

Cervarix Found More Immunogenic Than Gardasil

BY MIRIAM E. TUCKER

ATLANTA — The efficacy of GlaxoSmithKline's human papillomavirus vaccine against cervical intraepithelial neoplasia grade 2 or higher was confirmed in a final analysis of phase III data from more than 18,000 women in 14 countries.

And in a separate head-to-head comparison involving a total of more than 1,100 women, immune responses to the

oncogenic HPV strains 16 and 18 were significantly better with GSK's Cervarix than with Merck & Co.'s HPV vaccine Gardasil, Dr. Gary Dubin said at a meeting of the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices.

GlaxoSmithKline's phase III data on Cervarix were submitted to the Food and Drug Administration in March 2009 and are still under review. The vaccine is cur-

rently licensed in more than 95 countries, said Dr. Dubin, vice president, North American clinical development, GSK.

The final analysis enrolled 18,644 women aged 15-25 years in a double-blind, randomized, controlled trial using the hepatitis A vaccine as the control. Mean follow-up was 39 months following the first of three doses.

The primary objective was to assess efficacy against the development of cervi-

cal intraepithelial neoplasia-2 (CIN2+) associated with HPV-16 and HPV-18 in women who were DNA negative and seronegative at baseline and DNA negative at 6 months for the HPV type considered in the analysis.

Among the 14,656 seronegative women who had received all three doses of study vaccine, the overall efficacy of Cervarix against HPV-16/18 CIN2+ lesions was 93%. In total, 4/7,344 Cervarix recipients and 56/7,312 controls were found to have HPV-16/18 DNA in lesions during follow-up. Irrespective of baseline serostatus, vaccine efficacy was 91% for HPV-16/18.

In the subset of 11,641 totally vaccinated naive women, defined as those

In a separate head-to-head comparison involving 1,106 women, immune responses to the oncogenic HPV strains 16 and 18 were significantly better with Cervarix than with Gardasil.

who at baseline had normal cytology, had no HPV DNA for 14 oncogenic types, and were seronegative for HPV-16 and HPV-18, Cervarix efficacy was 98% against HPV-16/18 CIN2+ lesions. For the total vaccinated cohort of 18,644 women, vaccine efficacy against HPV-16/18 CIN2+ lesions was 53%, reflecting the fact that many women in this cohort had preexisting lesions, he said.

A safety analysis showed identical rates of serious adverse events (7.5% with both Cervarix and hepatitis A vaccine) and of new-onset autoimmune disease (0.8% for both).

The head-to-head comparison was the first for the two licensed vaccines using the same methodology for immunogenicity and safety.

The primary objective was to compare the geometric mean titers of HPV-16 and HPV-18 serum neutralizing antibodies at month 7 following vaccination in women aged 18-26 years. The observer-blinded study was conducted at 40 U.S. centers in a total of 1,106 women randomized to receive Cervarix or Gardasil according to the recommended administration schedules. Placebo injections were given to the Gardasil group at 1 month and the Cervarix group at 2 months.

Cervarix induced significantly higher serum neutralizing antibody titers than did Gardasil. In women aged 18-26, titers for Cervarix were 3.7-fold higher against HPV-16 and 7.3-fold higher against HPV-18 compared with results for Gardasil. In women aged 27-35 years, those differences were 4.8-fold and 9.1-fold, and for 36- to 45-year-olds, 2.3-fold and 6.8-fold.

The frequency of circulating antigen-specific memory B cells at month 7 was 2.7-fold higher with Cervarix vs. Gardasil for HPV-16 and HPV-18, and the frequency of CD4+ T-cell responses at month 7 was also significantly higher with Cervarix compared with Gardasil for both HPV-16 and HPV-18. ■

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/m²/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 ≥ 25 mg adapalene/kg/day representing 123 and 246 times MRHD, respectively. Findings included cleft palate, microphthalmia, encephalocele 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/m²) 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/m²/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/m²/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/m²/day; 98 times the MRHD based on mg/m²/day comparison) did not affect the reproductive performance and fertility of F₀ males and females, or growth, development and reproductive function of F₁ 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.

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Manufactured by:

Galderma Production Canada Inc.

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Revised: December 2008


P51356-0

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Galderma Laboratories, L.P.
14501 N. Freeway
Fort Worth, TX 76177
EPI-268 Printed in USA 06/09

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