

POLICY & PRACTICE

Influenza Update

Federal health officials are applauding the progress made in the first year of vaccinating children between the ages of 6 months and 23 months. As of mid-December, nearly 37% of children in that age group had received the vaccine, according to Julie Gerberding, M.D., director of the Centers for Disease Control and Prevention. "We're considering this a very excellent coverage rate for the first year out," Dr. Gerberding said at a press conference on the influenza vaccine. Dr. Gerberding also addressed charges that officials at the

Health and Human Services Department had inappropriately used state immunization grant funds to purchase additional nonpediatric influenza vaccine from Glaxo-SmithKline in Germany. The money was taken from there, Dr. Gerberding said, because it was the only money available at the time, and it was important to close the deal to procure more vaccine quickly. She added that the children's vaccine money is only available for use by states annually through the end of the calendar year and that \$14 million still remained in the fund during the final days of December.

BRIEF SUMMARY

47002/Issued: December 2000

Protopic® (tacrolimus)

Ointment 0.03%
Ointment 0.1%

FOR DERMATOLOGIC USE ONLY NOT FOR OPHTHALMIC USE

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 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. Reproductive toxicology studies were not performed with topical tacrolimus.

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.

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, 310 (6.3%) 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 or 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				Open-Label Studies (up to 1 year)	
	12-Week Adjusted Incidence Rate (%)				0.1% Tacrolimus Ointment Incidence (%)	
	Adult		Pediatric		Adult	Pediatric
	Vehicle n=212	0.03% Tacrolimus Ointment n=210	0.1% Tacrolimus Ointment n=209	Vehicle n=116	0.03% Tacrolimus Ointment n=116	n=255
Skin Burning ¹	26	46	58	29	43	47
Pruritus ¹	37	46	46	27	41	25
Flu-like symptoms ²	19	23	31	25	28	35
Allergic Reaction	8	12	6	8	4	22
Skin Erythema	20	25	28	13	12	9
Headache ³	11	20	19	8	5	10
Skin Infection	11	12	5	14	10	11
Fever	4	4	1	13	21	2
Infection	1	1	2	9	7	14
Cough Increased	2	1	1	14	18	3
Asthma	4	6	4	6	6	16
Herpes Simplex	4	4	4	2	0	12
Eczema Herpeticum	0	1	1	0	2	0
Pharyngitis	3	3	4	11	6	5
Accidental Injury	4	3	6	3	6	4
Pustular Rash	2	3	4	3	2	6
Folliculitis ⁴	1	6	4	0	2	11
Rhinitis	4	3	2	2	6	5

Teens Delaying Sexual Activity

Sexual activity among younger teenagers declined significantly between 1995 and 2002, while use of contraception increased, according to a study by the Centers for Disease Control and Prevention. Among never-married teenage girls aged 15-17 years, 30% of those surveyed in 2002 had ever had intercourse, compared with 38% in 1995. Among boys who were the same age, the percentage dropped from 43% in 1995 to 31% in 2002. The numbers were more mixed among teens aged 18-19; the percentage of boys in that group who had ever had sex dropped from 75% to 64%, but the percentage

among the girls actually went from 68% to 69%. More than three-quarters used contraception when they began having intercourse. "More teenagers are avoiding or postponing sexual activity, which can lead to sexually transmitted diseases, unwanted pregnancy, or emotional and societal responsibilities for which they are not prepared," according to a statement by the Department of Health and Human Services.

Abstinence Education Evaluated

Federally funded abstinence-only education programs contain errors and misinformation on the effectiveness of condoms, the risks of abortion, and the transmission of disease, according to a recent report from Rep. Henry Waxman (D-Calif.). The report reviewed school-based sex education curricula used by federally funded programs. For example, one curriculum states that data do not support

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FDA Issues Warning for ADHD Drug

The Food and Drug Administration has issued a new warning for atomoxetine HCl concerning the potential for severe liver injury. The drug, indicated for the treatment of attention-deficit hyperactivity disorder in adults and children, has been available since 2002.

Two cases of severe liver injury were reported in a teenager and an adult who had taken atomoxetine (Strattera) for several months. Both patients recovered normal liver function after discontinuing the medication.

The revised labeling will state that severe liver injury may progress to liver failure, which can result in death or the need for an organ transplant. It will point out that because of the possible underreporting of adverse events, the actual number of cases of liver injury is unknown, and atomoxetine should be discontinued in patients who have developed jaundice or have laboratory evidence of liver injury.

Eli Lilly & Co., manufacturer of the medication, will issue "Dear Healthcare Provider" letters to alert prescribers to this new warning. "Our thorough review of the clinical trial and real-world data indicate that the benefit-risk profile for Strattera is positive," Douglas Kelsey, M.D., a pediatrician and clinical research physician with Eli Lilly, said in a written statement.

Patient package inserts will also carry information detailing the signs and symptoms of liver problems.

Reports of any adverse events associated with Strattera can be reported directly to Eli Lilly at 800-LillyRx, or to the FDA's MedWatch program at 800-332-1088. MedWatch forms can be downloaded at <http://www.fda.gov/medwatch/safety/3500.pdf>. The agency can also take reports via fax at 800-FDA-0178, or by mail at MedWatch, HFD-410, FDA, 5600 Fishers Lane, Rockville, MD 20857.

—Deeanna Franklin

Otitis Media	4	0	1	6	12	1	7
Sinusitis ¹	1	4	2	8	3	3	7
Diarhea	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	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 ²	0	3	7	0	0	6	0
Acne ³	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 ¹	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 ¹	2	3	8	1	2	2	1
Face Edema	2	2	1	2	1	3	1
Dyspepsia ⁴	1	1	4	0	0	1	4
Dry Skin	7	3	3	0	1	0	1
Hypersensitivity ¹	1	3	7	0	0	3	0
Skin Neoplasm							
Balanitis ¹	1	1	1	0	0	2	3
Back Pain ¹	0	2	2	1	1	3	1
Peripheral Edema	2	4	3	0	0	2	1
Varicella Zoster ¹							
Herpes Zoster ¹	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 ⁴	0	3	2	0	0	1	0
Cyst ¹	0	1	3	0	0	0	0

¹ May be reasonably associated with the use of this drug product.

² 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.

³ Generally "wants".

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.**

Rx only

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