**Practice Trends** 

# FDA Demands Approval Data on Carbinoxamine

BY ALICIA AULT

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s 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), Pam-Lab 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.

### BRIEF SUMMARY Revised: January 2006

### FOR DERMATOLOGIC USE ONLY

Protopic<sup>®</sup>

NOT FOR OPHTHALMIC USE

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

TOPICAL CAPTIONS 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 a second-line hetapy 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.

### 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, reported in patients treated with a ncluding PROTOPIC Ointment.

- Indication:
  Continuous long-term use of topical calcineurin inhibitors including PROTOPIC Ointment, in any age group should b avoided, and application limited to areas of involvemen with atopic dermatitis.
- with adpit definations.

  PROTOPIC Dintment is not indicated for use in children le than 2 years of age. Only 0.03% PROTOPIC Dintment 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

or immunisosppression.

Based on the information above and the mechanism of action, there is a concern about potential risk with the use of topical caclineurin inhibitors, including PROTOPIC Ointment. While a causal relationship has not been established, rare cases of skin maginaroy and lymphoma have been reported in patients treated with topical calcineurin inhibitors, including PROTOPIC Ointment.

- 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

General
The use of PROTOPIC Ointment should be avoided on premalignant and malignant skin conditions. Some malignant skin
conditions, such as cutaneous T-cell lymphoma (CTCL), may
milinic atopic dermatitis.

mimic alopic 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.

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 ew 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).

(medial 20 minutes), (see Adverse Reactions).

Bacterial and Viral Skin Infections
Before commencing treatment with PROTOPIC Ointment,
culaneous 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
steps demandial.

virus inection, or eczena nerpeticum.

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.

lymphagenopatry resurves.

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.

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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 a reas. 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.

to the patient.

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

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 Dintment has not been shown. Because of this concern, instruct patients:

Do not use PROTOPIC Ointment continuously for a long time.

Use PROTOPIC Ointment on a child under 2 years old. PROTOPIC Dintment 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 old

### Advise patients to talk to their prescriber for more information. **How should PROTOPIC Ointment be used?**

- Use PROTOPIC Ointment exactly as prescribed.
- Use PROTOPIC Ointment only on areas of skin that
- 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 litching, rash, and redness go away, or as
- 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 eczerna.

### To apply PROTOPIC Ointment:

- Apply a thin layer of PROTOPIC olintment 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.
- Control the Sights and symposis of execute.

  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.
- Do not bathe, shower, or swim right after applying PROTOPIC. This could wash off the ointment.
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  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 ezerar 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? Adulgs nationals.

- Do not use ultraviolet light therapy, sun lamps, or tanning beds during treatment with PROTOPIC Ointment.
- uning installed in the HOLDPIC 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 avise what other types of protection from the sun patients should use.
- Avoid getting PROTOPIC Ointment in the eyes or mouth. Do not swallow PROTOPIC Ointment. Patients should call their doctor if they swallow PROTOPIC Ointment.

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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 CYPSA4 inhibitors in patients with widespread and/or erythrodermic disease should be done with caution. Some examples of such drugs are erythromycin, itraconazole, ketaconazole, fluconazole, calcium channel blockers and cimetidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No evidence of genotoxicity was seen in bacterial (*Salmonales and Ecofl*) or manmalian (Chinese hamster lung-derived cells) in
vitro assays of mutagenicity, the *in vitro* CHO/H6PRT assay
of mutagenicity, or *in vivo* clastogenicity assays performed in
mice. Tacrolimus did not cause unscheduled DNA synthesis in

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 Onliment when used by pregnant women is too limited
to permit assessment of the safety of its use during pregnancy. to permit assessment on the salety of its use during pregiatory. There are no adequate and well-controlled studies of systemically administered tearolimus in pregnant women. Tacrolimus is transferred across the placenta. The use of systemically administered tearolimus 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 plications of PROTOPIC Ointment is minimal relative to stemic administration, it is known that tacrolimus is excreted in man milk. Because of the potential for serious adverse reactions nursing infants from tacrolimus, a decision should be made ether to discontinue nursing or to discontinue the drug, taking a account the importance of the drug to the mother.

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

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 house)

on the developing immune system are unknown (see boxed WARNING, AND USAGE).

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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 scaler (mostly chicken pox), and vesiculobulous rash were more frequent in patients treated with PROTOPIC Dintment 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 bellow 2 years of age, its use in this age group is not recommended.

Geriatric Use

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IVERSE REACTIONS
phototoxicity and no photoallergenicity were detected in nical studies with 12 and 216 normal volunteers, respectively, e out of 198 normal volunteers showed evidence of issitization in a contact sensitization study.

If following table depicts the adjusted incidence of adverse ents pooled across the 3 identically designed 12-week ntrolled studies for patients in vehicle, PROTOPIC Ointment 39%, and PROTOPIC Ointment 0.1% treatment groups. The Ite also depicts the unadjusted incidence of adverse events in reader studies reparagles of relationship in shirty drug. Incidence of Treatment Emergent Adverse Events

### 12-Week, Randomized, Double-Blind, (up to 3 years)

12-Week, Randomized, Double-Blind, Phase 3 Studies 12-Week Adjusted Incidence Rate (%)					0.1% and 0.03% Tacrolimus Ointment Incidence Rate (%)		
Adult			Pediatric		Adult Pediatric Total		
Vehicle (n=212) %	0.03%	0.1% Tecrolimus Dintment (n=209) %	Vehicle	0.03% Tacrolimus Ointment (n+118) %	(0=4582)	(n=4481) %	(n:8163) %
26	46	58	29	43	28	20	24
37	46	46	27	41	25	19	22
19	23	31	25	28	22	34	28
8	12	6	8	4	9	13	-11
20	25	28	13	12	12	7	9
11	20	19	- 8	5	13	9	11
11	12	5	14	10	9	16	12
4	4	1	13	21	2	14	8
1	1	2	9	7	6	10	8
2	1	1	14	18	3	10	6
4	6	4	6	6	4	13	8
4	4	4	2	0	4	3	3
0	1	1	0	2	0	0	0
3	3	4	11	6	4	12	8
4	3	6	3	6	6	8	7
2	3	4	3	2	2	7	5
1	6	4	0	2	- 4	2	3
4	3	2	2	6	2	4	3
4	0	1	6	12		11	6
1	4	2	8	3	6	7	6
3	3	4	2	5	2	4	3
3	3	6	1	1	3	4	4
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	(m-212) %  26 37 19 8 20 11 11 11 12 4 4 4 4 1 1 2 1 1 3 3 1 0 0 2 1 1 3 0 0 2 1 1 3 0 0 2 1 1 1 1 2 2 4 4 4 4 4 4 4 4 4 4 4 4 4	Mate   Mate	Mate   Mate	Mark   Mark	Market   M	West   Let   West   W	Note   Early   Early

as chicken pox. If 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, absesses, anaphylactiol reaction, anemia, anorexia, amiety, arthritis, arthrosis, bilirubinemia, biepharitis, bone disorder, breast neoplasm benign, burstis, catareat NDS, chest pain, chills, colitis, conjunctival edema, constipation, cramps, cutaneous moniliasis, cysilis, dehydration, dizziness, dry eyes, dry mouth/hose, dyspnea, ear disorder, ecchymosis, edema, epistaxis, eye pain, furunculosis, gastritis, gastrointestinal disorder, hernia, hypertonical hypothryoidism, joint disorder, langdisorder, malaise, migraine, moniliasis, mouth ulceration, nail disorder, neck pain, neoplasm benign, oral moniliasis, otitis externa, photosensitivity reaction, rectal disorder, seborrhea, skin carcinoma, skin disooloration, skin hypertrophy, skin ulcer, stomatitis, tendon disorder, thinking abnormal, tooth caries, sweating, syncope, tachycardia, taste perversion, unintended pregnancy, vaqinal moniliasis, aquintis, valvular heart disease, vasoditation, and vertigo.

OVERDOSAGE
PROTOPIC Dintment is not for oral use. Oral ingestion
PROTOPIC Dintment may lead to adverse effects associated
systemic administration of facrolimus. If oral ingestion or
medical advice should be sought.

### DOSAGE AND ADMINISTRATION

### PROTOPIC Ointment 0.03% and 0.1%

- Apply a thin layer of PROTOPIC (tacrolimus) Ointment to the affected skin twice daily. The minimum amount should be rubbed in gently and completely to control signs and symptoms of alopic dermatitis. Stop using when signs and symptoms of atopic dermatitis resolve.
- symptoms of atopic dermatitis resolve. If signs and symptoms (e.g., litch, rash, and redness) do not improve within 6 weeks, patients should be re-examined by their healthcare provider to confirm the diagnosis of adopic dermatitis.

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

atopic dermatrus.

The safety of PROTOPIC Ointment under occlusion which may promote systemic exposure, has not been evaluated PROTOPIC Ointment should not be used with occlusive dressings PEDIATRIC - FOR CHILDREN 2-15 YEARS PROTOPIC Ointment 0.03%

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Astellas Pharma Manufacturing, Inc.

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# 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

Apply online for an NPI at https://NPPES. cms.hhs.gov; or call 800-465-3203 for a paper application. For more information, go to www.cms.hhs.gov/apps/npi/ 01 overview.asp.