CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-769

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-769

NOV 27 2000

Dermik Laboratories, Inc
Attention: James P. Thompson
Manager, Worldwide Regulatory Affairs
1050 Westlakes Drive
Berwyn PA 19312

Dear Mr. Thompson:

Please refer to your new drug application (NDA) 50-769, dated January 26, 2000, received January 27, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Benzamycin Pak (erythromycin 3%-benzoyl peroxide 5% topical gel).

We acknowledge receipt of your submissions dated February 21, March 22, May 25, June 8, July 25, August 4, September 26, October 6, 13 and 27, and November 3, 21, 22 (facsimile) and 27 (facsimile), 2000.

This new drug application provides for the use of Benzamycin Pak (erythromycin 3%-benzoyl peroxide 5% topical gel) for acne vulgaris.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug. Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 50-769." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your post marketing commitment specified in your submission dated November 27, 2000 (facsimile). This commitment, along with completion date agreed upon, is listed below.

Within 3 months of NDA Approval, conduct and report the results of a flammability or flashpoint study on the [redacted] erythromycin gel since it contains [redacted] hyl alcohol.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your post marketing commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these post marketing commitments must be clearly designated "Post Marketing Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving pediatric studies below the age of 12 years, because acne is not prevalent in the population from birth through 11 years, and this product would not represent a substantive therapeutic benefit as an acne therapy for that population. There are sufficient data to determine efficacy and safety down to and including age 12 years. The Agency grants you a partial waiver for pediatric acne studies for the age group from birth through 11 years of age, under 21 CFR 314.55(c)(4)

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call Frank H. Cross, Jr., Project Manager, at (301) 827-2020.

Sincerely,

/S/

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

Rx Only

Benzamycin® Pak

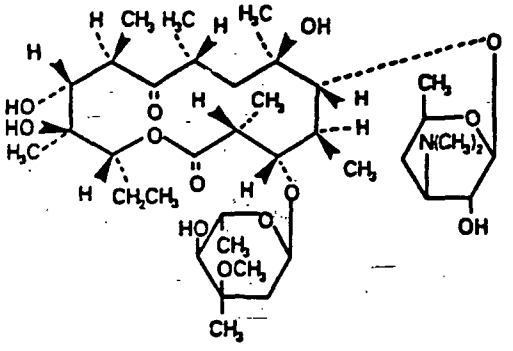
(erythromycin 3%-benzoyl peroxide 5% topical gel)

For Dermatological Use Only – Not for Ophthalmic Use

DESCRIPTION

Benzamycin® Pak contains 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]. 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.

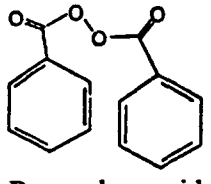
Chemically, erythromycin is ($C_{37}H_{67}NO_{13}$). It has the following structural formula:



Erythromycin has the molecular weight of 733.94. It is a white crystalline powder and has a solubility of approximately 1 mg/mL in water and is soluble in alcohol at 25°C.

Benzamycin® Pak also contains benzoyl peroxide for topical use. Benzoyl peroxide is an oxidizing agent demonstrating antibacterial activity.

Chemically, benzoyl peroxide is ($C_{14}H_{10}O_4$). It has the following structural formula:



Benzoyl peroxide has the molecular weight of 242.23. It is a white granular powder and is sparingly soluble in water and alcohol and soluble in acetone, chloroform and ether.

Each gram of product, as dispensed, contains 30 mg of erythromycin and 50 mg of benzoyl peroxide in a base of SD Alcohol 40B, purified water, hydroxypropyl cellulose, carbomer 934, sodium hydroxide, dioctyl sodium sulfosuccinate 75%. Each Benzamycin® Pak contains 0.8 grams of product.

CLINICAL PHARMACOLOGY

Pharmacokinetics: Benzoyl peroxide has been shown to be absorbed by the skin where it is converted to benzoic acid. A single dose pharmacokinetic study, involving the application of either one or three units of Benzamycin® Pak, was performed in 16 adult acne patients to determine systemic absorption

of erythromycin. Erythromycin (with a plasma lower limit of quantitation of 2 ng/ml) was not detectable, except in one patient who was in the one unit application group.

Pharmacodynamics: The exact mechanism by which erythromycin and benzoyl peroxide reduce lesions of acne vulgaris is not fully known.

CLINICAL STUDIES

In two adequate and well controlled clinical studies 228 patients used Benzamycin® Pak, 113 patients used the currently marketed Benzamycin® Topical Gel, and 183 patients used vehicle. Benzamycin® Pak applied twice daily for 8 weeks was significantly more effective than vehicle and comparable to Benzamycin® Topical Gel in the treatment of moderate to moderately severe facial acne vulgaris. Patients entering the study had a minimum of 15 and a maximum of 80 facial inflammatory lesions (papules and pustules) and a minimum of 20 and a maximum of 140 facial non-inflammatory lesions (open and closed comedones). The primary efficacy measures evaluated at week 8 were the lesion counts and the investigator's global assessment.

Patients were instructed to wash their face twice daily (morning and evening) with warm water and a mild cleanser provided by sponsor. No abrasive cloths or sponges, alcoholic toners, astringents or medicated solutions were used. The medication was to be applied 15 minutes after washing, in a thin film over the entire facial area. A moisturizer (supplied by the sponsor) or non-medicated make-up could be applied one hour after application, as needed. All medications were to be kept away from the eyes. Sun exposure to the face was to be limited.

Outcomes for mean percent reductions in lesion counts and investigators global assessment after 8 weeks of treatment are shown below:

Study 1	Benzamycin® Pak N = 119	Benzamycin ® Topical Gel N = 113	Benzamycin® Pal Vehicle N = 38	Benzamycin® Topical Gel Vehicle N = 37
Mean % Lesion Counts Reduction				
Inflammatory *	49%	45%	17%	28%
Non Inflammatory*	46%	43%	24%	20%
Total *	48%	44%	22%	26%
Investigator's Global				
Global Success *	28%	27%	3%	11%

* p-value < 0.05 is for the comparison between Benzamycin® Pak and Benzamycin® Pak vehicle

Study 2	Benzamycin Pak	Benzamycin Pak

	N = 109	Vehicle N = 108
Mean % Lesion Counts Reduction		
Inflammatory *	57%	34%
Non Inflammatory	36%	30%
Total *	45%	31%
Investigator's Global		
Global Success *	36%	12%

* p-value < 0.05

MICROBIOLOGY

Erythromycin acts by inhibition of protein synthesis in susceptible organisms by reversibly binding to 50 S ribosomal subunits, thereby inhibiting translocation of aminoacyl transfer-RNA and inhibiting polypeptide synthesis. Antagonism has been demonstrated *in vitro* between erythromycin, lincomycin, chloramphenicol and clindamycin.

Benzoyl peroxide has been shown to be effective *in vitro* against *Propionibacterium acnes,* an anaerobe found in sebaceous follicles and comedones. Benzoyl peroxide is believed to act by releasing active oxygen.

INDICATIONS AND USAGE

Benzamycin® Pak is indicated for the topical treatment of acne vulgaris.

CONTRAINDICATIONS

Benzamycin Pak® is contraindicated in those individuals who have shown hypersensitivity to any of its components.

PRECAUTIONS

General: For topical use only; not for ophthalmic use. Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating or abrasive agents. If severe irritation develops, discontinue use and institute appropriate therapy.

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

Avoid contact with eyes and all mucous membranes.

Information for Patients: Patients using Benzamycin® Pak should receive the following information and instructions:

1. Patients should be informed that they will need to mix this medication prior to use. The medication will be dispensed in one foil pouch which contains medication in two separated compartments.
2. The contents must be mixed thoroughly by the patient (in the palm of the hand), prior to application.
3. Patients should apply the product immediately after mixing, then the hands should be washed.

4. Do not mix or apply near an open flame.
5. Benzamycin® Pak may bleach hair or colored fabric.
6. Excessive or prolonged exposure to sunlight should be limited. To minimize exposure to sunlight, a hat or other clothing should be worn.
7. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes, mouth, and all mucous membranes as this product may be irritating
8. Patients should report to their physician any signs of local adverse reactions.
9. This medication should not be used for any disorder other than that for which it was prescribed.
10. Patients should not use any other topical acne preparation unless otherwise directed by physician.
11. Patients should be instructed to review the instructions for use on the product carton.
12. This medication should be stored at room temperature away from heat and any open flame.

Carcinogenesis, Mutagenesis, Impairment Of Fertility:
The combination of benzoyl peroxide and erythromycin in Benzamycin® Pak has not been evaluated for its carcinogenic or mutagenic potential or for its effects on fertility.

Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. The clinical significance of this is unknown.

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

Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *Salmonella typhimurium* tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells.

No animal studies have been performed to evaluate the carcinogenic potential or effects on fertility of topical erythromycin. However, long-term (2-year) oral studies in rats with erythromycin base and erythromycin ethylsuccinate and in rats and mice with erythromycin stearate did not provide evidence of tumorigenicity.

The genotoxicity of erythromycin stearate has been evaluated in the *Salmonella typhimurium* reverse mutation assay, the mouse L5178Y lymphoma cell assay, and for sister chromatid exchanges and chromosomal aberrations in CHO cells. These studies indicated that erythromycin stearate was not genotoxic.

There was no apparent effect on male or female fertility in rats fed erythromycin base at levels up to 0.25% of diet.

Pregnancy: Teratogenic Effects: Pregnancy CATEGORY C: Animal reproduction studies have not been conducted with Benzamycin® Pak or benzoyl peroxide.

There was no evidence of teratogenicity or any other adverse effect on reproduction in female rats fed erythromycin base (up to 0.25% diet) prior to and during mating, during gestation and through weaning of two successive litters.

There are no well-controlled trials in pregnant women with Benzamycin® Pak. It also is not known whether Benzamycin® Pak can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Benzamycin® Pak should be given to a pregnant woman only if clearly needed.

Nursing Women: It is not known whether the ingredients of Benzamycin® Pak are excreted in human milk after topical application. However, erythromycin is excreted in human milk following oral and parenteral erythromycin administration. Therefore, caution should be exercised when erythromycin is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of this product in pediatric patients below the age of 12 years of age have not been established.

ADVERSE REACTIONS

During clinical trials, 550 acne patients were studied. Of these patients, 236 were treated with Benzamycin® Pak. The most frequently reported adverse event considered at least possibly related was dry skin (7.6%) as compared to Vehicle (3.9%). Application site reactions (stinging, burning sensation, tingling, erythema) were reported in 2.5% of patients versus 1.3% for Vehicle patients. Blepharitis, pruritus and photosensitivity reactions were reported in <2% of patients who used the dual pouch product.

Treatment Group Summaries
Number of Patients (%)

COSTART Term	Benzamycin® Pak 236	Benzamycin® Pak Vehicle 153	Benzamycin® Topical Gel 121	Benzamycin® Topical Gel Vehicle 40
DRY SKIN	18 (7.6%)	6 (3.9%)	6 (5.0%)	0
APPLICATION SITE REACTION (stinging, erythema, and burning)	6 (2.5%)	2 (1.3%)	1 (0.8%)	0
BLEPHARITIS	4 (1.7%)	1 (0.7%)	0	1 (2.5%)
PRURITUS	4 (1.7%)	2 (1.3%)	3 (2.5%)	0
PHOTOSENSITIVITY REACTION (Sunburn, stinging with sun exposure)	3 (1.3%)	0	0	0
PEELING	1 (0.5%)	1 (0.7%)	0	0

DOSAGE AND ADMINISTRATION

Benzamycin® Pak requires thorough mixing by the patient immediately prior to each use. The medication 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.

HOW SUPPLIED

60 Pouches per carton **NDC 0066-0577-60**

Store at Room Temperature 20 to 25°C (68 to 77°F).
Keep away from heat and any open flame.

Keep out of the reach of children.

Manufactured by:

West Pharmaceutical Services, Inc.
Lakewood, NJ 08701
Manufactured for:
Dermik Laboratories, Inc.
Berwyn, PA, 19312 USA
Rev. 11/22/00 IN-7100