

# Analysis Refutes Hepatitis B Vaccine, RA Link

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BALTIMORE — The hepatitis B vaccine does not appear to be associated with an increased risk for rheumatoid arthritis, Dr. Roger P. Baxter and his associates reported at a vaccine research conference sponsored by the National Foundation for Infectious Diseases.

Both acute and chronic arthropathies have been reported in adults vaccinated

with the tetanus-diphtheria (Td), hepatitis B (HepB), and measles-mumps-rubella (MMR) vaccines. However, most of the evidence to support or refute a causal relationship between the Td or HepB vaccine and chronic arthritis has come from isolated case reports, uncontrolled observational studies, or studies that lacked sufficient statistical power, said Dr. Baxter, associate director of the Vaccine Study Center at Kaiser Permanente, Oakland, Calif., and his associates.

A case-control analysis designed to overcome the shortcomings of the previous studies included a cohort of continuous enrollees in Northern California Kaiser Permanente's health plan from Jan. 1, 1995, through Dec. 31, 1999, who were aged 15-59 years during Jan. 1, 1997-Dec. 31, 1999.

Individuals who had made clinic visits for rheumatoid arthritis (RA) and other inflammatory conditions prior to their follow-up start date were excluded.

A total of 416 incident cases of RA were identified (based on definitive diagnosis at the time or subsequent assessment by a rheumatologist), and each was matched with three controls based on age and the number of clinic visits made during the year prior to the onset date.

Rates of hepatitis B vaccination among the RA patients were compared with those of controls, with adjustment for sex, age, and exact number of clinic visits. Similar comparisons were made for the tetanus and influenza vaccines.

No statistically significant risk of RA was found for any of the three vaccines. Only 1% of RA patients versus 0.6% of controls had been exposed to the hepatitis B vaccine within 1-90 days of onset of RA symptoms, for an adjusted odds ratio of 1.48.

**'People who have RA are more likely to be higher utilizers and also more likely to have gotten vaccines than people who don't utilize the system as much.'**

Within 1-180 days, the percentages were 1.9% with RA versus 0.9% of controls, giving a still insignificant odds ratio of 2.01.

Within 1 year, 2.4% of RA cases and 1.6% of controls had been exposed to the

vaccine, again insignificant at 1.42.

In all, only 10 of the 416 RA patients had received the HepB vaccine within 1 year of symptom onset, suggesting that, "If there is an association, these data would imply that hepatitis B vaccine would only contribute to a small minority of cases," Dr. Baxter and his associates said in their poster.

Results for the other two vaccines were also not significant, with adjusted odds ratios of 0.77-1.06 for tetanus and 0.66-1.11 for influenza.

Health care utilization was higher among those with RA, which was a slight confounder in this study despite the attempt to control for number of visits: Even after adjustment, there was still a significant residual effect for number of visits, with an odds ratio of 1.15.

"Basically, people who get vaccines of all kinds are different from those who don't, and underlying differences may confound the relationship with things like RA. We try to control for these factors by matching and analyses, but still we think there are differences. ...

"People who have RA are more likely to be higher utilizers and also more likely to have gotten vaccines than people who don't utilize the system as much," Dr. Baxter commented in a follow-up interview.

However, he added, although the difference in utilization was statistically significant, it probably wasn't that different clinically.

"We thought initially this was an important confounder. But in the end we found that although they were different, in reality we could adjust for the vast majority of the difference," he said. ■

## BenzaClin® Topical Gel

(clindamycin - benzoyl peroxide gel)

**Brief summary. Please see full prescribing information for complete product information.**

**Topical Gel:** clindamycin (1%) as clindamycin phosphate, benzoyl peroxide (5%)  
**For Dermatological Use Only - Not for Ophthalmic Use**  
**\*Reconstitute Before Dispensing\***

### INDICATIONS AND USAGE

BenzaClin Topical Gel is indicated for the topical treatment of acne vulgaris.

### CONTRAINDICATIONS

BenzaClin Topical Gel is contraindicated in those individuals who have shown hypersensitivity to any of its components or to lincomycin. It is also contraindicated in those having a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.

### WARNINGS

**ORALLY AND PARENTERALLY ADMINISTERED CLINDAMYCIN HAS BEEN ASSOCIATED WITH SEVERE COLITIS WHICH MAY RESULT IN PATIENT DEATH. USE OF THE TOPICAL FORMULATION OF CLINDAMYCIN RESULTS IN ABSORPTION OF THE ANTIBIOTIC FROM THE SKIN SURFACE. DIARRHEA, BLOODY DIARRHEA, AND COLITIS (INCLUDING PSEUDOMEMBRANOUS COLITIS) HAVE BEEN REPORTED WITH THE USE OF TOPICAL AND SYSTEMIC CLINDAMYCIN. STUDIES INDICATE A TOXIN(S) PRODUCED BY CLOSTRIDIA IS ONE PRIMARY CAUSE OF ANTIBIOTIC-ASSOCIATED COLITIS. THE COLITIS IS USUALLY CHARACTERIZED BY SEVERE PERSISTENT DIARRHEA AND SEVERE ABDOMINAL CRAMPS AND MAY BE ASSOCIATED WITH THE PASSAGE OF BLOOD AND MUCUS. ENDOSCOPIC EXAMINATION MAY REVEAL PSEUDOMEMBRANOUS COLITIS. STOOL CULTURE FOR *Clostridium Difficile* AND STOOL ASSAY FOR *C. difficile* TOXIN MAY BE HELPFUL DIAGNOSTICALLY. WHEN SIGNIFICANT DIARRHEA OCCURS, THE DRUG SHOULD BE DISCONTINUED. LARGE BOWEL ENDOSCOPY SHOULD BE CONSIDERED TO ESTABLISH A DEFINITIVE DIAGNOSIS IN CASES OF SEVERE DIARRHEA. ANTIPERISTALTIC AGENTS SUCH AS OPIATES AND DIPHENOXYLATE WITH ATROPINE MAY PROLONG AND/OR WORSEN THE CONDITION. DIARRHEA, COLITIS, AND PSEUDOMEMBRANOUS COLITIS HAVE BEEN OBSERVED TO BEGIN UP TO SEVERAL WEEKS FOLLOWING CESSATION OF ORAL AND PARENTERAL THERAPY WITH CLINDAMYCIN.**

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

### PRECAUTIONS

**General:** For dermatological use only; not for ophthalmic use. Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents.

The use of antibiotic agents may be associated with the overgrowth of nonsusceptible organisms including fungi. If this occurs, discontinue use of this medication and take appropriate measures.

Avoid contact with eyes and mucous membranes.

Clindamycin and erythromycin containing products should not be used in combination. *In vitro* studies have shown antagonism between these two antimicrobials. The clinical significance of this *in vitro* antagonism is not known.

**Information for Patients:** Patients using BenzaClin Topical Gel should receive the following information and instructions:

1. BenzaClin Topical Gel is to be used as directed by the physician. It is for external use only. Avoid contact with eyes, and inside the nose, mouth, and all mucous membranes, as this product may be irritating.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. Patients should not use any other topical acne preparation unless otherwise directed by physician.
4. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using BenzaClin Topical Gel. To minimize exposure to sunlight, a wide-brimmed hat or other protective clothing should be worn, and a sunscreen with SPF 15 rating or higher should be used.
5. Patients should report any signs of local adverse reactions to their physician.
6. BenzaClin Topical Gel may bleach hair or colored fabric.
7. BenzaClin Topical Gel can be stored at room temperature up to 25°C (77°F) for 3 months. Do not freeze. Discard any unused product after 3 months.
8. Before applying BenzaClin Topical Gel to affected areas wash the skin gently, then rinse with warm water and pat dry.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. The clinical significance of this is unknown.

Benzoyl peroxide in acetone at doses of 5 and 10 mg administered twice per week induced skin tumors in transgenic Tg.AC mice in a study using 20 weeks of topical treatment.

In a 52 week dermal photocarcinogenicity study in hairless mice, the median time to onset of skin tumor formation was decreased and the number of tumors per mouse increased following chronic concurrent topical administration of BenzaClin Topical Gel with exposure to ultraviolet radiation (40 weeks of treatment followed by 12 weeks of observation).

In a 2-year dermal carcinogenicity study in rats, treatment with BenzaClin Topical Gel at doses of 100, 500 and 2000 mg/kg/day caused a dose-dependent increase in the incidence of keratoacanthoma at the treated skin site of male rats. The incidence of keratoacanthoma at the treated site of males treated with 2000 mg/kg/day (8 times the highest recommended adult human dose of 2.5 g BenzaClin Topical Gel, based on mg/m<sup>2</sup>) was statistically significantly higher than that in the sham- and vehicle-controls.

Genotoxicity studies were not conducted with BenzaClin Topical Gel. Clindamycin phosphate was not genotoxic in *Salmonella typhimurium* or in a rat micronucleus test. Clindamycin phosphate sulfoxide, an oxidative degradation product of clindamycin phosphate and benzoyl peroxide, was not clastogenic in a mouse micronucleus test. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *S. typhimurium* tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells. Studies have not been performed with BenzaClin Topical Gel or benzoyl peroxide to evaluate the effect on fertility. Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g BenzaClin Topical Gel, based on mg/m<sup>2</sup>) revealed no effects on fertility or mating ability.

### Pregnancy: Teratogenic Effects: Pregnancy Category C:

Animal reproductive/developmental toxicity studies have not been conducted with BenzaClin Topical Gel or benzoyl peroxide. Developmental toxicity studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (240 and 120 times amount of clindamycin in the highest recommended adult human dose based on mg/m<sup>2</sup>, respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (100 and 50 times the amount of clindamycin in the highest recommended adult human dose based on mg/m<sup>2</sup>, respectively) revealed no evidence of teratogenicity.

There are no well-controlled trials in pregnant women treated with BenzaClin Topical Gel. It also is not known whether BenzaClin Topical Gel can cause fetal harm when administered to a pregnant woman.

**Nursing Women:** It is not known whether BenzaClin Topical Gel is excreted in human milk after topical application. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, 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:** Safety and effectiveness of this product in pediatric patients below the age of 12 have not been established.

### ADVERSE REACTIONS

During clinical trials, the most frequently reported adverse event in the BenzaClin treatment group was dry skin (12%). The Table below lists local adverse events reported by at least 1% of patients in the BenzaClin and vehicle groups.

	Local Adverse Events - all causalities in >= 1% of patients	
	BenzaClin n = 420	Vehicle n = 168
Application site reaction	13 (3%)	1 (<1%)
Dry skin	50 (12%)	10 (6%)
Pruritus	8 (2%)	1 (<1%)
Peeling	9 (2%)	-
Erythema	6 (1%)	1 (<1%)
Sunburn	5 (1%)	-

The actual incidence of dry skin might have been greater were it not for the use of a moisturizer in these studies.

### DOSAGE AND ADMINISTRATION

BenzaClin Topical Gel should be applied twice daily, morning and evening, or as directed by a physician, to affected areas after the skin is gently washed, rinsed with warm water and patted dry.

### HOW SUPPLIED AND COMPOUNDING INSTRUCTIONS

Size (Net Weight)	NDC 0066-	Benzoyl Peroxide Gel	Active Clindamycin Powder (In plastic vial)	Purified Water To Be Added to each vial
25 grams	0494-25	19.7g	0.3g	5 mL
50 grams	0494-50	41.4g	0.6 g	10 mL
50 grams (pump)	0494-55	41.4g	0.6 g	10 mL

**Prior to dispensing, tap the vial until powder flows freely. Add indicated amount of purified water to the vial (to the mark) and immediately shake to completely dissolve clindamycin. If needed, add additional purified water to bring level up to the mark.** Add the solution in the vial to the gel and stir until homogenous in appearance (1 to 1½ minutes). For the 50 gram pump only, reassemble jar with pump dispenser. BenzaClin Topical Gel (as reconstituted) can be stored at room temperature up to 25°C (77°F) for 3 months. Place a 3 month expiration date on the label immediately following mixing.

Store at room temperature up to 25°C (77°F) (See USP).

**Do not freeze. Keep tightly closed. Keep out of the reach of children.**

US Patents 5,446,028; 5,767,098; 6,013,637

Brief Summary of Prescribing Information as of May 2007.

### Rx Only

### Dermik Laboratories

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