

FDA Demands Approval Data on Carbinoxamine

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As part of a wider crackdown on the marketing of unapproved drugs, the Food and Drug Administration has notified manufacturers of many unapproved carbinoxamine-containing products that they must submit safety and efficacy data by September or be subject to enforcement action, which could include a forced recall.

The FDA said it was targeting carbinoxamine because of safety concerns, including 21 deaths since 1983 in children under age 2 that may be related to the ingredient. Infants and young children are vulnerable to adverse events with products containing the drug because there are so many different strengths, formulations, and combinations of active ingredients, according to the FDA.

Carbinoxamine, a sedating antihistamine, was first marketed in 1953. Four

products are FDA-approved to treat allergic reactions: Palgic Carbinoxamine Maleate Oral Solution (4 mg/5 mL), PamLab LLC; Palgic Carbinoxamine Maleate Tablets (4 mg), PamLab LLC; Carbinox Maleate Solution, Physicians Total Care; and Palgic Carbinoxamine Maleate Tablets USP (4 mg), Physicians Total Care. All four are manufactured by Mikart Inc. of Atlanta, and were approved in 2003.

"We are satisfied that [these products] meet the FDA approval requirements," said

Deborah M. Autor, FDA associate director for compliance policy, at a press briefing sponsored by the agency. But as many as 120 carbinoxamine-containing drugs are being marketed without the agency's approval, Ms. Autor said, adding that there may be more not listed with the FDA.

Many are sold as prescription cough and cold formulations, but the FDA has not found carbinoxamine to be safe or effective for that indication. And they are often labeled for use in children under age 2, even as young as 1-3 months, said the agency.

Under the new directive, unapproved carbinoxamine products will be allowed to stay on pharmacy shelves through September, said Ms. Autor. But the companies must submit new drug applications by that time.

Before prescribing an unapproved carbinoxamine preparation, physicians should consider the patient's medical condition, previous response to the drug, and whether approved alternatives might be more suitable, according to the FDA.

Physicians, patients, and pharmacists can continue to check the FDA's Web site (www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm) to see if more products have been approved.

Apply Now for New Identifier, Physicians Urged

Physicians need to apply now for a national provider identifier number in order to start using them in May 2007, according to the Centers for Medicare and Medicaid Services.

The national provider identifier (NPI) is a 10-digit number that does not expire or change; it is used to speed claims processing. The Health Insurance Portability and Accountability Act mandates that the NPI be used for all standard health care transactions involving both public and private payers starting on May 23, 2007. Small health plans, defined as having annual receipts of \$5 million or less, are given an additional year to comply.

A physician needs only one NPI, regardless of the number of specialties, licenses, or practice locations he or she may have. Once assigned to the physician, that number will stay with him or her through job changes and relocations.

Physicians will need to have several numbers on hand before applying, such as their health care license number or certificate number and any "legacy identifiers," such as a unique physician identification number (UPIN).

Numbers issued by Medicaid and other health plans also need to be included in the application.

—Nancy Nickell

BRIEF SUMMARY

Revised: January 2006

Protopic® (tacrolimus) Ointment 0.03% Ointment 0.1%

FOR DERMATOLOGIC USE ONLY
NOT FOR OPHTHALMIC USE

Rx Only

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

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 as second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.

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

CONTRAINDICATIONS

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

WARNINGS

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.

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 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).

Bacterial and Viral Skin Infections

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

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

Patients with Lymphadenopathy

In clinical studies, 112/13494 (0.8%) cases of lymphadenopathy were reported and were usually related to infections (particularly of the skin) and noted to resolve upon appropriate antibiotic therapy. Of these 112 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, PROTOPIC Ointment should be discontinued. Patients who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves.

Sun Exposure

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

Immunocompromised Patients

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

Renal Insufficiency

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

Information for Patients

(See Medication Guide)

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

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

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

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

PROTOPIC Ointment comes in two strengths:

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

Advise patients to talk to their prescriber for more information.

How should PROTOPIC Ointment be used?

Advise patients to:

- Use PROTOPIC Ointment exactly as prescribed.
- Use PROTOPIC Ointment only on areas of skin that have eczema.
- Use PROTOPIC Ointment for short periods, and if needed, treatment may be repeated with breaks in between.
- Stop PROTOPIC Ointment when the signs and symptoms of eczema, such as itching, rash, and redness go away, or as directed.
- Follow their doctor's advice if symptoms of eczema return after treatment with PROTOPIC Ointment.
- Call their doctor if:
 - Their symptoms get worse with PROTOPIC Ointment.
 - They get an infection on their skin.
 - Their symptoms do not improve after 6 weeks of treatment. Sometimes other skin diseases can look like eczema.

To apply PROTOPIC Ointment:

Advise patients:

- Wash their hands before applying PROTOPIC.
- Apply a thin layer of PROTOPIC Ointment twice daily to the areas of skin affected by eczema.
- Use the smallest amount of PROTOPIC Ointment needed to control the signs and symptoms of eczema.
- 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 wash off the ointment.
- Do not bathe, shower, or swim right after applying PROTOPIC. This could wash off the ointment.
- 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.

What should patients avoid while using PROTOPIC Ointment?

Advise patients:

- Do not use ultraviolet light therapy, sun lamps, or tanning beds during treatment with PROTOPIC Ointment.
- 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.
- Do not cover the skin being treated with bandages, dressings or wraps. Patients can wear normal clothing.
- Avoid getting PROTOPIC Ointment in the eyes or mouth. Do not swallow PROTOPIC Ointment. Patients should call their doctor if they swallow PROTOPIC Ointment.

Drug Interactions

Formal topical drug interaction studies with PROTOPIC Ointment have not been conducted. Based on its 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 is not indicated for children less than 2 years of age.

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

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

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 open-label safety studies, the incidence of adverse events, including infections, did not increase with increased duration of study drug exposure or amount of ointment used. In about 4,400 pediatric patients treated with PROTOPIC Ointment, 24 (0.5%) were reported with 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

Four hundred and four (404) 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 were detected in clinical studies with 12 and 216 normal volunteers, respectively. One out of 198 normal volunteers showed evidence of sensitization in a contact sensitization study.

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

Adverse Event	12-Week, Randomized, Double-Blind, Phase 3 Studies		Open-Label Studies (up to 3 years)	
	12-Week Adjusted Incidence Rate (%)		6.1% and 6.0% Tacrolimus Ointment Incidence Rate (%)	
	Vehicle (n=102)	PROTOPIC Ointment (n=102)	Adult (n=402)	Pediatric (n=102)
Skin Burning†	26	46	58	29
Pruritus†	37	46	46	27
Flu-like symptoms†	19	23	31	25
Allergic Reaction	8	12	6	8
Skin Erythema	20	25	28	13
Headache†	11	20	19	8
Skin Infection	11	12	5	14
Fever	4	4	1	13
Infection	1	1	2	9
Cough Increased	2	1	1	14
Asthma	4	6	4	6
Herpes Simplex	4	4	4	2
Herpes Malignum	0	1	1	0
Pharyngitis	3	3	4	11
Accidental Injury	4	3	6	3
Pustular Rash	2	3	4	2
Folliculitis	1	6	4	2
Rhinitis	4	3	2	2
Oral Media	4	0	1	6
Sinusitis†	1	4	2	8
Diarrhea	3	3	4	2
Urticaria	3	3	6	1
Lack of Drug Effect	1	1	0	1
Bronchitis	0	2	2	3
Vomiting	0	1	1	7
Maculopapular Rash	2	2	2	3
Rash†	1	5	2	4
Abdominal Pain	3	1	1	4
Fungal Dermatitis	0	2	1	3
Gastroenteritis	1	2	2	3
Alcohol Intolerance†	0	3	7	0
Acne†	2	4	7	1
Sunburn	1	2	1	0
Skin Disorder	2	2	1	1
Conjunctivitis	0	2	2	1
Pain	2	2	1	2
Vesiculobullous Rash†	3	3	2	0
Lymphadenopathy	2	2	1	0
Nausea	4	3	2	1
Skin Tingling†	2	3	8	1
Face Edema	2	2	1	2
Dyspepsia†	1	1	4	0

Dry Skin	7	3	3	0	1	1	1	1
Hypertension†	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
Periorbital Edema	2	4	3	0	0	2	0	1
Varicella Zoster†††	0	1	0	0	5	1	2	2
Herpes Zoster†††	1	3	3	3	4	2	2	2
Congenital Dermatitis	1	2	3	0	0	1	0	1
Asthma	0	1	1	2	0	1	3	2
Pneumonia	2	2	2	0	0	1	0	1
Eczema	3	4	3	1	1	2	0	1
Insomnia	3	3	1	0	0	1	0	1
Exfoliative Dermatitis	3	3	1	0	0	0	1	0
Dysmenorrhea	2	4	4	0	0	2	1	1
Perioral Erythema	1	2	1	0	0	1	1	1
Malignant Cyst†	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
Atrialgia	1	1	3	2	0	2	1	2
Depression	1	2	1	0	0	1	0	1
Parosmia	1	3	3	0	0	2	1	2
Alpecia	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

† May be reasonably associated with the use of this drug product.
†† All the herpes zoster cases in the pediatric 12-week study and the majority of cases in the open-label pediatric studies were reported as chicken pox.
††† Generally warts.

Other adverse events which occurred at an incidence between 0.2% and less than 1% in clinical studies in the above table include: abnormal vision, abscess, anaphylactoid reaction, anemia, anorexia, anxiety, arthritis, arthrosis, bilirubinemia, blepharitis, bone disorder, breast neoplasm benign, bursitis, cataract NOS, chest pain, chills, colitis, conjunctival edema, constipation, cramps, cutaneous moniliasis, cystitis, dehydration, dizziness, dry eyes, dry mouth/dryness, dyspnea, ear disorder, ecchymosis, edema, epistaxis, eye pain, furunculosis, gastritis, gastrointestinal disorder, hernia, hypercholesterolemia, hypertension, hypothyroidism, joint disorder, laryngitis, leukoderma, lung disorder, malaise, migraine