

Universal Flu Vaccination Would Strain Delivery

BY KATE JOHNSON
Montreal Bureau

TORONTO — Alternative settings, such as schools, should be considered if universal influenza vaccination is recommended for all U.S. school-age children, Dr. Cynthia Rand said in a poster presentation at the annual meeting of the Pediatric Academic Societies

“Kids aged 6-18 years haven’t yet had a recommendation for universal influenza

vaccination, but we’re expecting this recommendation in the flu season of 2008,” Dr. Rand of the University of Rochester (N.Y.), said in an interview.

In the study, she calculated that more than 41.5 million extra visits to pediatric offices would be needed annually to meet the increased demand. Although the emergency department has been suggested as a potential site for universal influenza vaccination (UIV), a related study found the added value of this delivery site would be “modest,”

at least from a public health perspective, her colleague Christina Albertin, also of the university, reported in another poster.

With data from the 2003-2004 Medical Expenditure Panel Survey (MEPS), Dr. Rand’s study calculated the number of well-child and other primary care visits for 4,161 children. From this she estimated the number of extra visits between October and January that would be required for influenza vaccination. It was assumed that children under 9 years would need two vis-

its rather than one visit, if it was their first influenza vaccine. There are new updated American Academy of Pediatric recommendations that first-timers who failed to get their two flu shots should get two for the following year; this would boost the number of visits still further, she commented (*Pediatrics* 2007;119:846-51).

By focusing specifically on the 6- to 18-year-old age group that is expected to be captured in new UIV guidelines, the study found that for children under 9 years, 33% would need one extra visit and more than 50% would need two—accounting for 16 million additional visits. For 9- to 18-year-old children and teens, 73% would need one extra visit, accounting for more than 25 million additional visits. In total, the 6- to 18-year-old age group would require

BRIEF SUMMARY – See package insert for full prescribing information

CUTIVATE® LOTION, 0.05% (fluticasone propionate lotion)

FOR TOPICAL USE ONLY.

NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.
Rx Only

DESCRIPTION: CUTIVATE LOTION, 0.05% (fluticasone propionate lotion) contains fluticasone propionate [5-(fluoromethyl) 6 α ,9-difluoro-11 β ,17-dihydroxy-16 α -methyl-3-oxoandrostano-1,4-diene-17 β -carboxylate, 17-propionate], a synthetic fluorinated corticosteroid, for topical dermatologic use. The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and antipruritic agents.

Each gram of CUTIVATE LOTION contains 0.5mg fluticasone propionate in a base of cetearyl alcohol, isopropyl myristate, propylene glycol, cetomacrogol 1000, dimethicone 360, citric acid, sodium citrate, and purified water, with imidurea, methylparaben, and propylparaben as preservatives.

Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

INDICATIONS AND USAGE: CUTIVATE LOTION (fluticasone propionate) is indicated for the relief of the inflammatory and pruritic manifestations of atopic dermatitis in patients 1 year of age or older. The safety and efficacy of drug use for longer than 4 weeks in this population have not been established. The safety and efficacy of CUTIVATE LOTION in pediatric patients below 1 year of age have not been established.

CONTRAINDICATIONS: CUTIVATE LOTION is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

Absorption: The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusive dressing enhances penetration. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption.

Special Population (Pediatric): Plasma fluticasone levels were measured in patients 2 years - 6 years of age in an HPA axis suppression study. A total of 13 (62%) of 21 patients tested had measurable fluticasone at the end of 3 - 4 weeks of treatment. The mean \pm SD fluticasone plasma values for patients aged under 3 years were 47.7 \pm 31.7 pg/mL and 175.5 \pm 243.6 pg/mL. Three patients had fluticasone levels over 300 pg/mL, with one of these having a level of 819.81 pg/mL. No data was obtained for patients < 2 years of age.

CLINICAL STUDIES: CUTIVATE LOTION applied once daily was superior to vehicle in the treatment of atopic dermatitis in two studies. The two studies enrolled 438 patients with atopic dermatitis aged 3 months and older, of which 169 patients were selected as having clinically significant signs of erythema, infiltration/papulation and erosion/oozing/crusting at baseline. Table 1 presents the percentage of patients who completely cleared of erythema, infiltration/papulation and erosion/oozing/crusting at Week 4 out of those patients with clinically significant baseline signs.

Table 1: Complete Clearance Rate

	CUTIVATE LOTION	Vehicle
Study 1	9/45 (20%)	0/37 (0%)
Study 2	7/44 (16%)	1/43 (2%)

*Clinically significant was defined as having moderate or severe involvement for at least two of the three signs (erythema, infiltration/papulation, or erosion/oozing/crusting) in at least 2 body regions. Patients who had moderate to severe disease in a single body region were excluded from the analysis.

PRECAUTIONS:

General: Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal from treatment. Manifestations of Cushing’s syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Patients applying a potent topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using cosyntropin (ACTH₁₋₂₄) stimulation testing.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios (see PRECAUTIONS: Pediatric Use).

Fluticasone propionate Lotion, 0.05% may cause local cutaneous adverse reactions (see ADVERSE REACTIONS).

If irritation develops, CUTIVATE LOTION should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of CUTIVATE LOTION should be discontinued until the infection has been adequately controlled.

CUTIVATE LOTION should not be used in the presence of preexisting skin atrophy and should not be used where infection is present at the treatment site. CUTIVATE LOTION should not be used in the treatment of rosacea and perioral dermatitis.

Laboratory Tests: The cosyntropin (ACTH₁₋₂₄) stimulation test may be helpful in evaluating patients for HPA axis suppression.

Information for Patients: Patients using CUTIVATE LOTION should receive the following information and instructions:

- CUTIVATE LOTION is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
- CUTIVATE LOTION should not be used for any disorder other than that for which it was prescribed.
- The treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician.
- Patients should report to their physician any signs of local adverse reactions.
- Parents of pediatric patients should be advised not to use this medication in the treatment of diaper dermatitis unless directed by the physician. CUTIVATE LOTION should not be applied in the diaper area as diapers or plastic pants may constitute occlusive dressing (see DOSAGE AND ADMINISTRATION).
- CUTIVATE LOTION should not be used on the face, underarms, or groin areas unless directed by a physician.
- CUTIVATE LOTION therapy should be discontinued if control is achieved before 4 weeks. If no improvement is seen within 2 weeks, contact a physician. The safety of the use of CUTIVATE LOTION for longer than 4 weeks has not been established.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: No studies were conducted to determine the photoco-carcinogenic potential of CUTIVATE LOTION.

In an oral (gavage) mouse carcinogenicity study, doses of 0.1, 0.3 and 1 mg/kg/day fluticasone propionate were administered to mice for 18 months. Fluticasone propionate demonstrated no tumorigenic potential at oral doses up to 1 mg/kg/day (less than the MRHD in adults based on body surface area comparisons) in this study.

In a dermal mouse carcinogenicity study, 0.05% fluticasone propionate ointment (40 mg/l) was topically administered for 1, 3 or 7 days/week for 80 weeks. Fluticasone propionate demonstrated no tumorigenic potential at dermal doses up to 6.7 mg/kg/day (less than the MRHD in adults based on body surface area comparisons) in this study.

Fluticasone propionate revealed no evidence of mutagenic or clastogenic potential based on the results of five in vitro genotoxicity tests (Ames assay, E. coli fluctuation test, S. cerevisiae gene conversion test, Chinese hamster ovary cell chromosome aberration assay and human lymphocyte chromosome aberration assay) and one in vivo genotoxicity test (mouse micronucleus assay).

No evidence of impairment of fertility or effect on mating performance was observed in a fertility and general reproductive performance study conducted in male and female rats at subcutaneous doses up to 50 mg/kg/day (less than the MRHD in adults based on body surface area comparisons).

Pregnancy: Teratogenic Effects: Pregnancy Category C. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

Systemic embryofetal development studies were conducted in mice, rats and rabbits. Subcutaneous doses of 15, 45 and 150 mg/kg/day of fluticasone propionate were administered to pregnant female mice from gestation days 6 - 15. A teratogenic effect characteristic of corticosteroids (left palate) was noted after administration of 45 and 150 mg/kg/day (less than the MRHD in adults based on body surface area comparisons) in this study. No treatment-related effects on embryofetal toxicity or teratogenicity were noted at 15 mg/kg/day (less than the MRHD in adults based on body surface area comparisons).

Subcutaneous doses of 10, 30 and 100 mg/kg/day of fluticasone propionate were administered to pregnant female rats in two embryofetal development studies (one study administered fluticasone propionate from gestation days 6 - 15 and the other study from gestation days 7 - 17). In the presence of maternal toxicity, fetal effects noted at 100 mg/kg/day (less than the MRHD in adults based on body surface area comparisons) included decreased fetal weights, omphalocele, cleft palate, and retarded skeletal ossification. No treatment-related effects on embryofetal toxicity or teratogenicity were noted at 10 mg/kg/day (less than the MRHD in adults based on body surface area comparisons).

Subcutaneous doses of 0.08, 0.57 and 4 mg/kg/day of fluticasone propionate were administered to pregnant female rabbits from gestation days 6 - 18. Fetal effects noted at 4 mg/kg/day (less than the MRHD in adults based on body surface area comparisons) included decreased fetal weights, cleft palate and retarded skeletal ossification. No treatment-related effects on embryofetal toxicity or teratogenicity were noted at 0.57 mg/kg/day (less than the MRHD in adults based on body surface area comparisons).

Oral doses of 3, 30 and 300 mg/kg/day fluticasone propionate were administered to pregnant female rabbits from gestation days 8 - 20. No fetal or teratogenic effects were noted at oral doses up to 300 mg/kg/day (less than the MRHD in adults based on body surface area comparisons) in this study. However, no fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration.

Fluticasone propionate crossed the placenta following administration of a subcutaneous or an oral dose of 100 mg/kg tritiated fluticasone propionate to pregnant rats.

There are no adequate and well-controlled studies in pregnant women. During clinical trials of CUTIVATE LOTION, women of childbearing potential were required to use contraception to avoid pregnancy. Therefore, CUTIVATE LOTION should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when CUTIVATE LOTION is administered to a nursing woman.

Pediatric Use: CUTIVATE LOTION may be used in pediatric patients as young as 1 year of age. The safety and efficacy of CUTIVATE LOTION in pediatric patients below 1 year of age have not been established.

Forty-two pediatric patients (4 months to < 6 years of age) with moderate to severe atopic eczema who were treated with CUTIVATE LOTION for at least 3 - 4 weeks were assessed for HPA axis suppression and 40 of these subjects applied at least 90% of applications. None of the 40 evaluable patients suppressed, where the sole criterion for HPA axis suppression is a plasma cortisol level of less than or equal to 18 micrograms per deciliter after cosyntropin stimulation. Although HPA axis suppression was observed in 0 of 40 pediatric patients (upper 95% confidence bound is 7.2%), the occurrence of HPA axis suppression in any patient and especially with longer use cannot be ruled out.

In other studies with fluticasone propionate topical formulations, adrenal suppression has been observed. CUTIVATE (fluticasone propionate) Cream, 0.05% caused HPA axis suppression in 2 of 43 pediatric patients, ages 2 and 5 years old, who were treated for 4 weeks covering at least 35% of the body surface area. Follow-up testing 12 days after treatment discontinuation, available for 1 of the 2 patients, demonstrated a normally responsive HPA axis.

HPA axis suppression, Cushing’s syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients include low plasma cortisol levels to an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilloedema. In addition, local adverse events including cutaneous atrophy, striae, telangiectasia, and pigmentation change have been reported with topical use of corticosteroids in pediatric patients.

Geriatric Use: A limited number of patients above 65 years of age have been treated with CUTIVATE LOTION in US and non-US clinical trials. Specifically only 8 patients above 65 years of age were treated with CUTIVATE LOTION in controlled clinical trials. The number of patients is too small to permit separate analyses of efficacy and safety.

ADVERSE REACTIONS: In 2 multicenter vehicle-controlled clinical trials of once-daily application of CUTIVATE LOTION by 196 adult and 242 pediatric patients, the total incidence of adverse reactions considered drug related by investigators was approximately 4%. Events were local cutaneous events, usually mild and self-limiting, and consisted primarily of burning/stinging (2%). All other drug-related events occurred with an incidence of less than 1%, and inclusively were contact dermatitis, exacerbation of atopic dermatitis, folliculitis of legs, pruritus, pustules on arm, rash, and skin infection. [Actual number of drug-related events for CUTIVATE LOTION (N=221) were burning/stinging skin, 4 (2%); contact dermatitis, 0; exacerbation of atopic dermatitis, 0; folliculitis of legs, 2 (<1%); irritant contact dermatitis, 0; pruritus, 1 (<1%); pustules on arms, 1 (<1%); rash, 1 (<1%); and skin infection, 0. Actual number of drug-related events for Vehicle (N=217) were burning/stinging skin, 3 (1%); contact dermatitis, 1 (<1%); exacerbation of atopic dermatitis, 1 (<1%); folliculitis of legs, 0; irritant contact dermatitis, 1 (<1%); pruritus, 1 (<1%); pustules on arms, 0; rash, 2 (<1%); and skin infection, 3 (1%).]

The incidence of drug-related events on drug compared to vehicle (4% and 5%, respectively) was similar. The incidence of drug-related events between study populations of 242 pediatric patients (age 3 months to < 17 years) and 196 adult patients (17 years or older) (4% and 5%, respectively) was also similar.

In an open-label study of 44 pediatric patients applying CUTIVATE LOTION to at least 35% of body surface area twice daily for 3 or 4 weeks, the overall incidence of drug-related adverse events was 14%. Events were local, cutaneous, and inclusively were dry skin, 3 events (7%); stinging at application site, 2 events (5%); and excoriation, 1 event (2%).

During the clinical trials, eczema herpeticum occurred in a 33-year-old male patient treated with CUTIVATE LOTION. Additionally, a 4-month-old patient treated with CUTIVATE LOTION in the open-label trial had marked elevations of the hepatic enzymes AST and ALT. Reported systemic post-marketing systemic adverse events with CUTIVATE Cream and CUTIVATE Ointment have included: immunosuppression/Pneumocystis carinii pneumonia/leukopenia/thrombocytopenia; hyperglycemia/glycosuria; Cushing syndrome; generalized body edema/blurred vision; and acute urticarial reaction (edema, urticaria, pruritus, and throat swelling). A causal role of CUTIVATE in most cases could not be determined because of the concomitant use of topical corticosteroids, confounding medical conditions, and insufficient clinical information.

The following local adverse reactions have been reported infrequently with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions are listed in an approximately decreasing order of occurrence: irritation, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, and miliaria. Also, there are reports of the development of pustular psoriasis from chronic plaque psoriasis following reduction or discontinuation of potent topical corticosteroid products.

OVERDOSAGE: Topically applied CUTIVATE LOTION can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION: CUTIVATE LOTION may be used in adult and pediatric patients 1 year of age or older. The safety and efficacy of CUTIVATE LOTION in pediatric patients below 1 year of age have not been established (see PRECAUTIONS: Pediatric Use).

Atopic Dermatitis: Apply a thin film of CUTIVATE LOTION to the affected skin areas once daily. Rub in gently.

As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary. The safety and efficacy of drug use for longer than 4 weeks have not been established.

CUTIVATE LOTION should not be used with occlusive dressings or applied in the diaper area unless directed by a physician.

HOW SUPPLIED: CUTIVATE LOTION is supplied in 60mL bottle (NDC 0462-0434-60).

Store between 15° and 30°C (59° and 86°F). Do not refrigerate. Keep container tightly sealed.

PharmaDerm®

Manufactured By:
GlaxoSmithKline, Mississauga, Ontario, Canada
Distributed By:
PharmaDerm®
a division of ALTANA Inc
Duluth, GA 30096 USA
www.pharmaderm.com

May 2006

98LC311006



The numbers of visits needed are overwhelming, underscoring the need for new delivery systems.

DR. RAND

41.5 million extra visits to pediatricians during the influenza vaccination period, assuming no missed opportunities for vaccination and that 20% of the population had been vaccinated in a prior season.

Individuals who are black, Asian, uninsured, or living in poverty are more likely to need additional visits, she added. The numbers are overwhelming, underscoring the need for new delivery systems, said Dr. Rand. “School-based systems would require a lot of coordination because school nurses would help be overwhelmed. They would need help from the public health infrastructure.”

Emergency departments (ED) have been discussed as another possible vaccination delivery site, but the benefits of implementing an ED delivery system are unclear, Ms. Albertin said in an interview.

With data from the MEPS (2002-2004), her study analyzed the number of ED visits from a sample of 10,073 children aged 6 months to 18 years between October and December, and calculated how many of them had also had a primary care visit during that period.

“Overall 3.7% of the children had an ED visit, and about half of them had no primary care visit during that time period, and therefore might have benefited from being vaccinated in the ED,” she said. While it’s a small percentage of the population, it represents half of the pediatric ED population, suggesting that the benefits of an ED vaccine delivery system may be debatable, she said. “Of course, EDs are busy places, and vaccination probably won’t happen consistently, but is 1.9%—that’s the percentage who didn’t have a primary care visit—enough to start pushing for vaccination in the ED or not?” she asked.

While many pediatricians have been strong supporters of primary care vaccination, without reliance on the ED, Dr. Rand’s study suggests perhaps multiple options will be needed. ■