eczema,
403 such as itching, rash, and redness go away, or as directed.
- 404 • Follow their doctor's advice if symptoms of eczema return after treatment
405 with PROTOPIC Ointment.
- 406 • Call their doctor if:
 - 407 • Their symptoms get worse with PROTOPIC Ointment.

- 408
- They get an infection on their skin.
- 409
- Their symptoms do not improve after 6 weeks of treatment.
- 410
- Sometimes other skin diseases can look like eczema.

411
412

413 **To apply PROTOPIC Ointment:**

414

415 Advise patients:

- 416
- Wash their hands before applying PROTOPIC.
- 417
- Apply a thin layer of PROTOPIC Ointment twice daily to the areas of skin affected by eczema.
- 418
- Use the smallest amount of PROTOPIC Ointment needed to control the signs and symptoms of eczema.
- 419
- If they are a caregiver applying PROTOPIC Ointment to a patient, or if they are a patient who is not treating their hands, wash their hands with soap and water after applying PROTOPIC. This should remove any ointment left on the hands.
- 420
- Do not bathe, shower, or swim right after applying PROTOPIC. This could wash off the ointment.
- 421
- Moisturizers can be used with PROTOPIC Ointment. Make sure they check with their doctor first about the products that are right for them. Because the skin of patients with eczema can be very dry, it is important to keep up good skin care practices. If they use moisturizers, apply them after PROTOPIC Ointment.
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437 **What should patients avoid while using PROTOPIC Ointment?**

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439 Advise patients:

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- Do not use ultraviolet light therapy, sun lamps, or tanning beds during treatment with PROTOPIC Ointment.
- 441
- Limit sun exposure during treatment with PROTOPIC Ointment even when the medicine is not on their skin. If patients need to be outdoors after applying PROTOPIC Ointment, wear loose fitting clothing that protects the treated area from the sun. Doctors should advise what other types of protection from the sun patients should use.
- 442
- Do not cover the skin being treated with bandages, dressings or wraps. Patients can wear normal clothing.
- 443
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- 449 • Avoid getting PROTOPIC Ointment in the eyes or mouth. Do not
450 swallow PROTOPIC Ointment. Patients should call their doctor if they
451 swallow PROTOPIC Ointment.

452

453 **Drug Interactions**

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

462

463 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

469

470 Oral (feed) carcinogenicity studies have been carried out with systemically
471 administered tacrolimus in male and female rats and mice. In the 80-week
472 mouse study and in the 104-week rat study no relationship of tumor incidence
473 to tacrolimus dosage was found at daily doses up to 3 mg/kg [9X the Maximum
474 Recommended Human Dose (MRHD) based on AUC comparisons] and 5
475 mg/kg (3X the MRHD based on AUC comparisons), respectively.

476

477 A 104-week dermal carcinogenicity study was performed in mice with
478 tacrolimus ointment (0.03% - 3%), equivalent to tacrolimus doses of 1.1-118
479 mg/kg/day or 3.3-354 mg/m²/day. In the study, the incidence of skin tumors
480 was minimal and the topical application of tacrolimus was not associated with
481 skin tumor formation under ambient room lighting. However, a statistically
482 significant elevation in the incidence of pleomorphic lymphoma in high dose
483 male (25/50) and female animals (27/50) and in the incidence of
484 undifferentiated lymphoma in high dose female animals (13/50) was noted in
485 the mouse dermal carcinogenicity study. Lymphomas were noted in the mouse
486 dermal carcinogenicity study at a daily dose of 3.5 mg/kg (0.1% tacrolimus
487 ointment) (26X MRHD based on AUC comparisons). No drug-related tumors
488 were noted in the mouse dermal carcinogenicity study at a daily dose of 1.1
489 mg/kg (0.03% tacrolimus ointment) (10X MRHD based on AUC comparisons).

490

491 In a 52-week photocarcinogenicity study, the median time to onset of skin tumor
492 formation was decreased in hairless mice following chronic topical dosing with
493 concurrent exposure to UV radiation (40 weeks of treatment followed by 12
494 weeks of observation) with tacrolimus ointment at ≥0.1% tacrolimus.

495
496 Reproductive toxicology studies were not performed with topical tacrolimus. In
497 studies of oral tacrolimus no impairment of fertility was seen in male and female
498 rats. Tacrolimus, given orally at 1.0 mg/kg (0.12X MRHD based on body
499 surface area [BSA]) to male and female rats, prior to and during mating, as well
500 as to dams during gestation and lactation, was associated with embryoletality
501 and with adverse effects on female reproduction. Effects on female
502 reproductive function (parturition) and embryoletal effects were indicated by a
503 higher rate of pre-implantation loss and increased numbers of undelivered and
504 nonviable pups. When given at 3.2 mg/kg (0.43X MRHD based on BSA),
505 tacrolimus was associated with maternal and paternal toxicity as well as
506 reproductive toxicity including marked adverse effects on estrus cycles,
507 parturition, pup viability, and pup malformations.

508

509 **Pregnancy**

510 **Teratogenic Effects: Pregnancy Category C**

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

515

516 Reproduction studies were carried out with systemically administered
517 tacrolimus in rats and rabbits. Adverse effects on the fetus were observed
518 mainly at oral dose levels that were toxic to dams. Tacrolimus at oral doses of
519 0.32 and 1.0 mg/kg (0.04X-0.12X MRHD based on BSA) during organogenesis
520 in rabbits was associated with maternal toxicity as well as an increase in
521 incidence of abortions. At the higher dose only, an increased incidence of
522 malformations and developmental variations was also seen. Tacrolimus, at oral
523 doses of 3.2 mg/kg during organogenesis in rats, was associated with maternal
524 toxicity and caused an increase in late resorptions, decreased numbers of live
525 births, and decreased pup weight and viability. Tacrolimus, given orally at 1.0
526 and 3.2 mg/kg (0.04X-0.12X MRHD based on BSA) to pregnant rats after
527 organogenesis and during lactation, was associated with reduced pup weights.

528

529 No reduction in male or female fertility was evident.

530

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

537

538 **Nursing Mothers**

539 Although systemic absorption of tacrolimus following topical applications of
540 PROTOPIC Ointment is minimal relative to systemic administration, it is known

541 that tacrolimus is excreted in human milk. Because of the potential for serious
542 adverse reactions in nursing infants from tacrolimus, a decision should be made
543 whether to discontinue nursing or to discontinue the drug, taking into account
544 the importance of the drug to the mother.

545

546 **Pediatric Use**

547

548 **PROTOPIC Ointment is not indicated for children less than 2 years of age.**

549

550

551 Only the lower concentration, 0.03%, of PROTOPIC Ointment is recommended
552 for use as a *second-line therapy* for short-term and non-continuous chronic
553 treatment of moderate to severe atopic dermatitis in non-immunocompromised
554 children 2 to 15 years of age who have failed to respond adequately to other
555 topical prescription treatments for atopic dermatitis, or when those treatments
556 are not advisable.

557

558 The long-term safety and effects of PROTOPIC Ointment on the developing
559 immune system are unknown (see boxed **WARNING**, **WARNINGS** and
560 **INDICATIONS and USAGE**).

561

562 Four studies were conducted involving a total of about 4,400 patients 2-15
563 years of age: one 12-week randomized vehicle-controlled study and three open-
564 label safety studies of one to three years duration. About 2,500 of these
565 patients were 2 to 6 years of age.

566

567

568 The most common adverse events from these studies associated with
569 PROTOPIC Ointment application in pediatric patients were skin burning and
570 pruritus (see **ADVERSE REACTIONS**). In addition to skin burning and pruritus,
571 the less common events (< 5%) of varicella zoster (mostly chicken pox), and
572 vesiculobullous rash were more frequent in patients treated with PROTOPIC
573 Ointment 0.03% compared to vehicle. In the open-label safety studies, the
574 incidence of adverse events, including infections, did not increase with
575 increased duration of study drug exposure or amount of ointment used. In
576 about 4,400 pediatric patients treated with PROTOPIC Ointment, 24 (0.5%)
577 were reported with eczema herpeticum. Since the safety and efficacy of
578 PROTOPIC Ointment have not been established in pediatric patients below 2
579 years of age, its use in this age group is not recommended.

580

581 In an open-label study, immune response to a 23-valent pneumococcal
582 polysaccharide vaccine was assessed in 23 children 2 to 12 years old with
583 moderate to severe atopic dermatitis treated with tacrolimus ointment 0.03%.
584 Protective antibody titers developed in all patients. Similarly, in a seven-month,
585 double-blind trial, the vaccination response to meningococcal serogroup C was
586 equivalent in children 2 to 11 years old with moderate to severe atopic

587 dermatitis treated with tacrolimus ointment 0.03% (n=121), a hydrocortisone
 588 ointment regimen (n=111), or normal children (n=44).

589

590

591 **Geriatric Use**

592 Four hundred and four (404) patients ≥ 65 years old received PROTOPIC
 593 Ointment in phase 3 studies. The adverse event profile for these patients was
 594 consistent with that for other adult patients.

595

596 **ADVERSE REACTIONS**

597 No phototoxicity and no photoallergenicity were detected in clinical studies with
 598 12 and 216 normal volunteers, respectively. One out of 198 normal volunteers
 599 showed evidence of sensitization in a contact sensitization study.

600

601 In three 12 week randomized vehicle-controlled studies and four safety studies,
 602 655 and 9,163 patients respectively, were treated with PROTOPIC Ointment.
 603 The duration of follow-up for adult and pediatric patients in the safety studies is
 604 tabulated below.

605

606

Duration of Follow-up in Four Open-label Safety Studies

Time on Study	Adult	Pediatrics	Total
< 1 year	4682	4481	9163
≥ 1 year	1185	1349	2534
≥ 2 years	200	275	475
≥ 3 years	118	182	300

607

608 The following table depicts the adjusted incidence of adverse events pooled
 609 across the 3 identically designed 12-week controlled studies for patients in
 610 vehicle, PROTOPIC Ointment 0.03%, and PROTOPIC Ointment 0.1%
 611 treatment groups. The table also depicts the unadjusted incidence of adverse
 612 events in four safety studies, regardless of relationship to study drug.

613

614

615

Incidence of Treatment Emergent Adverse Events

	12-Week, Randomized, Double-Blind, Phase 3 Studies 12-Week Adjusted Incidence Rate (%)					Open-Label Studies (up to 3 years) 0.1% and 0.03% Tacrolimus Ointment Incidence Rate (%)		
	Adult			Pediatric		Adult	Pediatric	Total
	Vehicle (n=212) %	0.03% Tacrolimus Ointment (n=210) %	0.1% Tacrolimus Ointment (n=209) %	Vehicle (n=116) %	0.03% Tacrolimus Ointment (n=118) %	(n=4682) %	(n=4481) %	(n=9163) %
Skin Burning†	26	46	58	29	43	28	20	24
Pruritus†	37	46	46	27	41	25	19	22
Flu-like symptoms†	19	23	31	25	28	22	34	28
Allergic Reaction	8	12	6	8	4	9	13	11
Skin Erythema	20	25	28	13	12	12	7	9
Headache†	11	20	19	8	5	13	9	11

Skin Infection	11	12	5	14	10	9	16	12
Fever	4	4	1	13	21	2	14	8
Infection	1	1	2	9	7	6	10	8
Cough Increased	2	1	1	14	18	3	10	6
Asthma	4	6	4	6	6	4	13	8
Herpes Simplex	4	4	4	2	0	4	3	3
Eczema Herpeticum	0	1	1	0	2	0	0	0
Pharyngitis	3	3	4	11	6	4	12	8
Accidental Injury	4	3	6	3	6	6	8	7
Pustular Rash	2	3	4	3	2	2	7	5
Folliculitis†	1	6	4	0	2	4	2	3
Rhinitis	4	3	2	2	6	2	4	3
Otitis Media	4	0	1	6	12	2	11	6
Sinusitis†	1	4	2	8	3	6	7	6
Diarrhea	3	3	4	2	5	2	4	3
Urticaria	3	3	6	1	1	3	4	4
Lack of Drug Effect	1	1	0	1	1	6	6	6
Bronchitis	0	2	2	3	3	4	4	4
Vomiting	0	1	1	7	6	1	4	3
Maculopapular Rash	2	2	2	3	0	2	1	1
Rash†	1	5	2	4	2	2	3	3
Abdominal Pain	3	1	1	2	3	1	3	2
Fungal Dermatitis	0	2	1	3	0	2	4	3
Gastroenteritis	1	2	2	3	0	2	4	3
Alcohol Intolerance†	0	3	7	0	0	4	0	2
Acne†	2	4	7	1	0	3	2	3
Sunburn	1	2	1	0	0	2	1	1
Skin Disorder	2	2	1	1	4	2	2	2
Conjunctivitis	0	2	2	2	1	3	3	3
Pain	1	2	1	0	1	2	1	2
Vesiculobullous Rash†	3	3	2	0	4	2	1	1
Lymphadenopathy	2	2	1	0	3	1	2	1
Nausea	4	3	2	0	1	2	1	2
Skin Tingling†	2	3	8	1	2	2	1	1
Face Edema	2	2	1	2	1	1	1	1
Dyspepsia†	1	1	4	0	0	2	2	2
Dry Skin	7	3	3	0	1	1	1	1
Hyperesthesia†	1	3	7	0	0	2	0	1
Skin Neoplasm Benign††	1	1	1	0	0	1	2	2
Back Pain†	0	2	2	1	1	3	0	2
Peripheral Edema	2	4	3	0	0	2	0	1
Varicella Zoster/Herpes Zoster† ‡	0	1	0	0	5	1	2	2
Contact Dermatitis	1	3	3	3	4	2	2	2
Asthenia	1	2	3	0	0	1	0	1
Pneumonia	0	1	1	2	0	1	3	2
Eczema	2	2	2	0	0	1	0	1
Insomnia	3	4	3	1	1	2	0	1
Exfoliative Dermatitis	3	3	1	0	0	0	1	0
Dysmenorrhea	2	4	4	0	0	2	1	1
Periodontal Abscess	1	0	1	0	0	1	1	1
Myalgia†	0	3	2	0	0	2	1	1
Cyst†	0	1	3	0	0	1	0	1
Cellulitis	1	1	1	0	0	1	1	1
Exacerbation of Untreated Area	1	0	1	1	0	1	1	1
Procedural Complication	1	0	0	1	0	1	1	1
Hypertension	0	0	1	0	0	2	0	1
Tooth Disorder	0	1	1	1	0	2	1	1
Arthralgia	1	1	3	2	0	2	1	2
Depression	1	2	1	0	0	1	0	1
Paresthesia	1	3	3	0	0	2	1	2
Alopecia	0	1	1	0	0	1	1	1
Urinary Tract Infection	0	0	1	0	0	2	1	2

Ear Pain	1	0	1	0	1	0	1	1
----------	---	---	---	---	---	---	---	---

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

617 ‡ All the herpes zoster cases in the pediatric 12-week study and the majority of cases in the
618 open-label pediatric studies were reported as chicken pox.

619 †† Generally “warts”.

620

621 Other adverse events which occurred at an incidence between 0.2% and less
622 than 1% in clinical studies in the above table include: abnormal vision,
623 abscess, anaphylactoid reaction, anemia, anorexia, anxiety, arthritis, arthrosis,
624 bilirubinemia, blepharitis, bone disorder, breast neoplasm benign, bursitis,
625 cataract NOS, chest pain, chills, colitis, conjunctival edema, constipation,
626 cramps, cutaneous moniliasis, cystitis, dehydration, dizziness, dry eyes, dry
627 mouth/nose, dyspnea, ear disorder, ecchymosis, edema, epistaxis, eye pain,
628 furunculosis, gastritis, gastrointestinal disorder, hernia, hypercholesterolemia,
629 hypertonia, hypothyroidism, joint disorder, laryngitis, leukoderma, lung disorder,
630 malaise, migraine, moniliasis, mouth ulceration, nail disorder, neck pain,
631 neoplasm benign, oral moniliasis, otitis externa, photosensitivity reaction, rectal
632 disorder, seborrhea, skin carcinoma, skin discoloration, skin hypertrophy, skin
633 ulcer, stomatitis, tendon disorder, thinking abnormal, tooth caries, sweating,
634 syncope, tachycardia, taste perversion, unintended pregnancy, vaginal
635 moniliasis, vaginitis, valvular heart disease, vasodilatation, and vertigo.

636

637 **Post-Marketing Events**

638 The following adverse reactions have been identified during postapproval use of
639 PROTOPIC Ointment. Because these reactions are reported voluntarily from a
640 population of uncertain size, it is not always possible to reliably estimate their
641 frequency or establish a causal relationship to drug exposure.

642

643 **CNS**

644 Seizures

645

646 **Neoplasms**

647 Lymphomas, basal cell carcinoma, squamous cell carcinoma, malignant
648 melanoma

649

650 **Infections**

651 Bullous impetigo, osteomyelitis, septicemia

652

653 **Renal**

654 Acute renal failure in patients with or without Netherton’s syndrome, renal
655 impairment

656

657 **Skin**

658 Rosacea

659

660

661 **OVERDOSAGE**

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

665

666 **DOSAGE AND ADMINISTRATION**

667 **Adult**

668 **PROTOPIC Ointment 0.03% and 0.1%**

669 • Apply a thin layer of PROTOPIC (tacrolimus) Ointment to the affected
670 skin twice daily. The minimum amount should be rubbed in gently and
671 completely to control signs and symptoms of atopic dermatitis. Stop
672 using when signs and symptoms of atopic dermatitis resolve.

673 • If signs and symptoms (e.g. itch, rash, and redness) do not improve
674 within 6 weeks, patients should be re-examined by their healthcare
675 provider to confirm the diagnosis of atopic dermatitis.

676 • Continuous long-term use of topical calcineurin inhibitors, including
677 PROTOPIC Ointment should be avoided, and application should be
678 limited to areas of involvement with atopic dermatitis.

679 The safety of PROTOPIC Ointment under occlusion, which may promote
680 systemic exposure, has not been evaluated. PROTOPIC Ointment should not
681 be used with occlusive dressings.

682

683 **PEDIATRIC – FOR CHILDREN 2-15 YEARS**

684 **PROTOPIC Ointment 0.03%**

685 • Apply a thin layer of PROTOPIC (tacrolimus) Ointment, 0.03% to the
686 affected skin twice daily. The minimum amount should be rubbed in
687 gently and completely to control signs and symptoms of atopic
688 dermatitis. Stop using when signs and symptoms of atopic dermatitis
689 resolve.

690 • If signs and symptoms (e.g. itch, rash, and redness) do not improve
691 within 6 weeks, patients should be re-examined by their healthcare
692 provider to confirm the diagnosis of atopic dermatitis.

693

694 • Continuous long-term use of topical calcineurin inhibitors, including
695 PROTOPIC Ointment should be avoided, and application should be
696 limited to areas of involvement with atopic dermatitis.

697 The safety of PROTOPIC Ointment under occlusion, which may promote
698 systemic exposure, has not been evaluated. PROTOPIC Ointment should not
699 be used with occlusive dressings.

700

701 **HOW SUPPLIED**

702 **PROTOPIC® (tacrolimus) Ointment 0.03%**

703

704 NDC 0469-5201-30 Product Code 520130
705 30 gram laminate tube
706
707 NDC 0469-5201-60 Product Code 520160
708 60 gram laminate tube
709
710 NDC 0469-5201-11 Product Code 520111
711 100 gram laminate tube
712

713
714 **PROTOPIC® (tacrolimus) Ointment 0.1%**
715

716 NDC 0469-5202-30 Product Code 520230
717 30 gram laminate tube
718
719 NDC 0469-5202-60 Product Code 520260
720 60 gram laminate tube
721
722 NDC 0469-5202-11 Product Code 520211
723 100 gram laminate tube
724

725 Store at room temperature 25°C (77°F); excursions permitted to 15°-30°C (59°-
726 86°F).
727

728 **Marketed by:**
729 Astellas Pharma US, Inc.
730 Deerfield, IL 60015-2548
731

732 **Manufactured by:**
733 Astellas Pharma Manufacturing, Inc.
734 Grand Island, NY 14072
735

736

737

738

MEDICATION GUIDE

739

740

PROTOPIC® [pro-TOP-ik]
(tacrolimus)

741

742

743

Ointment 0.03%

744

Ointment 0.1%

745

746

747

748 Read the Medication Guide every time you or a family member gets PROTOPIC Ointment. There may
749 be new information. This Medication Guide does not take the place of talking to your doctor about your
750 medical condition or treatment. If you have questions about PROTOPIC Ointment, ask your doctor or
751 pharmacist.

751

752 **What is the most important information I should know about PROTOPIC Ointment?**

753 The safety of using PROTOPIC Ointment for a long period of time is not known. A very small number
754 of people who have used PROTOPIC Ointment have had cancer (for example, skin or lymphoma).
755 However, a link with PROTOPIC Ointment has not been shown. Because of this concern:

- 756 • Do not use PROTOPIC Ointment continuously for a long time.
- 757 • Use PROTOPIC Ointment only on areas of your skin that have eczema.
- 758 • Do not use PROTOPIC Ointment on a child under 2 years old.

759 **PROTOPIC Ointment comes in two strengths:**

- 760 • Only PROTOPIC Ointment 0.03% is for use on children aged 2 to 15 years.
- 761 • Either PROTOPIC Ointment 0.03% or 0.1% can be used by adults and children 16 years and
762 older.

763 Talk to your doctor for more information.

764

765 **What is PROTOPIC Ointment?**

766 PROTOPIC Ointment is a prescription medicine used on the skin (topical) to treat eczema (atopic
767 dermatitis). PROTOPIC Ointment is in a class of medicines called topical calcineurin inhibitors. It is for
768 adults and children 2 years of age and older who do not have a weakened immune system. PROTOPIC
769 Ointment is used on the skin for short periods, and if needed, treatment may be repeated with breaks in
770 between.

771 PROTOPIC Ointment is for use after other prescription medicines have not worked for you, or if your
772 doctor recommends that other prescription medicines should not be used.

773

774 **Who should not use PROTOPIC Ointment?**

775

776 **PROTOPIC Ointment should not be used:**

777

- 778 • on children younger than 2 years of age.
- 779 • if you are allergic to PROTOPIC Ointment or anything in it. See the end of this Medication
780 Guide for a complete list of ingredients.
- 781
- 782
- 783

784 **What should I tell my doctor before starting PROTOPIC Ointment?**

785

786 Before you start using PROTOPIC, you and your doctor should talk about all of your medical conditions,
787 including if you:

788

- 789 • have a skin disease called Netherton's syndrome (a rare inherited condition).
- 790 • have any infection on your skin including chicken pox or herpes.
- 791 • have been told you have a weakened immune system.
- 792 • are pregnant, breastfeeding, or planning to become pregnant.

793 Tell your doctor about all the medicines you take and skin products you use including prescription and
794 nonprescription medicines, vitamins, and herbal supplements.

795 Know the medicines you take. Keep a list of them with you to show your doctor and pharmacist each
796 time you get a new medicine.

797

798

799 **How should I use PROTOPIC Ointment?**

800

801 • Use PROTOPIC Ointment exactly as prescribed.

802

• Use PROTOPIC Ointment only on areas of your skin that have eczema.

803

• Use PROTOPIC Ointment for short periods, and if needed, treatment may be repeated with
804 breaks in between.

805

• Stop PROTOPIC Ointment when the signs and symptoms of eczema, such as itching, rash, and
806 redness go away, or as directed by your doctor.

807

• Follow your doctor's advice if symptoms of eczema return after treatment with PROTOPIC
808 Ointment.

809

• Call your doctor if :

810

• your symptoms get worse with PROTOPIC Ointment.

811

• you get an infection on your skin.

812

• your symptoms do not improve after 6 weeks of treatment. Sometimes other skin diseases
813 can look like eczema.

814

815 **To apply PROTOPIC Ointment:**

816

• Wash your hands before applying PROTOPIC.

817

• Apply a thin layer of PROTOPIC Ointment twice daily to the areas of skin affected by eczema.

818

819

• Use the smallest amount of PROTOPIC Ointment needed to control the signs and symptoms of
820 eczema.

821

822

• *If you are a caregiver applying PROTOPIC Ointment to a patient, or if you are a patient who is
823 not treating your hands, wash your hands with soap and water after applying PROTOPIC. This
824 should remove any ointment left on the hands.*

825

826

• Do not bathe, shower, or swim right after applying PROTOPIC. This could wash off the
827 ointment.

828

829

• You can use moisturizers with PROTOPIC Ointment. Make sure you check with your doctor
830 first about the products that are right for you. Because the skin of patients with eczema can be
831 very dry, it is important to keep up good skin care practices. If you use moisturizers, apply them
832 after PROTOPIC Ointment.

833

834

835

836 **What should I avoid while using PROTOPIC Ointment?**

837

838

• Do not use ultraviolet light therapy, sun lamps, or tanning beds during treatment with
839 PROTOPIC Ointment.

- 840
- 841
- 842
- 843
- Limit sun exposure during treatment with PROTOPIC Ointment even when the medicine is not on your skin. If you need to be outdoors after applying PROTOPIC Ointment, wear loose fitting clothing that protects the treated area from the sun. Ask your doctor what other types of protection from the sun you should use.
- 844
- Do not cover the skin being treated with bandages, dressings or wraps. You can wear normal clothing.
- 845
- Avoid getting PROTOPIC Ointment in the eyes or mouth. Do not swallow PROTOPIC Ointment. If you do, call your doctor.
- 846
- 847
- 848
- 849

850 **What are the possible side effects of PROTOPIC Ointment?**

851

852 **Please read the first section of this Medication Guide.**

853

854 **The most common side effects** of PROTOPIC Ointment at the skin application site are stinging, burning, 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 usually go away as your skin heals.

856

857

858 **Other side effects** include acne, swollen or infected hair follicles, headache, increased sensitivity of the skin to hot or cold temperatures, or flu-like symptoms such as the common cold and stuffy nose, skin tingling, upset stomach, muscle pain, swollen glands (enlarged lymph nodes), or skin infections including cold sores, chicken pox or shingles.

859

860

861

862

863 Talk to your doctor if you have a skin infection or if side effects (for example, swollen glands) continue or bother you.

864

865

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

867

868

869 These are not all the side effects with PROTOPIC Ointment. Ask your doctor or pharmacist for more information.

870

871 **How should I store PROTOPIC Ointment?**

872

- Store PROTOPIC Ointment at room temperature (59° to 86°F). Do not leave PROTOPIC Ointment in your car in cold or hot weather. Make sure the cap on the tube is tightly closed.

873

874

875

- **Keep PROTOPIC Ointment and all medicines out of the reach of children.**

876

877

878

879 **General advice about PROTOPIC Ointment**

880

881 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use PROTOPIC Ointment for a condition for which it was not prescribed. Do not give PROTOPIC Ointment to other people, even if they have the same symptoms you have. It may not be right for them.

882

883

884 This Medication Guide summarizes the most important information about PROTOPIC Ointment. If you would like more information, talk with your doctor.

885

886

887 Your doctor or pharmacist can give you information about PROTOPIC Ointment that is written for health care professionals. For more information, you can also visit the PROTOPIC website at www.protopic.com or call 1-800-727-7003.

888

889

890 **What are the ingredients in PROTOPIC Ointment?**

891

892 **Active Ingredient:** tacrolimus, either 0.03% or 0.1%
893 **Inactive Ingredients:** mineral oil, paraffin, propylene carbonate, white petrolatum and white wax.
894
895 Marketed by:
896 Astellas Pharma US, Inc.
897 Deerfield, IL 60015-2548
898
899 Manufactured by:
900 Astellas Pharma Manufacturing, Inc.
901 Grand Island, NY 14072
902
903 This Medication Guide has been approved by the U.S. Food and Drug Administration
904
905 Revised: January 2006
906