**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number** NDA 50-769

**MEDICAL REVIEW(S)**

**Medical Officer's Review of NDA 50-769**
**Original**

NOV 2 2000

**1.1 NDA Submission number/type NDA 50-769/3S**

**1.2 Applicant identification**

Dermik Laboratories, Inc.
500 Arcola Road
P.O. Box 5096
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**1.3 Submission/Review Dates**

| | | |
|---|---|---|
| 1.3.1 | Date of submission (date of applicant's letter) | 01-26-00 |
| 1.3.2 | CDER stamp date | 01-27-00 |
| 1.3.3 | Date submission received by reviewer | 02-14-00 |
| 1.3.4 | Date review initiated | 06-26-00 |
| 1.3.5 | Date review completed | 10-30-00 |

**1.4 Drug Identification:** erythromycin 3% and benzoyl peroxide gel 10%

1.4.1 Generic name

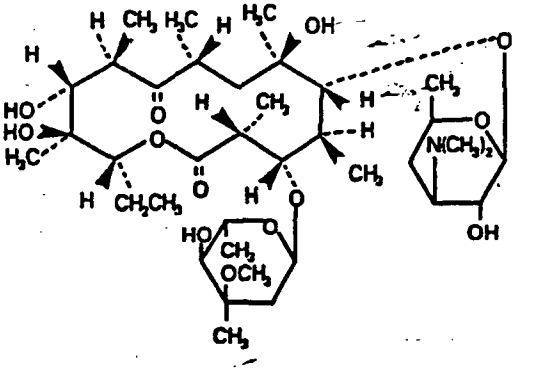
1.4.2 Proposed trade name Benzamycin®

1.4.3 Chemical name

Chemically, erythromycin is erythromycin[(3R*, 4S*, 5S*, 6R*, 7R*, 9R*, 11R*, 12R*, 13S*, 14R*)-4-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-a-L-ribo-hexopyranosyl)-oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexa-methyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-b-D-xylo-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione].

**1.4.4 Chemical structures for erythromycin and benzoyl peroxide follows:**

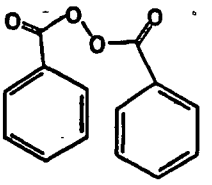
The molecular structure for erythromycin is depicted below:



Molecular formula: $C_{37}H_{67}NO_{13}$

Molecular weight: 733.94

The molecular structure of benzoyl peroxide is depicted below:



Molecular formula: $C_{14}H_{10}O_4$
Molecular weight: 242.23

1.5 Pharmacological Category: Anti-acne (antimicrobial)
1.6 Dosage form: Gel
1.7 Route of Administration: Topical
1.8 Proposed Indication & Usage section
Benzamycin Pak is indicated for the topical treatment of acne vulgaris
1.9 Proposed Dosage & Administration section
**Benzamycin Pak** should be applied twice daily, morning and evening, or as directed by a physician, to affected areas after the skin is thoroughly washed, rinsed with warm water and gently patted dry.
1.10 Related Drugs
Benzamycin Gel (NDA 50-557)

| | | |
|---|---|---|
| Related Reviews: | Biopharm Review dated: | 05-22-00 |
| | Chemistry Review dated: | Pending |
| | Microbiology Review dated: | Pending |
| | Pharm/Tox Review dated: | 08-31-00 |
| | Statistical Review dated: | 09-18-00 |

**1.11.1 NDA Volumes Reviewed**
This review is based on the following volumes: 1.1 and 1.11 – 1.21

| Document Identification | Date Received |
|---|---|
| 50-769 BZ | 02-23-00 |
| 50-769 SU | 05-26-00 |
| 50-769 BL | 07-27-00 |
| 50-769 BL | 09-27-00 |
| 50-769 BC | 10-10-00 |
| 50-769 BL | 10-17-00 |

**1.11.1 Other Documents Reviewed**
**1.11.2 Amendments with Dates**
Amendment No. 1 dated October 9, 1997,
Amendment No. 2 dated November 18, 1997, and
Amendment No. 3 dated April 2, 1998.
**1.12 Regulatory Background**
This drug product is considered a line-extension product of the approved Benzamycin Gel product approved in 1981 under NDA 50-557. End of Phase 2 and Pre-NDA meetings were held between the Division and the sponsor on 10-23-97 and 09-15-98, respectively.

DDDP indicated that, as a line extension product, the sponsor could demonstrate the efficacy and safety of the Benzamycin Dual Pouch product either via two separate placebo controlled trials or via a single study. If a single study were conducted, the sponsor should also include the currently marketed Benzamycin Gel as a study arm in order to confirm non-inferiority of the Benzamycin Dual Pouch to the marketed product.

The Division also agreed that the phototoxicity and photoallergy studies previously submitted for marketed Benzamycin could be utilized in lieu of repeating the studies with the Benzamycin Dual Pouch product. This was contingent upon demonstrating that the ultraviolet-visible (UV-Vis) spectrum absorbance profiles, for both the currently marketed Benzamycin product and the investigational formulation (Benzamycin Dual Pouch), were similar.

A photocarcinogenicity study of 5% benzoyl peroxide, sponsored by the Consumer Healthcare Products Association (CHPA), formerly known as the Non-Prescription Drug Manufacturer's Association (NDMA), was ongoing at the time of the End-of-Phase II (27 Oct 97) and Pre-NDA (15 Sept 98) meetings between Dermik and the Division of Dermatologic and Dental Drug Products of FDA. It was agreed at these meetings that, if this study was negative for promotion of UV-induced tumors, then Dermik would complete a photocarcinogenicity study on the Benzamycin Dual Pouch product as a Phase IV commitment. If the outcome of the CHPA study was positive, then Dermik could choose to either accept labeling consistent with the positive finding and not conduct a study, or conduct a photocarcinogenicity study on the product to determine if the photocarcinogenic properties of the Benzamycin Dual Pouch product differ from the material used in the NDMA study.

Throughout this NDA, Benzamycin Dual Pouch may also be referred to as, Benzamycin® Dual Chamber gel, Benzamycin® Dual Gel, [redacted], Benzamycin Pak, or DL-6026.

## List of INDs and NDAs

Formulations for topical treatment of acne vulgaris reviewed by the FDA under INDs or NDAs sponsored by are as follows:

### Related NDAs

| NDA Number | Drug Name | Indication | Date of Approval |
|---|---|---|---|
| 50-557 | Benzamycin® Topical Gel (erythromycin and benzoyl peroxide gel) | Topical treatment of acne vulgaris | 10-26-84 |

### Related INDs

| IND Number | Drug Name | Indication | Date of Submission |
|---|---|---|---|
| 12,193 | erythromycin and benzoyl peroxide gel | Topical treatment of acne vulgaris | 01-27-76 |

# Table of Content

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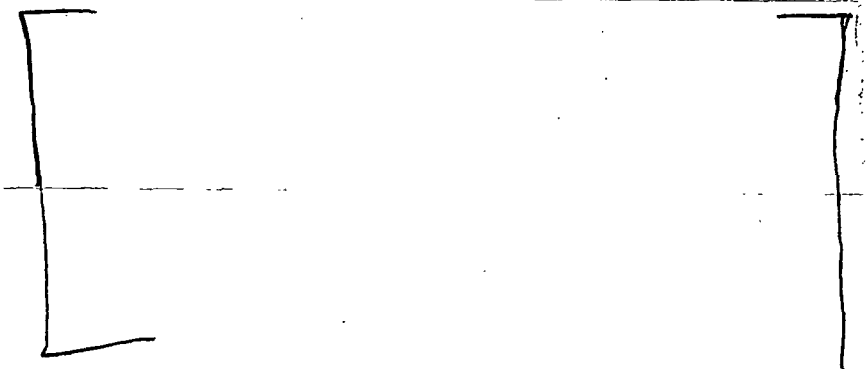
## 3 Chemistry/Manufacturing Controls

### Composition and Dosage Form

is supplied in single-use, dual-chambered pouches. Each chamber is filled with equal quantities of benzoyl peroxide gel and erythromycin gel, respectively. At time of use, the patient will open, empty, and blend the contents of the pouch.



The formulation after mixing by the patient is presented in Table 3.3.1 as follows.

**Table 1 (Sponsor's Table 3.3.1, Vol. 1.1, pg. 3-1-88)**

| Ingredient | %w/w |
|---|---|
| erythromycin, USP | |
| hydrous benzoyl peroxide, USP | |
| carbomer 934, NF | |
| sodium hydroxide, NF | |
| dioctyl sodium sulfosuccinate 75%, DF | |
| purified water, USP | |
| hydroxypropyl cellulose, NF | |
| SD Alcohol #40-B/ 190° | |

The "final-to-be-marketed" formulation was used in the Phase 3 studies 9708 & 9723 and in dermal safety study 9708.

## 4 Animal Pharmacology/Toxicology (See Pharm/Tox Review)

Pharmacology

Erythromycin is a macrolide antibiotic produced by *Streptomyces erthraeus*. BPO is an oxidizing agent that has bacteriostatic/bactericidal activities. There are no new pharmacology studies reported in this NDA.

Toxicology

Three subchronic toxicity studies, a primary dermal irritation (single application) assay, and a guinea pig sensitization assay were submitted with this NDA. Three subchronic toxicity studies were conducted using three closely related formulations of the combination product: marketed Benzamycin Topical Gel, an early and the current (to be marketed) Benzamycin

**Table 2 (Sponsor's Table 3.4.1, Vol. 1.1, pg. 3-1-98) Subchronic Toxicity Studies**

| Species | Strain/ Initial Group | Mode of Administration | Doses/ Duration | Laboratory | Report No. |
|---|---|---|---|---|---|
| Rat | Sprague-Dawley 5/sex/group | Topical | 20, 40, 400 µl/kg/day BID x90 days | | DL-PC-6026-9410(01)<br>CHV 2745-102[i] |
| Rabbit | New Zealand White 5/sex/group | Topical | 20, 40, 400 µl/kg/day BID x90 days | | DL-PC-6026-9410(02)<br>95-2371[ii]<br>CHV 2745-101 |
| Rabbit | New Zealand White 5/sex/group | Topical | 20, 40, 400 µl/kg/day BID x28-30 days | | DL-PC-6026-9725<br>ML-DKL-3N11-98-249[iii] |

The first two studies in the table above were performed with the early formulation of the product, referred to as Formulation "B", and the last study was a 28-day bridging study with the to be marketed formulation, referred to as Formulation "A". All of these studies included a group that received marketed Benzamycin Topical Gel.

The early formulation and Benzamycin Topical Gel were very slightly irritating in a primary dermal irritation (single application) assay. Both were considered to have the potential to be weak dermal sensitizers, as assessed in a guinea pig sensitization assay.

No toxicological differences were found between formulations. Treatment-related effects were limited to minor, dose-related dermal effects at the application site (erythema, hyperkeratosis, acanthosis), which were probably due to the benzoyl peroxide component. There were no systemic effects.

Summary of Toxicology Information From The Literature

A summary of toxicology information from the literature was submitted. Literature studies were reviewed for both erythromycin and BPO in support of this NDA. No toxicity studies on the combination of erythromycin and BPO are available from the literature. Both agents were negative in carcinogenicity bioassays, although BPO appears to be a promoter in tumor promotion assays. Based on the results of numerous genotoxicity assays, both agents are considered to lack genotoxic potential.

Reproduction studies in rats with erythromycin have not revealed evidence of impaired fertility. Subcutaneous doses of 10-25 mg/kg/day of erythromycin (approximately 17-fold higher than the topical dose that would be applied using Benzamycin) were reported to induce a low frequency (less than 3%) of urogenital abnormalities in rats. However, of 10 antibiotics investigated in this study, erythromycin had the lowest incidence of malformations. Furthermore, long term use of erythromycin and BPO in topical products has not indicated that they are developmentally toxic.

Photocarcinogenicity Study

According to the submission, the Consumer Healthcare Products Association (CHPA) sponsored study was recently completed and results submitted to the Agency (ref. *The Toxicologist,* 48, 1-S, page 320, Abstract 1511, Mar., 1999) and this study was negative for promotion of UV-induced tumors. In light of the CHPA study results and in the context of the scientific consensus for appropriate photocarcinogenicity assessment,

According to the submission, the acute oral toxicity of erythromycin in rats is very low. The median lethal dose (LD 50) is in excess of 9000 mg/kg. The median lethal dose (LD 50) of benzoyl peroxide in rats is also low, >950 mg/kg. Accidental or intentional ingestion of an entire Dual Pouch unit dose (approximately 0.8 gm of product) would result in a much lower acute exposure of ~24 mg of Erythromycin (<0.5 mg/kg for a 50 kg adult), and ~40 mg of benzoyl peroxide (<1 mg/kg for a 50 kg adult), so acute poisoning with the product is highly unlikely.

Conclusions of the Pharm/Tox Review indicates that the dual pouch formulation is unlikely to produce toxicity different from the approved Benzamycin Gel product. Benzoyl peroxide is a tumor promoter and progression agent in animal models of skin cancer; however, epidemiologic studies have not indicated an increase in skin tumors in humans.

## 5 Microbiology

Dermik is not seeking an antimicrobial indication for Benzamycin

## 6 Human Pharmacokinetics/Pharmacodynamics

The following three studies were performed in support of this NDA: 1) a pivotal *in vivo* pharmacokinetic study entitled "Single Dose Pharmacokinetics of Topical 3% Erythromycin / 5% Benzoyl peroxide Gel in Patients Diagnosed with Acne Vulgaris" (DL-6026-9717), 2) a supportive *in vitro* skin permeation study (DL-6026-9805), and 3) a supportive *in vitro* release study (DL-6026-Zatz IVRT).

The results of the pharmacokinetic study (DL-6026-9717) demonstrated that there is virtually no systemic absorption of erythromycin following a single application of either 0.8 or 2.4 grams of Benzamycin (one or three times the usual dose, respectively). Only one concentration was above the lower limit of quantitation (LLOQ) and that was found to be 2.04 ng/mL. This concentration is minimal and is below concentrations observed following oral and intravenous administration of erythromycin.

A skin permeation study (DL-6026-9805) assessed the permeation of erythromycin through the skin following the application of various erythromycin/benzoyl peroxide formulations. The results of this study demonstrated that a minimal amount of erythromycin was absorbed by the skin following the 24 hour experimental period, and of that, the majority of erythromycin resided within the skin (in the stratum corneum and viable tissue). Additionally, the study demonstrated that the permeation profile of

erythromycin for the dual pouch formulation is similar to that of the currently marketed product.

The *in vitro* release study (DL-6026-Zatz IVRT) assessed the effects of different mixing protocols ('poorly-mixed' vs. 'well-mixed') on the *in vitro* release of erythromycin from the dosage form. The results of this study demonstrated that the major difference between the 'well-mixed' and the 'poorly mixed' samples was in the variability of release, rather than the rate of release. The variability, most evident in the 'poorly mixed' sample, was attributed to unequal contact of each drug with the membrane. The 'well-mixed' preparation resulted in more uniform contact of each drug with the membrane. Although the sample preparation was extreme, the 'well-mixed' scenario is more indicative of application of an equal amount of each individual drug applied in a thin layer to the skin. The differences in the sample preparation may have contributed to the variability and bias in the results.

The overall conclusion based on the Clinical Pharmacology/Biopharmaceutics Review is that systemic exposure of erythromycin from Benzamycin® ——— ; was very low. One patient out of 16showing a detectable level 0.04 ng/ml above the level of detection (LOQ 2ng/ml).

## 7 Human Clinical Experience

### 7.1 Foreign Experience

Benzamycin ——— is not marketed, nor are applications pending, in any country. At the time of filing of this original NDA, Benzamycin ——— has not been withdrawn from any market, and no applications have been withdrawn in any country for any reason.

### 7.2 Post-Marketing Experience

Benzamycin® Topical Gel (a 3% erythromycin / 5% benzoyl peroxide combination product) is an approved product for the treatment of acne vulgaris and has been marketed in the United States since 1985.

## 8 Clinical Studies

### 8.1 Introduction

The subject of this NDA is Benzamycin® ——— which after compounding contains both 3% erythromycin and 5% benzoyl peroxide for treatment of acne vulgaris. Erythromycin is a macrolide antibiotic produced from a strain of Saccharopolyspora erythraea (formerly Streptomyces erythreus). It is a base and readily forms salts with acids. Benzoyl peroxide is an oxidizing agent.

The rationale for use of the erythromycin/benzoyl peroxide combination product in acne is based at least in part on the fact that both benzoyl peroxide and erythromycin are active against *P. acnes*. Both active ingredients have been used separately for many years in the treatment of acne vulgaris at concentrations that are similar to those in Benzamycin ——— (3% erythromycin/ 5% benzoyl peroxide, as applied). The combination of 3% erythromycin and 5% benzoyl peroxide has been used clinically for more than a decade as Benzamycin® Topical Gel, NDA #50-557.

The currently marketed formulation of Benzamycin® requires compounding by the pharmacist, and refrigeration of the product by the patient. Benzamycin DL-6026, is a modification of the original formulation and packaging. Benzamycin contains a erythromycin gel and a % benzoyl peroxide gel that are individually packaged *within* a dual pouch single use package.

The application is unique in that the patient will perform compounding prior to each application. The modified formulation and dispensing system does not require refrigeration or compounding by the pharmacist; instead, the patient squeezes the entire contents of the dual pouch into his/her palm and mixes the two gels with the fingertip. With compounding, a 3% erythromycin/ 5% benzoyl peroxide combination gel is formed that is similar to the marketed product.

Dermik conducted three separate 'use' studies to address patients' abilities to properly use the unique dual pouch package. These studies were conducted in healthy volunteers and concentrated on the various steps of package opening, and in two of the studies on blending of product by the participants with an application to the face.

The clinical development program included Phase 1 studies: a Repeat Insult Patch Test safety study, a pharmacokinetic study, three consumer use studies; and two multi-center efficacy and safety Phase 3 studies. In one of these Phase 3 studies a marketed Benzamycin treatment group (along with its matching placebo group) was included. This dual pouch product is a combination product; however as a line extension of an approved drug product, the request to demonstrate the contribution of each component of the combination product was not requested.

According to the submission, similarity was demonstrated in the UV-Vis profiles between the two products; therefore, results of the previously submitted phototoxicity and photoallergy studies were submitted with the NDA. The phototoxicity study and photoallergy study performed using the currently marketed formulation of Benzamycin are included in this submission for reference (originally submitted in NDA #50-557).

Table of clinical studies follows.

## Table 3 (Sponsor's Table 1., Vol. 1.11, pg. 8-1-2) Table Of Studies

| Study Number | Title | Investigators | | Completion Status (Starting Date) | Weeks of Drug Treatment (Frequency) | Dose (concentration) of | | Age Range | M/F (%) | Total Patients enrolled | Medical Summary Location: Volume, Page |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Name | Location | | | Benzoyl peroxide | Erythro-mycin | | | | |
| DL 6026-9708 | Evaluation of the Skin-irritating and Skin-sensitizing Propensities of Benzamycin Dual Pouch Product | M. Shelanski, M.D. | Conshohocken, PA | Complete (09/08/97) | 16 repeat applications (0.15ml) over a 5 week period | 5%<br>0%<br>0%<br>0%<br>-<br>5% | 3%<br>0%<br>6%<br>-<br>0%<br>3% (mktd.) | 18-83 | 20/80 | 211 | 1.11, 8-1-315 |
| DL 6026-9709 | A Multi-Centered Controlled, Double-Blind, Comparative Study of the Safety and Efficacy of the Benzamycin Dual Pouch, Benzamycin®, and Their Vehicles | M.T. Jarratt, M.D.<br>Phoebe Rich, M.D.<br>Toivo E. Rist, M.D.<br>D. Rodriquez, M.D.<br>D. Thiboutot, M.D.<br>Edward Ryan, D.O. | Austin, TX<br>Portland, OR<br>Knoxville, TN<br>Miami, FL<br>Hershey, PA<br>Conshohocken, PA | Complete (08/03/98) | 8 Weeks (b.i.d.) | 5%<br>0%<br>5% | 3%<br>0%<br>3% (mktd.) | 13-31<br>12-43<br>13-46<br>12-42<br>13-34<br>13-21 | 55/45<br>50/50<br>38/62<br>43/57<br>61/39<br>71/29 | 66<br>72<br>58<br>88<br>36<br>7 | 1.13, 8-3-12 |
| DL 6026-9717 | Single Dose Pharmacokinetics of Topical 3% Erythromycin 5% Benzoyl Peroxide in Patients Diagnosed with Acne Vulgaris | Aziz Laurent, M.D. | Austin, Texas | Complete (03/29/98) | Single dose 0.8g or 2.4 g | 5% | 3% | 18-37 | 38/62 | 16 | 1.11, 8-1-19 |
| DL 6026-9723 | A Multi-Centered Controlled, Double-Blind, Comparative Study of the Safety and Efficacy of the Benzamycin Dual Pouch and Vehicle | E. Monroe, M.D.<br>Terry Jones, M.D.<br>J. Weiss, M.D.<br>Leslie Mark, M.D. | Milwaukee, WI<br>Bryan, TX<br>Snellville, GA<br>San Diego, CA | Complete (08/22/98) | 8 Weeks (b.i.d.) | 5%<br>0% | 3%<br>0% | 13-33<br>13-40<br>13-35<br>13-40 | 50/50<br>59/41<br>56/44<br>32/68 | 64<br>76<br>36<br>47 | 1.16, 8-6-277 |
| DL 6026-9802 | Consumer Ease of Use Evaluation of the Benzamycin Dual Gel Pouch | M. Shelanski, M.D.<br>J.B. Shelanski | Conshohocken, PA | Complete (03/10/98) | One Day | 5% | 3% | 13-40 | 41/59 | 150 | 1.19, 8-9-1 |
| DL 6026-9819 | Consumer Ease Evaluation of the Benzamycin Dual Gel Pouch Comparing Two Direction Variants | M. Shelanski, M.D.<br>R. Donovan, M.D. | Conshohocken, PA<br>Modesto, CA | Complete (08/06/98) | One Day | 5% | 3% | 13-40 | 46/54 | 498 | 1.20, 8-10-1 |

## Table 3 (Sponsor's Table 1.) Table Of Studies (Cont'd)

| Study Number | Title | Investigators | | Completion Status (Starting Date) | Weeks of Drug Treatment (Frequency) | Dose (concentration) of | | Age Range | M/F (%) | Total Patients enrolled | Medical Summary Location: Volume, Page |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Name | Location | | | Benzoyl peroxide | Erythro-mycin | | | | |
| PI10281 | Consumer Evaluation of the Opening Ease of the Benzamycin Dual Gel Pouch | M. Shelanski, M.D. | Conshohocken, PA | Complete (11/20/97) | One Day | 0% | 0% | 13-40 | 51/49 | 80 | 1.18, 8-8-335 |
| IVY #4476/04* | Determination of the Phototoxic Potential of Benzamycin and Placebo | Kays Kaidbey, M.D. | Philadelphia, PA | Complete (12/15/80) | Single dose (50µl/cm²), occluded 6hrs | 5% | 3% | 18-23 | 0/100 | 10 | 1.12, 8-2-326 |
| IVY #4477/05* | Determination of the Photocontact Allergenic Potential of Benzamycin and Placebo | Kays Kaidbey, M.D. | Philadelphia, PA | Complete (12/15/80) | Single dose (10µl/cm²), Occluded 24 hrs., repeat twice weekly for 3 weeks, challenge | 5% | 3% | 19-31 | 4/96 | 25 | 1.12, 8-2-331 |
| DER 9801 (analytical report) | Ultraviolet-Visible UV-VIS Spectrum Scans of Benzamycin Dual Gel Preparations, Benzamycin Topical Gel Preparations, and Selected Components | Faina Verkh, Ph.D. | Collegeville, PA | Complete (06/16/98) | N/A | 10% | 6% | N/A | N/A | N/A | 1.12, 8-2-334 |

* Studies IVY #4476/04 and IVY #4477/05 were performed with the currently marketed Benzamycin Topical Gel (previously submitted in NDA #50-557)

**8.2 Indication #1 Acne Vulgaris**

**8.2.1 Study No. DL-6026-9709 (Study dates: March 11, 1998 to August 3, 1998)**

**Title: "A Multi-Centered, Controlled, Double Blind Comparative Study of the Safety and Efficacy of DL-6026 vs. Benzamycin® and Their Vehicles"**

**8.2.1.1 Objective/Rationale**

The objective of Study 9709 was to determine whether the Benzamycin treatment was more effective than the Placebo Dual Pouch treatment. A second objective of this study was to demonstrate whether the Benzamycin treatment met a non-inferiority criterion in a comparison to the currently marketed Benzamycin Topical Gel.

**8.2.1.2 Study Design**

Study No. DL-6026-9709 was a randomized, double-blinded, parallel group, study that was conducted at six investigational study sites located in the United States to compare safety and efficacy among the following four treatments: Benzamycin ; Placebo Dual Pouch; Benzamycin Topical Gel; and Placebo Topical Gel. Patients who qualified for entry into Study 9709 were randomly assigned to one of four double-blind treatment groups.

**8.2.1.3 Protocol Overview**

**8.2.1.3.1 Population/Procedures**

Significant Inclusion/Exclusion criteria

Patients were male and female, ages 13 years and older, with moderate to moderately-severe acne with the following at baseline:

- a minimum score of 1.5 on the global acne severity scale;
- have at least 15 and no more than 80 facial inflammatory lesions;
- have at least 20 and no more than 140 facial comedones (not including the nose or nasolabial area);
- have no more than 2 facial nodules/cysts (> 5 mm);
- if female, must practice an adequate form of birth control throughout the study.

Patients were excluded if they:

- were either pregnant or nursing mothers, or
- were involved in activities that had excessive or prolonged exposure to sunlight (to minimize exposure to sunlight, a hat or other clothing was to be worn).

Concomitant Medication

No concomitant topical or systemic acne medication, or topical antibiotic was to be used during the course of this study.

**Blinding**

Each active treatment had a matching blinded placebo treatment. The Benzamycin and the Benzamycin Topical Gel products differed in packaging (dual pouch product and jar product, respectively. In order to blind the investigator, medication was dispensed by investigative site personnel who were not directly involved in any of the patient evaluations.

**Randomization**

The randomization plan assigned patients to the following treatments, Benzamycin Dual Pouch; Placebo Dual Pouch; Benzamycin Topical Gel; and Placebo Topical Gel, in 3:1:3:1 proportions, respectively.

**Study Medication**

Study medication for each patient was supplied in boxes that contained individual units of either:

1). DL 6026 Benzamycin [redacted] (Batch No. 97J003);
2). matching placebo vehicle for Benzamycin [redacted] (Batch No. 98B001);
3). Benzamycin Topical Gel (DL 6008; Batch No. 97J004); or
4). matching placebo vehicle for Benzamycin Topical Gel (Batch No. 97J001).

**Study Plan**

Screening and Baseline Visit

A physical exam was performed and a medical history was obtained. A urine pregnancy test was also obtained for females of childbearing potential.

Baseline acne severity was graded by the investigator, and facial lesions were counted. Comedones of the nose and nasolabial fold area were not counted nor assessed. Qualified patients were assigned a patient number and dispensed study medication. The first application of study medication was made in the presence of the investigator or his/her designee.

Treatment Phase

Follow-up visits were to be scheduled at 2, 4, 6, and 8 weeks of therapy, and were calculated from the date that the patient first received study medication. Patients were evaluated within a ± one-week window in order to make the visit windows continuous.

At each follow up visit, the Physicians Global Acne Severity score, facial acne lesion counts, and the degree of oiliness were evaluated. Any adverse events were recorded, unused medication was retrieved, compliance assessed, and medication was dispensed. Change in dose, frequency of application, or missed doses were recorded on the CRF.

At the final visit, the patient evaluated the acceptability of the therapy and amount of improvement. Urine pregnancy test was repeated, where applicable.

Application of Drug

1. Patients washed their face twice daily, morning and evening, before each application. Patients washed their face and neck with warm water and the mild cleanser using hands only, rinsing thoroughly and drying with a clean towel. No abrasive cloths or sponges, alcoholic toners, astringents or medicated solutions were to be used.
2. Fifteen minutes after washing the study medication was to be applied in a thin film over the entire facial area including the face, forehead, cheeks, nose and chin area. Patients were instructed not to apply the medication or moisturizer within six hours prior to the follow-up visit.

3. On the day of treatment evaluations (Weeks 2, 4, 6, and 8) patients were not allowed to wear facial make-up (except lipstick and eye make-up) until after the study visit. Otherwise, the medication was to be used as scheduled, without interruption. On days other than evaluation days, if needed, a moisturizer provided by the sponsor may be applied one hour after application of the medication. Non-medicated make-up may be applied one hour after the medication. All medications were to be kept away from the eyes.
4. Sun exposure to the face was to be limited. On days other than visit days, non-medicated make-up could be applied one hour after the medication.

**8.2.1.3.3 Endpoints**

Primary efficacy variables were:

- lesion reductions from baseline in inflammatory lesions, non-inflammatory (comedones), and total lesions (inflammatory and comedones) and
- treatment success defined as physician's global severity scores of 0 (0=clear, no inflammatory lesions) or 0.5 (0.5=sparse comedones, with very few or no inflammatory lesions present).

**Secondary Efficacy Parameters**

Secondary efficacy evaluations were the physician's global acne severity scores, facial oiliness scores, and the endpoint patient evaluations of global improvement and treatment acceptability.

The Physician's Global Acne Severity Score

The Physician's Global Acne Severity Score was the physician's comprehensive evaluation of the patient's *overall acne condition* at the time of evaluation. The following 9 point scoring scale was used:

0 = Clear; no inflammatory lesions.
0.5 = Sparse comedones, with very few or no inflammatory lesions present.
1 = Comedones, with some small inflammatory lesions present; minimal erythema
1.5 = Comedones with an increasing number of inflammatory lesions compared to grade 1.
2 = Comedones, a moderate number of small inflammatory lesions extending over a wide area of the face; erythema is increasing.
2.5 = Comedones, an increasing number of inflammatory lesions vs. grade 2, with some larger inflamed lesions.
3 = Numerous comedones, papules, and pustules with larger inflamed lesions extending over much of the face; erythema may be pronounced.
3.5 = Comedones, with profuse papulopustular lesions with numerous large inflammatory lesions; some deep, pustular lesions may be present.
4 =Patient has severe or cystic (nodular) acne and is excluded from this study.

Photographic reprints were provided to serve as a representative example of grades 1, 2, and 3 on this scale and are to be used as a guide.

Current Severity Score of Facial Oiliness

The degree of oiliness was evaluated at base line and at all follow up visits by the investigator. The following scale was used.

Oiliness = Sebaceous facial oil

0 = None
1 = Mild; slight shine on a limited area of the face
2 = Moderate; shine clearly evident over entire face
3 = Severe; facial oiliness is excessive requiring removal more than once per day

**Reviewer's comments:** *Facial oiliness will not be assessed under this NDA. All subjects with moderate or moderately severe acne vulgaris do not necessarily have seborrhea. The clinical relevance was not established and the significance of the absence of oiliness to the patient was not assessed. No minimum entry criterion for the oiliness (seborrhea) endpoint was established for this study. The sponsor is encouraged to develop objective measure of seborrhea, a clinically meaningful scale with static descriptors by which to objectively evaluate seborrhea as a separate indication.*

Patients Global Improvement scores were obtained from the patients at the final visit on a 4-point scale.

**8.2.1.3.4 Statistical Considerations** (See Statistical Review dated 09-12-00)

**Data Analysis**

According to the submission, two treatment efficacy contrasts represented the primary study objectives:

- The superiority contrast compared efficacy outcomes between the active DL6026 and placebo DL6026 treatment groups.
- The non-inferiority contrast, between active DL6026 and active DL6008, evaluated the range of true treatment mean differences which were consistent with the observed efficacy outcomes.

For the evaluation of the superiority contrast, the patient population of primary interest was the Intent-to-treat patients, and this included all patients randomized to treatment with active study medication or with the placebo. The determination of relative treatment efficacy was primarily based upon the results of the Week 8 last-observation-carried-forward (LOCF) summaries.

For evaluation of the non-inferiority contrast, evaluable patients were the patient population of primary interest. The determination of Dual Pouch Product non-inferiority relative to the Topical gel was primarily based upon the Evaluable Observed Week 8 results of the evaluable patients. Results of earlier visit intervals provided additional information about the relative efficacy of active DL6026 compared to the placebo or to the active reference treatment.

**Safety Measurements**

Safety was assessed during the study by reporting of adverse events. All adverse events will be classified according to type of event, and body system affected. Laboratory measurements

were not taken during the course of the study except for urine pregnancy screening at the baseline and endpoint visits for females of childbearing potential.

**Financial Disclosure**
The Sponsor has submitted certification for financial interests and arrangements of clinical investigators participating in Study 9709. According to the Sponsor, no investigator participating in the study received compensation that was dependent on favorable study outcome, has ownership in of stock in the company that cannot be readily determined through reference to public prices, nor has a proprietary interest in the drug product.

### 8.2.1.4 Study Results (Study #9709)

A total of 327 patients participated in the study. List of principal investigators and number of patients enrolled at each site follows:

**Table 4 (Sponsor's Table 1, Vol. 13, pg. 8-3-23)**
**List of Principal Investigators and Number of Patients Enrolled at Each Site**

| Investigator's Name<br>Affiliation<br>Address | Dermik Inv # | Number of Patients Enrolled |
|---|---|---|
| Michael Jarratt, M.D.<br>Dermatology Research, Inc., 8140 N. Mopak, Bldg. 3, Suite 120, Austin, TX 78759 | US00708 | 66 |
| Phoebe Rich, M.D.<br>NW Cutaneous Research Specialists, 2222 NW Lovejoy, #419,<br>Portland, OR 97219 | US03004 | 72 |
| Toivo E. Rist, M.D.<br>Dermatology Assoc. of Knoxville, P.C., P.O. Box 3850<br>St. Mary's Professional Bldg. #511, 930 Emerald Ave.<br>Knoxville, TN 37917 | US03034 | 58 |
| David Rodriguez, M.D.<br>International Dermatology Research, Inc., 8370 Flagler St., #200, Miami, FL 33144 | US03006 | 88 |
| Edward Ryan, D.O.<br>Product Investigations, Inc., 151 E. 10th Ave.<br>Conshohocken, PA 19428 | US04094 | 7 |
| Diane M. Thiboutot, M.D.<br>University Physician's Center-2, Room 4300<br>Penn State University / Hershey Medical Center<br>500 University Drive, Hershey, PA 17033-0850 | US03069 | 36 |

#### 8.2.1.4.1 Demographics, Evaluability

A summary of the demographic characteristics among treatment groups of the Intent-to-treat (ITT) population follows.

**Table 5 (Sponsor's Table 2 Modified, Vol. 1.13, pg. 8-3-44) Demographics and Patient Characteristics - Intent-to-Treat Patients (ITT)**

| Characteristic | Active DL6026 | Active DL6008 | Placebo DL6026 | Placebo DL6008 | All Patients | Global Contrasts (p=)* Main Effect | by Site |
|---|---|---|---|---|---|---|---|
| Age (yr) | | | | | | | |
| Mean (±Std) | 19.6(±6.4) | 20.4(±7.4) | 19.6(±5.4) | 19.8(±5.2) | 19.9(±6.6) | TRT: >0.50 | 0.464 |
| n (range) | 124 (12-43) | 121 (12-46) | 42 (13-31) | 40 (14-30) | 327 (12-46) | SITE: 0.016 | |
| Sex | | | | | | | |
| Female | 65 (52.4%) | 57 (47.1%) | 24 (57.1%) | 22 (55.0%) | 168 (51.4%) | TRT: >0.50 | |
| Male | 59 (47.6%) | 64 (52.9%) | 18 (42.9%) | 18 (45.0%) | 159 (48.6%) | SITE: 0.106 | |
| Race | | | | | | | |
| Caucasian | 86 (69.4%) | 82 (67.8%) | 30 (71.4%) | 29 (72.5%) | 227 (69.4%) | TRT: >0.50 | |
| Black | 10 (8.1%) | 9 (7.4%) | 2 (4.8%) | 2 (5.0%) | 23 (7.0%) | SITE: <0.001 | |
| Asian | 2 (1.6%) | 1 (0.8%) | 1 (2.4%) | 0 (0.0%) | 4 (1.2%) | | |
| Hispanic | 24 (19.4%) | 27 (22.3%) | 8 (19.0%) | 9 (22.5%) | 68 (20.8%) | | |
| Other | 2 (1.6%) | 2 (1.7%) | 1 (2.4%) | 0 (0.0%) | 5 (1.5%) | | |

* Means contrasts from analysis of variance (treatment, site, interaction).
ANOVA for Ht & Wt included sex of patient. Frequency contrasts from CMH test (general association)
for site effects or treatment stratified by site.

No treatment group differences or treatment by study site interactions were statistically significant.

## Disposition of Patients

Table 6, below provides the end-of-study status of all patients who enrolled into the study submitted by the sponsor. The proportions of patients who completed in the placebo treatment groups, 78.6 and 87.5%, were approximately similar to the proportions who completed in the active treatment groups, 92.7% and 90.9%. The single patient in the study who discontinued due to an adverse event, Patient No. 00078 in the active DL6026 treatment group, experienced severe sunburn.

**Table 6 (Sponsor's Table 3, Vol. 1.13, pg. 8-3-40) Patient Disposition**

Treatment Group Summaries

| End of Study Status | Active DL6026 n | % | (Evaluable) | Active DL6008 n | % | (Evaluable) | Placebo DL6026 n | % | (Evaluable) | Placebo DL6008 n | % | (Evaluable) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Total Enrolled | 124 | | (116) | 121 | | (113) | 42 | | (36) | 40 | | (35) |
| Patient Completed | 115 | 92.7 | (115) | 110 | 90.9 | (110) | 33 | 78.6 | (33) | 35 | 87.5 | (35) |
| Discontinued due to: | | | | | | | | | | | | |
| Adverse Event | 1 | 0.8 | (0) | 0 | | (0) | 0 | | (0) | 0 | | (0) |
| Lost to follow-up | 3 | 2.4 | (0) | 3 | 2.5 | (0) | 2 | 4.8 | (0) | 1 | 2.5 | (0) |
| Protocol Deviations | 1 | 0.8 | (0) | 3 | 2.5 | (1) | 2 | 4.8 | (1) | 3 | 7.5 | (0) |
| Voluntarily Left Study | 4 | 3.2 | (1) | 5 | 4.1 | (2) | 5 | 11.9 | (2) | 1 | 2.5 | (0) |

Abstracted from Appendix II.F.1.1. Listing in Appendix IV.A.1.1.
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**Protocol Deviations**

Protocol deviations that occurred in the study were of the following types:

- patient younger than 13 years,
- baseline severity score less than 1.5,
- patients with too few or too many baseline inflammatory lesions or comedones,
- patients were pregnant or nursing mothers,
- patient had a medical history of sensitivity to oral erythromycin, patients used proscribed concomitant medications (with potential effect to treat acne),
- patients who did not apply the study medication, and completed visits were not within scheduled intervals.
- efficacy evaluations from photos of 8 patients (Vol. 14, pg. 8-4-16)

**Reviewer's comments:** *The sponsor's number of protocol deviations differs from those cited in the FDA Statistical review; however, these differences did not have an adverse impact on efficacy outcome results. There were no significant differences between treatment groups with respect to the subject inclusion ITT and Per Protocol populations.*

### 8.2.1.4.2 Efficacy

#### 8.2.1.4.2.1 Clinical

Baseline lesions counts followed by primary efficacy variable results at end of study (Week 8) follow for the ITT population.

Table 7 (Partial Extraction, Sponsor's Table 7, Vol. 1.13, pg. 8-3-46) Baseline Lesion Counts (Intent-to-Treat Patients)

| Baseline | Treatment Groups | | | | | Global Contrasts (p=) | |
|---|---|---|---|---|---|---|---|
| | Active DL6026 | Active DL6008 | Placebo DL6026 | Placebo DL6008 | All Patients | Main Effect | trt by site |
| Comedones | | | | | | | |
| Mean (±Std) | 54.7(±28.5) | 55.4(±29.4) | 58.2(±33.6) | 53.7(±29.6) | 55.3(±29.5) | TRT: >0.50 | 0.460 |
| n (range) | 124 (15-139) | 121 (4-163) | 42 (0-170) | 40 (4-158) | 327 (0-170) | SITE:<0.001 | |
| Inflammatory Lesions | | | | | | | |
| Mean (±Std) | 28.0(±14.6) | 27.0(±12.7) | 25.8(±10.1) | 28.2(±15.2) | 27.4(±13.5) | TRT: >0.50 | 0.389 |
| n (range) | 124 (15-85) | 121 (14-88) | 42 (15-53) | 40 (4-77) | 327 (4-88) | SITE:<0.001 | |
| Total Lesions | | | | | | | |
| Mean (±Std) | 82.7(±34.3) | 82.4(±35.2) | 84.0(±37.9) | 81.9(±37.7) | 82.6(±35.4) | TRT:>0.50 | 0.201 |
| n (range) | 124 (35-191) | 121 (27-187) | 42 (24-191) | 40 (39-235) | 327 (24-235) | SITE:<0.001 | |
| Cysts | | | | | | | |
| Mean (±Std) | 0.1(±0.4) | 0.2(±0.4) | 0.0(±0.2) | 0.1(±0.3) | 0.1(±0.4) | | |
| n (range) | 124 (0-2) | 121 (0-2) | 42 (0-1) | 40 (0-1) | 327 (0-2) | | |

Abstracted from Appendix II.F.3.1 (means), II.F.3.2 (frequencies), II.E.2.2.1 (means contrasts), and II.E.2.2.2 (Frequency Contrasts)

* Means contrasts from analysis of variance (treatment, site, interaction). Frequency contrasts from CMH test (row mean scores) for site effects or treatment stratified by site. Sites -- pool 1 & 5.

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No treatment group difference or treatment by study site interaction of baseline lesion counts was noted.

**Table 8 Comparison of Lesion Reduction from Baseline to Week 8: Study DL-6026-9709 (Extracted from Statistical Review, Table 2)**

| | AD | AG | DP | PG | comparison | p-value |
|---|---|---|---|---|---|---|
| | **Non-inflammatory Lesions** | | | | | |
| Mean # lesion reduction | 24.0 | 23.3 | 14.6 | 13.9 | AD vs. PD | 0.003 |
| Mean % lesion reduction | 45.9% | 42.8% | 24.4% | 20.2% | AD vs. PD | <0.001 |
| | **Inflammatory Lesions** | | | | | |
| Mean # lesion reduction | 13.5 | 11.9 | 4.3 | 6.5 | AD vs. PD | <0.001 |
| Mean % lesion reduction | 49.1% | 45.4% | 16.8% | 27.6% | AD vs. PD | <0.001 |
| | **Total Lesions (Non-inflammatory + Inflammatory Lesions)** | | | | | |
| Mean # lesion reduction | 37.4 | 35.2 | 18.9 | 20.4 | AD vs. PD | <0.001 |
| Mean % lesion reduction | 48.1% | 43.8% | 22.2% | 25.8% | AD vs. PD | <0.001 |

AD = active dual pouch; PD = placebo dual pouch; AG = active topical gel; PG = placebo topical gel

At Week 8, the active dual pouch (AD) is significantly more effective than the placebo dual pouch (PD) in inflammatory, non-inflammatory, and total lesion reduction (p-value ≤ 0.003).

Investigator's Global (Treatment Success)

At the end of the study (Week 8), the active dial pouch (AD) was significantly more effective than the dual pouch in achieving treatment success in the investigator's global (p-value = <0.001) as noted in Table 9 that follows.

**Table 9: Treatment Success at Week 8 Study DL-6026-9709 (Extracted from Statistical Review, Table 3)**

| Treatment | | | | Comparison | |
|---|---|---|---|---|---|
| AD (n=119) | AG (n=113) | PD (n=38) | PG (n=37) | AD vs. PD (p-value) | Lower bound of 97.5% CI |
| 33 (27.7%) | 30 (26.5%) | 1 (2.6%) | 4 (10.8%) | <0.001 | -11.2% |

AD = active dual pouch; PD = placebo dual pouch; AG = active topical gel; PG = placebo topical gel

According to the FDA Statistical Review, the active dual pouch is non-inferior to the active gel in lesion reduction at Week 8 since the lower bounds of the 97.5% confidence interval for mean differences are all on and above –20% of the active topical gel.

### 8.2.1.4.3 Safety

The majority of the patients participated in the study for 8 weeks. There were no deaths reported in this study. There was one discontinuation due to an adverse event coded as Photosensitivity. One serious adverse event, a diskectomy performed for an accidental back injury, was recorded for patient No. 00048 (Benzamycin

The most frequently occurring skin-related adverse event was dry skin that occurred in 3.2% of the patients receiving active DL 6026 vs. 0% of the patients receiving the matching placebo. The incidence of dry skin reported in the Dual Pouch product was comparable to the currently marketed formulation of Benzamycin (3.2% versus 5.0%, respectively). The overall incidence of patients reporting adverse events was similar across all treatments (approximately 30% of the patients in each treatment group reported at least one adverse event).

A total of 38 patients (30.6%) and 43 patients (35.5%) reported at least one adverse event in the active DL 6026 (Dual Pouch) and active DL 6008 (marketed Benzamycin) treatment groups, respectively. This incidence rate was similar in both of the placebo treatments. The most frequently reported adverse event in this study was headache (9.7%, 9.1%, 4.8% and 7.5% in the active DL 6026, active DL 6008, placebo DL 6026, and placebo DL 6008 treatments, respectively).

Patients who experienced adverse events coded as Photosensitivity included two cases of sunburn that were not considered related to the study medication (patients # 00078 and # 00119). One patient (# 00322) who reported a 10minute episode of moderate stinging under the eyes when in the sun that was considered possibly related to the study medication. Photosensitivity and blepharitis are the COSTART terms that are assigned to other body systems, but could be related to the skin.

# Adverse Events

## Table 10 (Sponsor's Table 29, Vol. 1.13, pg. 8-3-80) Summary of Adverse Experience Incidences by Body System

| Body System Summary | COSTART Pref. Term | TREATMENT GROUP FREQUENCIES (%) Active DL6026 | Active DL6008 | Placebo DL6026 | Placebo DL6008 |
|---|---|---|---|---|---|
| Summary | All Patients | 124 (100.0%) | 121 (100.0%) | 42 (100.0%) | 40 (100.0%) |
| | Incidence of AE | 38 (30.6%) | 43 (35.5%) | 12 (28.6%) | 13 (32.5%) |
| | Occurrence of AE | 45 | 50 | 18 | 13 |
| Body as a Whole | | 23 (18.5%) | 20 (16.5%) | 8 (19.0%) | 5 (12.5%) |
| | HEADACHE | 12 | 11 | 2 | 3 |
| | VIRAL INFECTION | 4 | 4 | 2 | 1 |
| | ABDOMINAL PAIN | | 2 | 2 | 1 |
| | FLU SYNDROME | 3 | 1 | 1 | |
| | ACCIDENTAL INJURY | 3 | 1 | | |
| | PHOTOSENSITIVITY REACTI | 3 | | | |
| | BACK PAIN | | 1 | | |
| | FEVER | | 1 | | |
| | INFECTION PARASITIC | | | 1 | |
| | PAIN | | 1 | | |
| Cardiovascular | | | 1 (0.8%) | | |
| | MIGRAINE | | 1 | | |
| Digestive | | 2 (1.6%) | 2 (1.7%) | 2 (4.8%) | |
| | MOUTH ULCERATION | | 1 | 1 | |
| | NAUSEA | 1 | | 1 | |
| | DYSPEPSIA | 1 | | | |
| | TOOTH DISORDER | | 1 | | |
| Nervous | | | 2 (1.7%) | | |
| | DEPRESSION | | 2 | | |
| Respiratory | | 6 (4.8%) | 7 (5.8%) | 4 (9.5%) | 4 (10.0%) |
| | PHARYNGITIS | 3 | 4 | 3 | 3 |
| | RHINITIS | 2 | 2 | 1 | 1 |
| | SINUSITIS | 1 | 1 | | |
| | EPISTAXIS | | 1 | | |
| Skin & Appendages | | 9 (7.3%) | 10 (8.3%) | 3 (7.1%) | 2 (5.0%) |
| | DRY SKIN | 4 | 6 | | |
| | PRURITUS | 1 | 3 | | |
| | RASH | | 1 | 2 | 1 |
| | APPLICATION SITE REACTI | 2 | 1 | | |
| | CONTACT DERMATITIS | | 1 | | |
| | ECZEMA | | | 1 | |
| | EXFOLIATIVE DERMATITIS | 1 | | | |
| | NAIL DISORDER | | | | 1 |
| | SEBORRHEA | 1 | | | |
| Special Senses | | | 2 (1.7%) | | 1 (2.5%) |
| | ABNORMAL VISION | | 1 | | |
| | BLEPHARITIS | | | | 1 |
| | OTITIS MEDIA | | 1 | | |
| Urogenital | | 3 (2.4%) | 1 (0.8%) | 1 (2.4%) | 1 (2.5%) |
| | DYSMENORRHEA | 1 | | 1 | |
| | UNINTENDED PREGNANCY | 1 | 1 | | |
| | URINARY TRACT INFECTION | | | | 1 |
| | VAGINAL MONILIASIS | 1 | | | |

Listings in Appendices IV.A.5.1 and IV.A.5.2 (COSTART preferred terms)
Each patient counted only once in each row (except count of occurrences)
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Laboratory Evaluation
As previously stated, except for urine pregnancy testing, clinical safety laboratory evaluations were not performed in this study. Two pregnancies occurred in patients on active therapy (Pts. # 55 and 64). Pregnancy outcome results are pending.

**8.2.1.5 Reviewer's Comments/Conclusions of Study Results**
Facial oiliness was not assessed since all subjects with moderate or moderately severe acne vulgaris do not necessarily have seborrhea. The sponsor did not provide clinical relevance or the significance of the absence of oiliness to the patient. No minimum entry criterion for the oiliness (seborrhea) endpoint was established for this study. The sponsor is encouraged to develop objective measure of seborrhea and a clinically meaningful scale with static descriptors by which to evaluate seborrhea as a separate indication.

Benzamycin ——— is effective in treatment of acne vulgaris and is non-inferior to the marketed Benzamycin Topical Gel. At Week 8, the active dual pouch (AD) is statistically superior to placebo in reduction of inflammatory, non-inflammatory, and total lesion reduction (p-value ≤ 0.003). At the end of the study (Week 8), the active dual pouch (AD) was significantly more effective than the dual pouch in achieving treatment success (p-value = <0.001). Benzamycin ——— is non-inferior to the Benzamycin Topical Gel in lesion reduction at Week 8.

The majority of the patients participated in the study for 8 weeks. There were no deaths reported in this study. A total of 38 patients (30.6%) and 43 patients (35.5%) reported at least one adverse event in the active DL 6026 (Dual Pouch) and active DL 6008 (marketed Benzamycin) treatment groups, respectively. This incidence rate was similar in both of the placebo treatments. The most frequently occurring skin-related adverse event was dry skin that occurred in 3.2% of the patients receiving active DL 6026 vs. 0% of the patients receiving the matching placebo. The incidence of dry skin reported in the Dual Pouch product was comparable to the currently marketed formulation of Benzamycin (3.2% versus 5.0%, respectively). The overall incidence of patients reporting adverse events was similar across all treatments (approximately 30% of the patients in each treatment group reported at least one adverse event).

**Financial Disclosure**
The Sponsor has submitted certification for financial interests and arrangements of clinical investigators participating in Study 9723. According to the Sponsor, no investigator participating in the study received compensation that was dependent on favorable study outcome, has ownership in of stock in the company that cannot be readily determined through reference to public prices, nor has a proprietary interest in the drug product.

**8.2 Indication #1 Acne Vulgaris**
**8.2.2 Trial #2 Study No. DL-6026-9723**
**Title: "A Multi-Centered, Controlled, Double Blind Comparative Study of the Safety and Efficacy of DL-6026 vs. Vehicle"**
**(Study dates: March 17, 1998 to July 22, 1998.)**

### 8.2.2.1 Objective/Rationale

Study No. DL-6026-9723 was a randomized, double-blinded, parallel group, study that was conducted at four investigational study sites to compare safety and efficacy among the following treatments: Benzamycin and Placebo Dual Pouch.

### 8.2.2.2 Study Design

This was a double blind, randomized, parallel group, multi-center study of 223 patients with moderate to moderately-severe acne. Investigators evaluated the safety and efficacy of Benzamycin against matching placebo for treatment duration of eight weeks. Patients visited the study center at Baseline (Week 0), and at 2, 4, 6, and 8 weeks of therapy. To determine comparative efficacy, facial lesions were counted and an investigator's global acne severity score was obtained at each visit.

The inclusion and exclusion criteria for this study and overall study procedures were identical to the criteria utilized in Study 9709 (except for the number of study arms). The randomization plan assigned an equal number of patients to each treatment group.

**Study medication**

- Benzamycin (3% erythromycin 5% benzoyl peroxide) (Batch Number 97J003)
- Matching Vehicle for Benzamycin (Batch Number 98B001)

Efficacy Parameters

Efficacy parameters in this study were identical to the parameters utilized in Study 9709 for comparisons of the active dual pouch to the placebo dual pouch.

### 8.2.1.4 Study Results (Study #9723)

A total of 223 patients participated in the study at the following centers:

**Table 11: List of Principal Investigators and Number of Patients Enrolled at Each Site**

| Investigator's Name, Affiliation, and Address | Dermik Inv # | Number of Patients Enrolled |
|---|---|---|
| Terry Jones, M.D., J & S Studies, Inc., 4309 Wellborn Rd. Bryan, TX 77801 USA (409)846-5933 | US02619 | 76 |
| Leslie Mark, M.D., Skin Surgery Medical Group, 5222 Balboa Avenue, 6th Floor, San Diego, CA USA (619)292-5101 | US04220 | 47 |
| Eugene Monroe, M.D., Advanced Healthcare, S.C., 3003 West Good Hope Rd., Milwaukee, WI USA (414)352-3100 | US 01960 | 64 |
| Jonathan Weiss, M.D., Gwinnett Clinical Research Center, 2366 Lenora Church Road, Snellville GA USA (770)972-2241 | US01962 | 36 |

### 8.2.1.4.1 Demographics, Evaluability

Sponsor's Table 11 proves a summary of the demographic characteristics by treatment group for the Intent-to-treat population. Except for the racial classification, no treatment group differences or treatment by study site interactions were evident (all p>0.15). The treatment contrast for race categories had p=0.075 and the difference appeared to be a higher relative proportion of Caucasian patients to Black patients (84% to 11%, in the active DL6026 treatment group compared to the placebo group (74% to 16%).

**Table 12: (Sponsor's Table 6, Vol. 16, pg.8.6.304) Demographics and Patient Characteristics - Intent-to-Treat (ITT) Patients**

| Characteristic | Treatment Groups: Benzamycin DL-6026 | Treatment Groups: Placebo | All Patients | Global Contrasts (p=)*: Main Effect | | Global Contrasts (p=)*: Treatment by Site |
|---|---|---|---|---|---|---|
| Age (yr) | | | | | | |
| Mean (±Std) | 18.7(±6.2) | 18.2(±5.4) | 18.5(±5.8) | TRT: | >0.50 | 0.234 |
| n (range) | 112 (13-40) | 111 (13-39) | 223 (13-40) | SITE: | 0.392 | |
| Sex | | | | | | |
| Female | 57 (50.9%) | 54 (48.6%) | 111 (49.8%) | TRT: | >0.50 | |
| Male | 55 (49.1%) | 57 (51.4%) | 112 (50.2%) | SITE: | 0.028 | |
| Race | | | | | | |
| Caucasian | 94 (83.9%) | 82 (73.9%) | 176 (78.9%) | TRT: | 0.075 | |
| Black | 12 (10.7%) | 18 (16.2%) | 30 (13.5%) | SITE: | 0.002 | |
| Asian | 3 (2.7%) | 1 (0.9%) | 4 (1.8%) | | | |
| Hispanic | 3 (2.7%) | 10 (9.0%) | 13 (5.8%) | | | |

Abstracted from Appendix II.F.2.1 (means), II.F.2.2 (frequencies), II.E.2.1.1 (means contrasts), and II.E.2.1.2 (Frequency Contrasts)

* Means contrasts from analysis of variance (treatment, site, interaction). ANOVA for Ht & Wt included sex of patient. Frequency contrasts from CMH test (general association) for site effects or treatment stratified by site.

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### Disposition of Patients

The proportions of patients who completed were similar between treatment groups. Most patients who failed to complete the study in either treatment group either voluntarily left the study or were lost to follow-up. Patient No. 00175 in the placebo treatment group experienced dryness and itchiness and was the only patient who prematurely discontinued due to an adverse event. Patient No. 00012 in the Benzamycin Dual Gel (DL6026) treatment group discontinued at Day 29 due to treatment failure. Four patients in the placebo treatment group who discontinued due to treatment failure were Patients No. 00187 at Day 33, No. 00210 at Day 43, No. 00211 at Day 45, and No. 00220 at Day 30.

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Table 13 (Sponsor's Table 3, Vol. 16, pg. 8-6-301) Patient Disposition

| | Treatment Group Summaries | | | | | |
|---|---|---|---|---|---|---|
| | Benzamycin DL-6026 | | | Placebo | | |
| End of Study Status | n | % | (Evaluable) | n | % | (Evaluable) |
| Total Enrolled | 112 | | (98) | 111 | | (95) |
| Patients Completed | 95 | 84.8 | (93) | 93 | 83.8 | (91) |
| Patients Discontinued for: | | | | | | |
| Adverse Event | 0 | 0.0 | (0) | 1 | 0.9 | (0) |
| Treatment Failure | 1 | 0.9 | (1) | 4 | 3.6 | (3) |
| Lost to follow-up | 9 | 8.0 | (0) | 5 | 4.5 | (0) |
| Voluntarily Left Study | 7 | 6.3 | (4) | 8 | 7.2 | (1) |

Abstracted from Appendix II.F.1.1. Listing in Appendix IV.A.1.1.
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## Protocol Deviations

Protocol deviations that occurred were entry criteria violations and non-compliance issues. No patient was discontinued from the study as a result of protocol deviations or non-compliance.

The sponsor's number of protocol deviations differs from those cited in the FDA Statistical Review; however, this did not adversely impact efficacy outcome results. There were no significant differences between treatment groups with respect to the subject inclusion ITT and PP populations

## 8.2.2.4.2 Efficacy

### 8.2.2.4.2.1 Clinical

Baseline lesion counts followed by end of study results (Week 8) for the ITT population follows.

Table 14 (Sponsor's Partial Table 4.) Baseline Lesion counts of Intent-to-Treat Patients

| Baseline | Treatment Groups | | | Global Contrasts (p=)* | | |
|---|---|---|---|---|---|---|
| Evaluation | Benzamycin DL-6026 | Placebo | All Patients | Main Effect | | Treatment by Site |
| Comedones | | | | | | |
| Mean (±Std) | 41.3(±26.0) | 42.2(±21.4) | 41.8(±23.7) | TRT: | >0.50 | 0.491 |
| n (range) | 112 (12-139) | 111 (2-108) | 223 (2-139) | SITE: | <0.001 | |
| Inflammatory Lesions | | | | | | |
| Mean (±Std) | 31.1(±15.7) | 29.3(±11.7) | 30.2(±13.9) | TRT: | 0.265 | 0.485 |
| n (range) | 112 (15-83) | 111 (15-58) | 223 (15-83) | SITE: | <0.001 | |
| Total Lesions | | | | | | |
| Mean (±Std) | 72.4(±31.0) | 71.5(±25.5) | 72.0(±28.3) | TRT: | >0.50 | >0.50 |
| n (range) | 112 (37-192) | 111 (23-155) | 223 (23-192) | SITE: | <0.001 | |
| Cysts | | | | | | |
| Mean (±Std) | 0.1(±0.4) | 0.2(±0.5) | 0.1(±0.4) | | | |
| n (range) | 112 (0-2) | 111 (0-2) | 223 (0-2) | | | |

Abstracted from Appendix II.F.3.1 (means), II.F.3.2 (frequencies), II.E.2.2.1 (means contrasts), and II.E.2.2.2 (Frequency Contrasts)
* Means contrasts from analysis of variance (treatment, site, interaction). Frequency contrasts from CMH test (row mean scores) for site effects or treatment stratified by site.
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**Table 15: Comparison of Lesion Reduction from Baseline to Week 8: Study DL-6026-9723 (Extracted from Statistical Review, Table 4)**

| | Treatment | | |
|---|---|---|---|
| Lesion Reduction | Active Dual (N=109) | Placebo Dual (N+108) | p-value |
| | Non-inflammatory Lesions (comedones) | | |
| Number reduction | 15.07 | 12.82 | 0.262 |
| % reduction | 36.2% | 29.6% | 0.175 |
| | Inflammatory Lesions | | |
| Number reduction | 16.63 | 9.44 | <0.001 |
| % reduction | 57.2% | 34.1% | <0.001 |
| | Total Lesions (Non-inflammatory + Inflammatory Lesions) | | |
| Number reduction | 31.71 | 22.27 | 0.002 |
| % reduction | 45.3% | 31.4% | <0.001 |

The active dual pouch (AD) is significantly superior to placebo (PD) in reduction of inflammatory and total lesions at Week 8 (p-value ≤ 0.002). For non-inflammatory lesion however, AD is not significantly superior to placebo (p-value≥ 0.175). For treatment success, active dual pouch is significantly more effective than placebo at Week 8 (p-value <0.001) as noted in Table 16 that follows:

**Table 16: Treatment Success at Week 8: Study DL-6026-9723 (Partial Extraction from Statistical Review, Table 5)**

| Treatment | | |
|---|---|---|
| Active Dual (N=109) | Placebo Dual (N=108) | p-value |
| 39 (35.8%) | 13 (12.0%) | <0.001 |

8.2.2.4.3 Safety

Tnere were no deaths reported in this study. One patient (#175, placebo treatment) was discontinued prematurely due to adverse events (dryness, itching) within the first two weeks of treatment.

Two serious adverse events were reported during the study, and both were considered unrelated to the study medication. Patient No. 00019, a 19-year-old male Caucasian in the Benzamycin [redacted] DL6026) treatment group was diagnosed with Hodgkin's disease on study day 41. Patient No. 00221, a 16-year-old male Caucasian in the Benzamycin Gel (DL6026) treatment group was diagnosed with mononucleosis on study day 31. Although these patients experienced serious adverse events, both completed the study.

**Adverse Events**

Table 10 (Sponsor's Table 20, Vol. 16. Pg. 8-6-325) is a summary of all the adverse experiences that were reported in the study.

Table 17 (Sponsor's Table 5, Vol. 16, pg. 8-6-325) Summary of Adverse Experience Incidences by Body System

| Body System Summary | COSTART Pref. Term | TREATMENT GROUP FREQUENCIES (%) Active DL-6026 | Vehicle DL-6026 |
|---|---|---|---|
| Summary | All Patients | 112 (100.0%) | 111 (100.0%) |
| | Incidence of AE | 43 (38.4%) | 30 (27.0%) |
| | Occurrence of AE | 72 | 42 |
| Body as a Whole | | 17 (15.2%) | 13 (11.7%) |
| | INFECT VIRAL | 7 | 6 |
| | HEADACHE | 5 | 3 |
| | INJURY ACCID | 3 | 2 |
| | FLU SYND | 2 | 2 |
| | PAIN ABDO | 1 | 1 |
| | NECK RIGID | | 1 |
| | PAIN BACK | 1 | |
| Digestive | | 3 (2.7%) | |
| | ABSCESS PERIODON | 1 | |
| | DYSPEPSIA | 1 | |
| | NAUSEA | 1 | |
| | VOMIT | 1 | |
| Hemic/Lymphatic | | 1 (0.9%) | |
| | LYMPHADENO | 1 | |
| | LYMPHOMA LIKE RE | 1 | |
| Musculoskeletal | | 2 (1.8%) | 1 (0.9%) |
| | ARTHRALGIA | 2 | |
| | BONE DIS | | 1 |
| Respiratory | | 12 (10.7%) | 10 (9.0%) |
| | PHARYNGITIS | 5 | 2 |
| | RHINITIS | 5 | 2 |
| | SINUSITIS | 3 | 3 |
| | COUGH INC | 1 | 2 |
| | ASTHMA | | 1 |
| | BRONCHITIS | 1 | |
| Skin & Appendages | | 20 (17.9%) | 9 (8.1%) |
| | SKIN DRY | 14 | 6 |
| | APPLICAT SITE RE | 4 | 2 |
| | PRURITUS | 3 | 2 |
| | DERM CONTACT | 1 | |
| | DERM EXFOL | | 1 |
| | GRANULOMA SKIN | 1 | |
| | RASH | | 1 |
| Special Senses | | 5 (4.5%) | 1 (0.9%) |
| | BLEPHARITIS | 4 | 1 |
| | CONJUNCTIVITIS | 1 | |
| Urogenital | | 2 (1.8%) | 3 (2.7%) |
| | DYSMENORRHEA | 1 | 3 |
| | MONILIA VAGINA | 1 | |

Listings in Appendices IV.A.5.1.1 and IV.A.5.1.2 (COSTART preferred terms)
Each patient counted only once in each row (except count of occurrences)
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Laboratory Evaluation

Clinical safety laboratory evaluations were not performed in this study except for urine pregnancy testing.

## Clinical Evaluations

Clinical evaluations (physical examination and vital signs) were reported for the baseline visit. No post-treatment follow-up evaluations were made.

### 8.2.2.5 Reviewer's Comments/Conclusions of Study Results

Benzamycin Dual Pouch is effective in treatment of acne vulgaris based on results of Study 9723. Benzamycin Dual Pouch was found to be statistically superior to placebo in reduction of inflammatory and total lesions at Week 8 (p-value ≤ 0.002). For non-inflammatory lesion however, Benzamycin Dual Pouch is not significantly superior to placebo (p-value ≥ 0.175). Statistical superiority over placebo was only needed in two of the three measures of lesion reduction. For treatment success, active dual pouch is significantly more effective than placebo at Week 8 (p-value <0.001).

There were no deaths reported in this study. One patient in the placebo treatment group was discontinued prematurely due to adverse events (dryness, itching) within the first two weeks of treatment. Two serious adverse events were reported during the study, and both were considered unrelated to the study medication. Patient No. 00019, a 19 year old male Caucasian in the Benzamycin Dual Gel (DL6026) treatment group was diagnosed with severe Hodgkin's disease on study day 41. Patient No. 00221, a 16 year old male Caucasian in the Benzamycin Dual Gel (DL6026) treatment group was diagnosed with severe mononucleosis on study day 31. Although these patients experienced serious adverse events, both completed the study.

A total of 43 patients (38%) vs. 30 patients (27%) reported at least one adverse event in the active and placebo treatment groups, respectively. The most frequent adverse event in this study was dry skin reported in 14 (12.5%) of the patients in the active treatment vs. 6 (5.4%) patients in the placebo treatment. Other commonly reported treatment related adverse events were application site reaction (*e.g.*, burning, stinging) in 3.6% and 1.8% of the patients receiving the active and placebo treatments, respectively); and pruritis in 2.7% and 1.8% of the patients in the active and placebo treatments, respectively.

## 9 Overview of Efficacy

Results of data analyses from two independent, randomized, double blind, parallel group, Phase 3 studies (DL 6026-9709 and DL 6026-9723), supports the efficacy of Benzamycin Dual Pouch applied twice daily for 8 weeks in the treatment of acne vulgaris. Based on last observation carried forward (LOCF) for missing data, efficacy results indicate that Benzamycin Dual Pouch is clinically and statistically superior to placebo in reduction of inflammatory, reduction of total lesions (non-inflammatory and inflammatory), and treatment success. Treatment success is defined as an investigator's global severity score of clear with no inflammatory lesions or with sparse conedones, with very few or no inflammatory lesions present.

**Table 18: Summary of Primary Efficacy Endpoint Variables**

| | | Lesion Reduction | | | |
|---|---|---|---|---|---|
| **Study** | **Comparisons** | **Non-inflammatory** | **Inflammatory** | **Total lesions** | **Investigator's Global** |
| #9709 | AD vs. PD | superior | superior | superior | superior |
| #9723 | AD vs. PD | Not significant | superior | superior | superior |

There were four-study arms, Benzamycin Dual Pouch vs. Benzamycin Topical Gel vs. the corresponding vehicle formulations, in Study 9708. Results from Study 9708 indicate that

Benzamycin Dual Pouch is non-inferior to the currently marketed Benzamycin Topical Gel.

**Table 19: Secondary Efficacy Endpoint**

| | Lesion Reduction | | | | |
|---|---|---|---|---|---|
| **Study** | **Comparisons** | **Non-inflammatory** | **Inflammatory** | **Total lesions** | **Investigator's Global** |
| #9709 | AD vs. AG | Non-inferior | Non-inferior | Non-inferior | Non-inferior |

## 9 Overview of Safety

## 10 Significant/Potentially Significant Events

### 10.1.1 Deaths

**No deaths were reported.**

### 10.1.2 Other Significant/Potentially Significant Events (Serious adverse events, dropouts/withdrawals)

Serious adverse events occurred in three patients; however, were not considered related to study drug. These patients are listed in Table 20.

**TABLE 20 (SPONSOR'S TABLE 18, VOL. 1.21, PG. 8-11-75): LIST OF SERIOUS ADVERSE EVENTS**

| Treatment Group* | Study No. | Patient Number | Sex/ Age | Investigator | Adverse Event (verbatim term) | Onset Day Rx | Duration | Outcome | Relation to Study Drug |
|---|---|---|---|---|---|---|---|---|---|
| A6026 | 9709 | 48 | M/15 | Jarratt | diskectomy secondary to accidental back injury | 17 | 4 hrs | Recovered | None |
| A6026 | 9723 | 19 | M/19 | Monroe | Hodgkin's disease | 42 | Ongoing | AE present, treatment | None |
| A6026 | 9723 | 221 | M/16 | Monroe | mononucleosis | 32 | 8 D | Recovered | None |

* Treatment groups were: A6026 active Benzamycin Dual Pouch, P6026 Placebo Dual Pouch, A6008 active Benzamycin Topical Gel, and P6008 Placebo Topical Gel.

Table 21 displays a listing of patients discontinued due to adverse events. Patient #175 was assigned to placebo treatment arm.

**TABLE 21 (SPONSOR'S TABLE 19, VOL. 1.21, PG. 8-11-77): PATIENTS DISCONTINUED BECAUSE OF ADVERSE EVENTS**

| Treatmnt Group* | Study No. | Pt. No. | Sex/ Age | Study Site | COSTART Term | Verbatim Term | Onset Day | Dura-Tion | Action re Study Drug | Severity | Relation to Study Drug |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A6026 | 9709 | 78 | M/16 | Rich | PHOTO-SENSITIVITY | sunburn | 8 | 7 D | Test Drug Discontinued | Severe | None |
| P6026 | 9723 | 175 | F/16 | Mark | SKIN DRY | dryness | 1 | 13 D | Test Drug Discontinued | Moderate | Probable |
| | | | | | SKIN DRY | dryness | 13 | NA | Test Drug Discontinued | Mild | Probable |
| | | | | | PRURITUS | itchiness | 2 | 12 D | Test Drug Discontinued | Severe | Probable |

* Treatment groups were: A6026 active Benzamycin Duel Pouch, P6026 Placebo Dual Pouch, A6008 active Benzamycin Topical Gel, & P6008 Placebo Topical Gel.

### 10.1.3 Over-dosage exposure

Benzamycin Dual Pouch Gel (3% erythromycin / 5 % benzoyl peroxide) is intended for cutaneous use only and therefore accidental overdose is highly unlikely. Average duration of drug exposure by study number and treatment is summarized in Table 22.

**TABLE 22 (SPONSOR'S TABLE 4, VOL.1.21, PG. 8-11-58)**
**AVERAGE DURATION OF DRUG EXPOSURE BY STUDY NUMBER AND TREATMENT**

| | Treatment[a] Group Summaries | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | A6026 | | P6026 | | A6008 | | P6008 | |
| Study | N | Avg Days | N | Avg Days | N | Avg Days | N | Avg Days |
| -9709 | 124 | 54.4 | 42 | 49.7 | 121 | 54.1 | 40 | 52.7 |
| -9723 | 112 | 51.9 | 111 | 51.8 | | | | |
| All | 236 | 53.2 | 153 | 51.2 | 121 | 54.1 | 40 | 52.7 |

[a] Treatment groups were: A6026 active Benzamycin Dual Pouch, P6026 Placebo Dual Pouch, A6008 active Benzamycin Topical Gel, and P6008 Placebo Topical Gel.

Long -Term Adverse Effects

The long term effects, that is beyond 8 weeks, of 3% erythromycin 5% benzoyl peroxide were not studied as part of this clinical program. The incidence of spontaneously reported adverse events reported over the past 14 years for the Benzamycin Topical Gel product is relatively low. The benzoyl peroxide component of the mixture is a tumor promoter and progression agent in animal models of skin cancer; however, epidemiologic studies have not indicated an increase in skin tumors in humans.

## 10.2 Other Safety Findings

### 10.2.1 ADR Incidence Tables

**TABLE 23 (SPONSOR'S TABLE 11, VOL 1.21, PG. 8-11-68): INCIDENCE OF ADVERSE EVENTS BY BODY SYSTEM AND TREATMENT GROUP**

| N % of patients | Treatment[a] Group Summaries | | | | Frequency Contrasts[b] A6026 vs. | |
|---|---|---|---|---|---|---|
| | A6026 N=236 | P6026 N=153 | A6008 N=121 | P6008 N=40 | P6026 | A6008 |
| with at least one AE | 81 (34%) | 42 (27%) | 43 (36%) | 13 (33%) | 0.109[c] | >0.50[d] |
| **Body System** | | | | | | |
| Body as a Whole | 40 (17%) | 21 (14%) | 20 (17%) | 5 (13%) | >0.50[c] | >0.50[d] |
| Cardiovascular System | | | 1 (<1%) | | | |
| Digestive System | 5 (2%) | 2 (1%) | 2 (2%) | | >0.50[e] | >0.50[e] |
| Hemic and Lymphatic System | 1 (<1%) | | | | | |
| Musculoskeletal System | 2 (<1%) | 1 (<1%) | | | | |
| Nervous System | | | 2 (2%) | | | |
| Respiratory System | 18 (8%) | 14 (9%) | 7 (6%) | 4 (10%) | >0.50[c] | >0.50[d] |
| Skin and Appendages | 29 (12%) | 12 (8%) | 10 (8%) | 2 (5%) | 0.060[c] | 0.249[d] |
| Special Senses | 5 (2%) | 1 (<1%) | 2 (2%) | 1 (3%) | 0.410[e] | >0.50[e] |
| Urogenital System | 5 (2%) | 4 (3%) | 1 (<1%) | 1 (3%) | >0.50[e] | >0.50[e] |

[a] Treatment groups were: A6026 active Benzamycin Dual Pouch, P6026 Placebo Dual Pouch, A6008 active Benzamycin Topical Gel, and P6008 Placebo Topical Gel.
[b] Methods selected based on frequency counts.
[c] Cochran-Mantel-Haenszel (CMH) test was stratified by study.
[d] CMH test of the single two by two table.
[e] Fisher's exact test.

**TABLE 24 (SPONSOR'S TABLE 13, VOL 1.21, PG. 8-11-70): INCIDENCE OF MOST FREQUENTLY OCCURRING ADVERSE EVENTS BY TREATMENT GROUP**

| N (% of all patients[b]) | Treatment[a] Group Summaries | | | | Frequency Contrasts[c] A6026 vs. | |
|---|---|---|---|---|---|---|
| | A6026 | P6026 | A6008 | P6008 | P6026 | A6008 |
| All Patients: | 236 | 153 | 121 | 40 | | |
| **COSTART TERM** | | | | | | |
| HEADACHE | 17 (7.2%) | 5 (3.3%) | 11 (9.1%) | 3 (7.5%) | 0.101[d] | >0.50[d] |
| DRY SKIN | 18 (7.6%) | 6 (3.9%) | 6 (5.0%) | 0 (0%) | 0.138[d] | 0.341[d] |
| PHARYNGITIS | 8 (3.4%) | 5 (3.3%) | 4 (3.3%) | 3 (7.5%) | >0.50[e] | >0.50[e] |
| VIRAL INFECTION | 11 (4.7%) | 8 (5.2%) | 4 (3.3%) | 1 (2.5%) | >0.50[d] | >0.50[e] |
| RHINITIS | 7 (3.0%) | 3 (2.0%) | 2 (1.7%) | 1 (2.5%) | >0.50[e] | >0.50[e] |
| DYSMENORRHEA | 2 (0.8%) | 4 (2.6%) | 0 (0%) | 0 (0%) | 0.217[e] | |
| ACCIDENTAL INJURY | 6 (2.5%) | 2 (1.3%) | 1 (0.8%) | 0 (0%) | 0.488[e] | 0.430[e] |
| APPLICATION SITE REACTION | 6 (2.5%) | 2 (1.3%) | 1 (0.8%) | 0 (0%) | 0.488[e] | 0.430[e] |
| ABDOMINAL PAIN | 1 (<0.5%) | 3 (2.0%) | 2 (1.7%) | 1 (2.5%) | | |
| BLEPHARITIS | 4 (1.7%) | 1 (0.7%) | 0 (0%) | 1 (2.5%) | | |
| NAIL DISORDER | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2.5%) | | |
| RASH | 0 (0%) | 3 (2.0%) | 1 (0.8%) | 1 (2.5%) | | |
| URINARY TRACT INFECTION | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2.5%) | | |
| PRURITUS | 4 (1.7%) | 2 (1.3%) | 3 (2.5%) | 0 (0%) | >0.50[e] | >0.50[e] |
| FLU SYNDROME | 5 (2.1%) | 3 (2.0%) | 1 (0.8%) | 0 (0%) | >0.50[e] | >0.50[e] |

[a] Treatment groups were: A6026 active Benzamycin Dual Pouch, P6026 Placebo Dual Pouch, A6008 active Benzamycin Topical Gel, and P6008 Placebo Topical Gel.
[b] Include all COSTART terms reported by at least 2% of patients in any treatment group.
[c] Methods selected based on frequency counts.
[d] CMH test of the single two by two table.
[e] Fisher's exact test.

Verbatim terms for application site reaction were as follows: tingling, stinging, erythema, and burning. Verbatim terms for exfoliative dermatitis were peeling and flakiness.

**TABLE 25 (SPONSOR'S TABLE 14, VOL. 1.21, PG. 8-11-71): ADVERSE EVENTS CONSIDERED AT LEAST POSSIBLY DRUG RELATED BY TREATMENT GROUP**

| N (% of all patients) | Treatment[a] Group Summaries | | | | Frequency Contrasts[b] A6026 vs. | |
|---|---|---|---|---|---|---|
| | A6026 | P6026 | A6008 | P6008 | P6026 | A6008 |
| All Patients: | 236 | 153 | 121 | 40 | | |
| **COSTART TERM** | | | | | | |
| DRY SKIN | 18 (7.6%) | 6 (3.9%) | 6 (5.0%) | 0 (0%) | 0.138[c] | 0.341[c] |
| APPLICATION SITE REACTION | 6 (2.5%) | 2 (1.3%) | 1 (0.8%) | 0 (0%) | 0.488[d] | 0.430[d] |
| PRURITUS | 2 (0.8%) | 2 (1.3%) | 2 (1.7%) | 0 (0%) | | |
| RASH | 0 (0%) | 0 (0%) | 1 (0.8%) | 0 (0%) | | |
| RHINITIS | 0 (0%) | 0 (0%) | 1 (0.8%) | 0 (0%) | | |
| BLEPHARITIS | 1 (<0.5%) | 1 (0.7%) | 0 (0%) | 0 (0%) | | |
| EXFOLIATIVE DERMATITIS | 1 (<0.5%) | 1 (0.7%) | 0 (0%) | 0 (0%) | | |
| HEADACHE | 1 (<0.5%) | 1 (0.7%) | 0 (0%) | 0 (0%) | | |
| CONJUNCTIVITIS | 1 (<0.5%) | 0 (0%) | 0 (0%) | 0 (0%) | | |
| NAUSEA | 1 (<0.5%) | 0 (0%) | 0 (0%) | 0 (0%) | | |
| PHOTOSENSITIVITY REACTION | 1 (<0.5%) | 0 (0%) | 0 (0%) | 0 (0%) | | |
| SKIN GRANULOMA | 1 (<0.5%) | 0 (0%) | 0 (0%) | 0 (0%) | | |

[a] Treatment groups were: A6026 active Benzamycin Dual Pouch, P6026 Placebo Dual Pouch, A6008 active Benzamycin Topical Gel, and P6008 Placebo Topical Gel.
[b] Methods selected based on frequency counts.
[c] CMH test of the single two by two table.

**TABLE 26 (SPONSOR'S TABLE 20, VOL. 1.21, PG. 8-11-78): ADVERSE EVENTS OF THE SKIN**

Number of Patients (%) — Treatment[a] Group Summaries

| COSTART Term[b] All Patients: | A6026 236 | P6026 153 | A6008 121 | P6008 40 |
|---|---|---|---|---|
| DRY SKIN | 18 (7.6%) | 6 (3.9%) | 6 (5.0%) | 0 |
| APPLICATION SITE REACTION | 6 (2.5%) | 2 (1.3%) | 1 (0.8%) | 0 |
| BLEPHARITIS | 4 (1.7%) | 1 (0.7%) | 0 | 1 (2.5%) |
| NAIL DISORDER | 0 | 0 | 0 | 1 (2.5%) |
| PRURITUS | 4 (1.7%) | 2 (1.3%) | 3 (2.5%) | 0 |
| RASH | 0 | 3 (2.0%) | 1 (0.8%) | 1 (2.5%) |
| PHOTOSENSITIVITY REACTION | 3 (1.3%) | 0 | 0 | 0 |
| CONTACT DERMATITIS | 1 (<0.5%) | 0 | 1 (0.8%) | 0 |
| ECZEMA | 0 | 1 (0.7%) | 0 | 0 |
| EXFOLIATIVE DERMATITIS | 1 (<0.5%) | 1 (0.7%) | 0 | 0 |
| SEBORRHEA | 1 (<0.5%) | 0 | 0 | 0 |
| SKIN GRANULOMA | 1 (<0.5%) | 0 | 0 | 0 |

[a] Treatment groups were: A6026 active Benzamycin Dual Pouch, P6026 Placebo Dual Pouch, A6008 active Benzamycin Topical Gel, and P6008 Placebo Topical Gel.

[b] Includes adverse events with body system = skin and appendages, and also blepharitis (body system = special senses) and sunburn (photosensitivity, body system = body as a whole).

## Adverse Events from Sources Other Than Clinical Trials

According to the submission, during the period December 24, 1984 through June 29, 1998, Dermik Laboratories received a total of 92 spontaneous adverse event reports for the marketed Benzamycin Topical Gel product. These reports contain 181 individual adverse event terms. These cases have been reported to the FDA as part of Dermik's periodic submissions to NDA# 50-557. In addition, Benzamycin® safety data from the FDA's epidemiology branch was reviewed and no additional cases were noted. These adverse events are organized by body system and COSTART adverse event preferred terms for each report in Table 26 that follows.

**TABLE 26 (SPONSOR'S TABLE 27, VOL. 1.21, PG. 8-11-89): SPONTANEOUS ADVERSE EVENTS REPORTED TO DERMIK FOR BENZAMYCIN® TOPICAL GEL**

| COSTART Term (by Body System) | Number of Patients | Number of Events Reported | % of Reported Events |
|---|---|---|---|
| **Total Reported** | **92** | **181** | |
| **Body as a Whole** | | | |
| Pain | 20 | 20 | 11.1% |
| Face Edema | 11 | 14 | 7.7% |
| Lack of Drug Effect | 7 | 7 | 3.9% |
| Reaction Unevaluable | 3 | 3 | 1.7% |
| Accidental Injury | 2 | 2 | 1.1% |
| Allergic Reaction | 2 | 2 | 1.1% |
| Aggravation Reaction | 1 | 1 | 0.6% |
| Headache | 1 | 1 | 0.6% |
| Infection | 1 | 1 | 0.6% |
| **Total** | **42** | **51** | **28.2%** |
| **Digestive System** | | | |
| Diarrhea | 1 | 1 | 0.6% |
| Nausea | 1 | 1 | 0.6% |
| **Total** | **2** | **2** | **1.1%** |

| | | | |
|---|---|---|---|
| **Metabolic and Nutritional Disorders** | | | |
| Edema | 2 | 2 | 1.1% |
| SGPT Increased | 1 | 1 | 0.6% |
| **Total** | 3 | 3 | 1.7% |
| **Nervous System** | | | |
| Paresthesia | 11 | 11 | 6.1% |
| Vasodilation | 9 | 9 | 5.0% |
| Insomnia | 1 | 1 | 0.6% |
| Twitching | 1 | 1 | 0.6% |
| **Total** | 21 | 22 | 12.2% |
| **Respiratory System** | | | |
| Asthma | 1 | 1 | 0.6% |
| Dyspnea | 1 | 1 | 0.6% |
| **Total** | 1 | 2 | 1.1% |
| **Skin and Appendages** | | | |
| Rash | 29 | 36 | 19.9% |
| Pruritis | 12 | 12 | 6.6% |
| Skin Discoloration | 7 | 7 | 3.9% |
| Acne | 6 | 7 | 3.9% |
| Dry Skin | 6 | 6 | 3.3% |
| Exfoliative Dermatitis | 5 | 5 | 2.8% |
| Skin Disorder | 4 | 5 | 2.8% |
| Alopecia | 3 | 3 | 1.7% |
| Contact Dermatitis | 2 | 2 | 1.1% |
| Maculopapular Rash | 2 | 2 | 1.1% |
| Skin Ulcer | 2 | 2 | 1.1% |
| Urticaria | 2 | 2 | 1.1% |
| Vesiculobullous Rash | 2 | 3 | 1.7% |
| Furunculosis | 1 | 1 | 0.6% |
| Erythema Multiforme | 1 | 1 | 0.6% |
| **Total** | 57 | 94 | 51.9% |
| **Special Senses** | | | |
| Conjunctival Edema | 3 | 3 | 1.7% |
| Conjunctivitis | 3 | 3 | 1.7% |
| Taste Perversion | 1 | 1 | 0.6% |
| **Total** | 7 | 7 | 3.9% |

Source: Item 8, Section 10. Integrated Summary of Safety Information, Appendix A.11.

## Other Potential Safety Issues

A potential safety issue with use of antibacterial agents such as erythromycin is the risk of pseudomembraneous colitis. The risk of pseudomembraneous colitis is relatively low as compared to the higher systemic exposure of those patients who take erythromycin via the oral or intravenous routes of administration based on detectable plasma levels from Study DL 6026-9717. In a single dose pharmacokinetic study of the Benzamycin Dual Pouch product (Study DL 6026-9717), virtually no systemic absorption of erythromycin was detected in the plasma of acne patients following a single application of either 1 or 3 Benzamycin Dual Pouch units (approximately 0.8 or 2.4 gms, respectively).

Pseudomembraneous colitis has not been reported to Dermik for any patients receiving the currently marketed Benzamycin® Topical Gel product over the past 14 years. According to the sponsor, since the relationship of pseudomembraneous colitis with the use of the new Benzamycin Dual Pouch product has not been clearly established, the sponsor is recommending retention of the pseudomembraneous colitis warning in the labeling of the this product as per the labeling of the currently marketed Benzamycin® Topical Gel product.

**Reviewer's comment:**
*Removal of the pseudomembraneous colitis warning in the labeling of the this product as well as from the label of the currently marketed Benzamycin® Topical Gel product should be considered based on current data.*

According to the submission, although the matter remains controversial in the literature, benzoyl peroxide has not been proven to be carcinogenic or mutagenic in humans. Clinically, benzoyl peroxide has been prescribed for the treatment of acne for decades. It is also available as an over-the-counter product to the general public. In addition, no carcinogenic potential has been identified with erythromycin.

**10.2.2 Laboratory Findings**
Clinical laboratory testing was not done in any of the controlled clinical trials (DL 6026-9709 or DL 6026-9723), or in the RIPT dermal safety study (DL 6026-9708). In the pharmacokinetic study (DL 6026-9717), screening laboratories were performed; however, no post-baseline laboratory testing was performed. In studies DL 6026-9709, DL 6026-9723, and DL 6026-9717, pregnancy tests were performed at beginning and end of treatment for women of child-bearing potential. Two patients in the DL 6026-9709 study had a positive test result at endpoint (Patient # 55 and Patient # 64).

**Reviewer's comments:**
*Pregnancy outcome results are pending.*

**10.2.3 Special Studies**
Clinical dermal safety studies (Study No. DL-6026-9708, Study No. IVY #4476/0, and Study No. IVY #4477/05) and three consumer use studies (Study PI 10281, Study DL 6026-9802, and Study DL 6026-9819) are summarized in this section.

**Clinical Dermal Safety Studies**
Three studies provide clinical dermal safety data on Benzamycin Dual Pouch (3% erythromycin and 5% benzoyl peroxide gel) are included in this NDA and are identified in Table 1. Two studies, IVY #4476/04 (a Phase 1 Phototoxicity Assay) and IVY #4477/05 (a Phase 1 Photoallergy Study), are supportive studies which were performed with the currently marketed Benzamycin® product and were submitted with the previous Benzamycin® NDA# 50-557. Study summaries follow.

Study No. DL-6026-9708 Evaluation of the Skin-irritating and Skin-Sensitizing Propensities of Benzamycin Dual Pouch Product

A Phase 1 Repeat Insult Patch Test (RIPT) was conducted to evaluate the irritancy and sensitization (allergic) potential of the Benzamycin Dual Pouch product and to compare it to the marketed Benzamycin product. Two hundred and eleven healthy volunteers were patched with the following eight test articles: Benzamycin Dual Pouch (DL-6026); Marketed Benzamycin® (DL 6008); 6% erythromycin gel; placebo erythromycin gel;

placebo benzoyl peroxide gel; a mixture of the placebo gels; 0.1% sodium lauryl sulfate (positive control); and normal saline (negative control). Active benzoyl peroxide gel (as the individual component) was omitted since it is a known irritant and sensitizer. Once daily, Monday through Thursday for three weeks, subjects had each test material applied (0.15ml) and occluded to skin sites measuring 15mm in diameter on the upper back. After 24 hours, the skin sites were inspected and graded for irritation. Sensitization was assessed following a one-week rest period.

Products containing benzoyl peroxide are expected to have a high irritancy potential, which is maximized under occlusion. Benzamycin Dual Pouch was found to be a very weak to moderate cumulative irritant under study conditions. Additionally, the placebo benzoyl peroxide gel demonstrated weak to moderate irritancy potential. Virtually no irritation was seen with the erythromycin gel, erythromycin placebo, or a mixture of the placebo gels.

**Conclusion**
Benzamycin Dual Pouch exhibited some sensitizing potential (confirmed in 8 of 203 subjects who completed the challenge phase); 8 subjects also exhibited sensitization to marketed Benzamycin. Neither erythromycin gel, erythromycin placebo, nor a mixture of the placebo gels exhibited sensitizing potential. In this study, the irritancy and sensitizing potential of Benzamycin Dual Pouch was virtually identical to that of marketed Benzamycin®.

Study No. IVY #4476/04 Determination of the Phototoxic Potential (Phototoxicity Bioassay) of Benzamycin® and Benzamycin® Placebo Base to the Skin (referenced from NDA# 50-557)

This study was previously reviewed under NDA 50-557. According to the sponsor, the conclusion from that review was that none of the products tested possessed a detectable phototoxic potential in humans.

Study No. IVY #4477/05 Determination of the Photocontact Allergenic Potential (Photoallergy Bioassay) of Benzamycin® and Benzamycin® Placebo Base Applied Topically to the Skin (referenced from NDA# 50-557)

This study was also previously reviewed under NDA 50-557. According to the sponsor, no reactions suggestive of photo-contact sensitization were seen in any of the 25 panelists.

**Conclusion Dermal Safety Studies**
The results of these three dermal safety studies are consistent with what has been seen with other benzoyl peroxide products and revealed no additional safety issues with regard to the addition of erythromycin to benzoyl peroxide as in this combination product.

**Consumer Use Studies**
Three "use" studies were conducted to assess patients' abilities to properly use the unique dual pouch package. These studies are summarized below.

**Table 27 (Sponsor's Table 1) Table of Consumer Use Studies**

| Study Number | Title | Investigators | | Completion Status (Starting Date) | Weeks of Drug Treatment (Frequency) | Dose (concentration) of | | Age Range | M/F (%) | Total Patients enrolled |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Name | Location | | | Benzoyl peroxide | Erythro-mycin | | | |
| PI10281 | Consumer Evaluation of The Opening Ease of the Benzamycin Dual Gel Pouch | M. Shelanski, M.D. | Conshohocken, PA | Complete (11/20/97) | One Day | 0% | 0% | 13-40 | 51/49 | 80 |
| DL 6026-9802 | Consumer Ease of Use Evaluation of the Benzamycin Dual Gel Pouch | M. Shelanski, M.D. J.B. Shelanski | Conshohocken, PA | Complete (03/10/98) | One Day | 5% | 3% | 13-40 | 41/59 | 150 |
| DL 6026-9819 | Consumer Ease Evaluation of the Benzamycin Dual Gel Pouch Comparing Two Direction Variants | M. Shelanski, M.D. R. Donovan, M.D. | Conshohocken, PA Modesto, CA | Complete (08/06/98) | One Day | 5% | 3% | 13-40 | 46/54 | 498 |

**Summary of Consumer Use Studies**

Study PI 10281 was a one day, two trial packaging opening study to evaluate the ability of the consumer to open the Benzamycin Dual Pouch unassisted by scissors and to compare the ease of opening in two separate opening trials. The study indicated a statistically significant decrease in the time needed to open the pouch from the first attempt to the second attempt.

Study DL 6026-9802 was also a one day, two trial packaging opening study but participants were randomized and provided with one of two sets of instructions, either tearing or cutting open the pouch with scissors. Results indicate that the correct procedure was followed by a large majority of the subjects in both trials at all process stages. Differences between the tear and cut groups were primarily limited to the "read and opening' stage of the process. All process stages demonstrated a strong learning curve effect between the first and second trials. As in the first study, there was a statistically significant decrease in the time needed to open the pouch from the first attempt to the second attempt.

Study DL 6026-9819 was a one day, three trial packaging opening study with the participants randomized to one of two opening methods; tearing or cutting open the pouch with scissors. This study confirmed the results of the previous study while using a much larger subject population. Differences were again primarily limited to the "read and open" stage of the process. All process stages showed a strong learning effect between the first and second trials and to a lesser extent between the second and third trials. These results demonstrate that volunteers can successfully use the pouch without individual instruction or demonstration. This applies even to young teens, both boys and girls. The majority of people master the opening and application by the second use of the pouch.

submission, the following article, *Reed, BR. Dermatologic drugs, pregnancy and lactation - A conservative guide. Archives of Dermatology, 1997, 133/7 (894-898)* reviews the use of drugs for the treatment of dermatologic disorders during pregnancy and lactation. Data on the safety of erythromycin and benzoyl peroxide from the TERIS (Teratogen Information Service) are presented. Neither drug has a known contraindication during lactation. Dermik Laboratories has received no direct reports of any adverse events occurring with the use of Benzamycin during pregnancy or lactation.

## 11 Resistance

According to the submission, studies performed with Benzamycin® (3% erythromycin/5% benzoyl peroxide) have demonstrated that an increased antibacterial resistance can be avoided by the concomitant use of benzoyl peroxide with erythromycin. The use of a combination erythromycin/ benzoyl peroxide therapy may advantages over using erythromycin alone.

**Reviewer's comment:**
*The Microbiologist will review the issue of resistance.*

## 10.3 Safety Conclusion

There were no deaths reported in any of the studies performed with Benzamycin ——— There were three patients who reported serious adverse events (diskectomy secondary to accidental back injury, Hodgkin's disease, and mononucleosis), and none of these serious adverse events were considered to be related to the study medication. Although these adverse events were classified as serious, all three of the patients went on to complete the study.

Evaluation of the skin-irritating and skin-sensitizing propensities of the Benzamycin ——— product (Study DL-6026-9708) demonstrated that the Benzamycin ——— product exhibited some sensitizing potential (confirmed in 8 of 203 subjects who completed the challenge phase). In Study DL-6026-9708, the irritancy and sensitizing potential of Benzamycin ——— was virtually identical to that of marketed Benzamycin®; therefore, not posing any new hazards.

Two supportive studies, a phototoxicity bioassay study (IVY #4476/04) and a photocontact allergy study (IVY #4477/05), were performed with the currently marketed Benzamycin® Topical Gel product and were submitted in the previous NDA for that product (NDA# 50-557). These studies demonstrated that the currently marketed Benzamycin® does not possess the potential for phototoxicity or photoallergy reactions. Since the Benzamycin ——— formulation was demonstrated to have similar absorbance properties as the currently marketed formulation of Benzamycin® Topical Gel, it has been concluded the Dual Pouch formulation also does not possess any phototoxic or photocontact allergy potential based upon the results of the phototoxicity bioassay study (IVY #4476/04) and the photocontact allergy study (IVY #4477/05).

A potential safety issue for the use of antibacterial agents such as erythromycin is the risk of pseudomembraneous colitis. In a single dose pharmacokinetic study of the Benzamycin

——— product (Study DL 6026-9717), virtually no systemic absorption of erythromycin was detected in the plasma of acne patients following a single application of either 1 or 3 Benzamycin ——— units (approximately 0.8 or 2.4 gms, respectively). This would indicate that the risk of pseudomembraneous colitis is relatively low as compared to the higher systemic exposure of those patients who take erythromycin via the oral or intravenous routes of administration. In addition, pseudomembraneous colitis has not been reported to Dermik for any patients receiving the currently marketed Benzamycin® Topical Gel product over the past 14 years. However, since the relationship of pseudomembraneous colitis with the use of the new Benzamycin ——— product has not been clearly established, it is Dermik's recommendation to retain the pseudomembraneous colitis warning in the labeling of the this product as per the labeling of the currently marketed Benzamycin® Topical Gel product.

Although the matter remains controversial in the literature, benzoyl peroxide has not been proven to be carcinogenic or mutagenic in humans. Clinically, benzoyl peroxide has been prescribed for the treatment of acne for decades. It is also available as an over-the-counter product to the general public. In addition, no carcinogenic potential has been identified with erythromycin.

## 12 Labeling (See Labeling Review Attached)

## 13 Recommendations

Recommending approval of NDA 50-769 for use of Benzamycin ——— in treatment of acne vulgaris.

### 13.2 Phase 4

No Phase 4 studies are being requested.

### 13.3 Labeling Changes

Based on current data, removal of the pseudomembraneous colitis warning from the label of this drug product should be considered.

/S/ 10/30/00

Brenda Vaughan, M.D.
Medical Reviewer

cc:
Orig NDA 50-769
HFD-540
HFD-540/DIV DIR/Wilkin
HFD-540/DERM TL/Walker
HFD-540/MO/Vaughan
HFD-540/CHEM TL/DeCamp
HFD-540/CHEM/Vidra
HFD-540/PH TOX TL/Jacobs
HFD-540/PHARM/Brown
HFD-520/MICRO TL/Sheldon

/S/ 10/30/00

There is no evidence for this product that the presence of BP in this product will reduce the incidence of resistance to erythromycin.

Labeling dtg 11/1/00; new draft labeling



/S/ 11/2/00

no DFS version 11/15/00