

# Flu Treatment for Upcoming Season Clarified

BY BRUCE JANCIN

VAIL, COLO. — The recommended antiviral therapy during the coming influenza season will depend on whether a patient has laboratory-confirmed novel influenza A(H1N1).

In patients with confirmed novel influenza A(H1N1), or in patients with laboratory-confirmed influenza A(H3N2) or B, the first-line antiviral is oseltamivir

(Tamiflu). However, in patients with a positive laboratory test for influenza A or seasonal A(H1N1), the preferred agent is zanamivir (Relenza), according to Centers for Disease Control and Prevention recommendations based on antiviral resistance patterns.

Zanamivir is also the first-line agent in patients who are suspected of having influenza on clinical grounds but who did not have laboratory tests or had negative

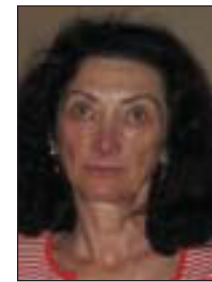
results, Dr. Adriana Weinberg explained at a conference on pediatric infectious diseases sponsored by the Children's Hospital in Denver.

Novel H1N1, A(H3N2), and B viruses share the same antiviral susceptibility pattern—all are susceptible to both zanamivir and oseltamivir. However, oseltamivir is preferred because as an oral agent it is easier to administer than the inhalation powder zanamivir, has fewer

side effects, and is approved for use across a wider age range, added Dr. Weinberg, professor of pediatrics and medicine and medical director of the clinical virology laboratory at the University of Colorado Hospital, Aurora.

The recommended alternative to zanamivir in patients with laboratory evidence of influenza A, a negative test result, or no testing is the combination of oseltamivir plus rimantadine (Flumadine). For patients who are positive for seasonal influenza A(H1N1), the fallback antiviral regimen is rimantadine alone.

Alternatives to the inhalation-only zanamivir are important because that administration route is problematic in patients who are intubated or have asthma



**A big concern is that the novel H1N1 virus will become resistant to oseltamivir, as did seasonal A(H1N1).**

DR. WEINBERG

or other airway disease. Plus, zanamivir isn't approved for use in children younger than age 7 years, she noted.

In contrast, in April the Food and Drug Administration approved a 1-year Emergency Use Authorization for the use of oseltamivir for treatment and prophylaxis in infants.

A big concern, according to Dr. Weinberg, is that the novel H1N1 virus will become resistant to oseltamivir, as did seasonal A(H1N1). This could occur if the novel H1N1 in a patient coinfects with seasonal A(H1N1)—a not-uncommon scenario—acquired the oseltamivir-resistance mutation.

To date three cases of oseltamivir-resistant novel H1N1 have been reported to the World Health Organization. But in addition to the emergence of resistance, there is also a phenomenon known as regression of resistance, which works in favor of public health.

Numerous investigational antiviral agents are well along in clinical trials. One that could prove particularly valuable is an intravenous formulation of zanamivir, a drug still active against all strains of influenza. Another promising drug is peramivir, a neuraminidase inhibitor that appears to be effective and well tolerated.

"Peramivir has the same resistance pattern as oseltamivir. Its big advantage is it can be administered parenterally. That's going to be really important in patients with severe influenza, in whom oral drugs aren't going to be reliable," Dr. Weinberg noted.

Ribavirin and several interferons commercially available for other indications are known to have some activity against influenza. In severe influenza that's not responding to treatment, combination therapy with neuraminidase inhibitors, adamantanes, interferon, and ribavirin is appropriate, Dr. Weinberg said. ■

## EPIDUO™

(adapalene and benzoyl peroxide) Gel 0.1% / 2.5%

For Topical Use Only

Not For Ophthalmic, Oral, or Intravaginal Use.

BRIEF SUMMARY

### INDICATIONS AND USAGE

EPIDUO Gel is a combination of adapalene, a retinoid, and benzoyl peroxide, and is indicated for the topical treatment of acne vulgaris in patients 12 years of age and older.

### CONTRAINDICATIONS

None.

### WARNINGS AND PRECAUTIONS

Ultraviolet Light and Environmental Exposure: Avoid exposure to sunlight and sunlamps. Wear sunscreen when sun exposure cannot be avoided. Erythema, scaling, dryness, and stinging/burning may occur with use of EPIDUO Gel.

### ADVERSE REACTIONS

Observed local adverse reactions in patients treated with EPIDUO Gel were erythema, scaling, dryness, stinging, and burning. Other most commonly reported adverse events ( $\geq 1\%$ ) in patients treated with EPIDUO Gel were dry skin, contact dermatitis, application site burning, application site irritation, skin irritation.

### DRUG INTERACTIONS

Exercise caution in using preparations containing sulfur, resorcinol, or salicylic acid, medicated or abrasive soaps and cleansers and products with high concentrations of alcohol or astringents in combination with EPIDUO Gel. Concomitant use of topical products with a strong drying effect can increase irritation. Use with caution.

### Pregnancy

Pregnancy Category C. There are no well-controlled trials in pregnant women treated with EPIDUO Gel. Animal reproduction studies have not been conducted with the combination gel or benzoyl peroxide. Furthermore, such studies are not always predictive of human response; therefore, EPIDUO Gel should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

No teratogenic effects were observed in rats treated with oral doses of 0.15 to 5.0 mg adapalene/kg/day, up to 25 times (mg/m<sup>2</sup>/day) the maximum recommended human dose (MRHD) of 2 grams of EPIDUO Gel. However, teratogenic changes were observed in rats and rabbits when treated with oral doses of  $\geq 25$  mg adapalene/kg/day representing 123 and 246 times MRHD, respectively. Findings included cleft palate, microphthalmia, encephalocoele and skeletal abnormalities in rats; and umbilical hernia, exophthalmos and kidney and skeletal abnormalities in rabbits.

Dermal teratology studies conducted in rats and rabbits at doses of 0.6-6.0 mg adapalene/kg/day [25-59 times (mg/m<sup>2</sup>) the MRHD] exhibited no fetotoxicity and only minimal increases in supernumerary ribs in both species and delayed ossification in rabbits.

### Nursing Mothers

It is not known whether adapalene or benzoyl peroxide is excreted in human milk following use of EPIDUO Gel. Because many drugs are excreted in human milk, caution should be exercised when EPIDUO Gel is administered to a nursing woman.

### Pediatric Use

Safety and effectiveness of EPIDUO Gel in pediatric patients under the age of 12 have not been established.

### Geriatric Use

Clinical studies of EPIDUO Gel did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity, phototoxicity, genotoxicity, or fertility studies were conducted with EPIDUO Gel.

Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.4, 1.3, and 4.0 mg/kg/day (1.2, 3.9, and 12 mg/m<sup>2</sup>/day), and in rats

Rx only

at oral doses of 0.15, 0.5, and 1.5 mg/kg/day (0.9, 3.0, and 9.0 mg/m<sup>2</sup>/day). In terms of body surface area, the highest dose levels are 9.8 (mice) and 7.4 times (rats) the MRHD of 2 grams of EPIDUO Gel. In the rat study, an increased incidence of benign and malignant pheochromocytomas in the adrenal medulla of male rats was observed.

No significant increase in tumor formation was observed in rodents topically treated with 15-25% benzoyl peroxide carbopol gel (6-10 times the concentration of benzoyl peroxide in EPIDUO Gel) for two years. Rats received maximum daily applications of 138 (males) and 205 (females) mg benzoyl peroxide/kg. In terms of body surface area, these levels are 27-40 times the MRHD. Similar results were obtained in mice topically treated with 25% benzoyl peroxide carbopol gel for 56 weeks followed by intermittent treatment with 15% benzoyl peroxide carbopol gel for rest of the 2 years study period, and in mice topically treated with 5% benzoyl peroxide carbopol gel for two years.

The role of benzoyl peroxide as a tumor promoter has been well established in several animal species. However, the significance of this finding in humans is unknown.

In a phototoxicity study conducted with 5% benzoyl peroxide carbopol gel, no increase in UV-induced tumor formation was observed in hairless mice topically treated for 40 weeks.

No phototoxicity studies were conducted with adapalene. However, animal studies have shown an increased tumorigenic risk with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in the laboratory or sunlight. Although the significance of these findings to humans is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial irradiation sources.

Adapalene did not exhibit mutagenic or genotoxic effects *in vitro* (Ames test, Chinese hamster ovary cell assay, mouse lymphoma TK assay) or *in vivo* (mouse micronucleus test).

Bacterial mutagenicity assays (Ames test) with benzoyl peroxide has provided mixed results, mutagenic potential was observed in a few but not in a majority of investigations. Benzoyl peroxide has been shown to produce single-strand DNA breaks in human bronchial epithelial and mouse epidermal cells, it has caused DNA-protein cross-links in the human cells, and has also induced a dose-dependent increase in sister chromatid exchanges in Chinese hamster ovary cells. In rat oral studies, 20 mg adapalene/kg/day (120 mg/m<sup>2</sup>/day; 98 times the MRHD based on mg/m<sup>2</sup>/day comparison) did not affect the reproductive performance and fertility of F<sub>0</sub> males and females, or growth, development and reproductive function of F<sub>1</sub> offspring. No fertility studies were conducted with benzoyl peroxide.

### PATIENT COUNSELING INFORMATION

— Advise patients to cleanse the area to be treated with a mild or soapless cleanser; pat dry. Apply EPIDUO Gel as a thin layer, avoiding the eyes, lips and mucous membranes.

— Advise patients not to use more than the recommended amount and not to apply more than once daily as this will not produce faster results, but may increase irritation.

— EPIDUO Gel may cause irritation such as erythema, scaling, dryness, stinging or burning.

— Advise patients to minimize exposure to sunlight, including sunlamps. Recommend the use of sunscreen products and protective apparel, (e.g., hat) when exposure cannot be avoided.

— EPIDUO Gel may bleach hair and colored fabric.

Marketed by:

GALDERMA LABORATORIES, L.P.

Fort Worth, Texas 76177 USA

Manufactured by:

Galderma Production Canada Inc.

Baie d'Urfé, QC, H9X 3S4 Canada

Made in Canada.

GALDERMA is a registered trademark.

Revised: December 2008

P51356-0

**References:** 1. Thiboutot D, Gollnick H, Bettoli V, et al: Global Alliance to Improve Outcomes in Acne. New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne Group. *J Am Acad Dermatol.* 2009;60(5)(suppl):S1-S50. 2. Michel S, Jomard A, Démarchez M. Pharmacology of adapalene. *Br J Dermatol.* 1998;139(suppl 52):3-7. 3. Shroot B, Michel S. Pharmacology and chemistry of adapalene. *J Am Acad Dermatol.* 1997;36(6, pt 2):S96-S103. 4. Leyden JJ, Del Rosso JQ, Webster GF. Clinical considerations in the treatment of acne vulgaris and other inflammatory skin disorders: focus on antibiotic resistance. *Cutis.* 2007;79(suppl 6):9-25. 5. Data on file. Galderma Laboratories, L.P. Phase 3 data.

Galderma is a registered trademark.  
©2009 Galderma Laboratories, L.P.  
Galderma Laboratories, L.P.  
14501 N. Freeway  
Fort Worth, TX 76177  
EPI-267 Printed in USA 06/09

www.epiduo.com

**GALDERMA**  
Committed to the future  
of dermatology

**Epiduo™**  
(adapalene and benzoyl  
peroxide) Gel 0.1% / 2.5%