CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-769

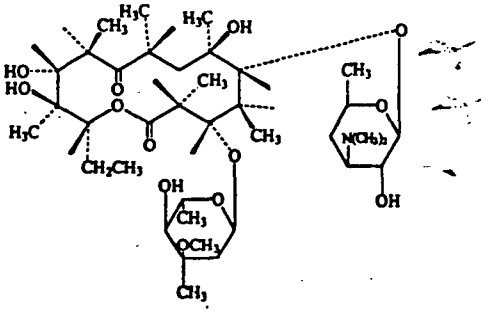
PHARMACOLOGY REVIEW(S)

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

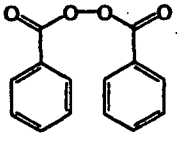
KEY WORDS: carcinogenicity, photocarcinogenicity, tumor promoter
Reviewer Name: Paul C. Brown
Division Name: Division of Dermatologic and Dental Drug Products
HFD#540
Review Completion Date: August 30, 2000
Review number: 1
NDA number: 50-769
Serial number/date/type of submission: 000 / 27 January 2000 / original
Information to sponsor: Yes
Sponsor (or agent): Dermik Laboratories
Manufacturer for drug substances:
Erythromycin, USP: [redacted]
Hydrous Benzoyl Peroxide, USP: [redacted]

Drug:

Generic Name: erythromycin
Chemical Name: (3R*, 4S*, 5S*, 6R*, 7R*, 9R*, 11R*, 12R*, 13S*, 14R*)-4-[(2,6-Dideoxy-3- *C* -methyl-3- *O* -methyl-(alpha)-L- *ribo* -hexopyranosyl)-oxy]-14-ethyl-7,12,13-trihydroxy- 3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-(beta)-D- *xylo* -hexopyranosyl]oxy]oxacyclotetradecane- 2,10-dione
CAS Registry Number: 114-07-8
Molecular Formula/ Molecular Weight: $C_{37}H_{67}NO_{13}$ / MW=733.94
Structure:



Generic name: benzoyl peroxide
Chemical name: hydrous benzoyl peroxide
CAS Registry Number: 94-36-0
Molecular Formula/ Molecular Weight: $C_{14}H_{10}O_4$ / MW=242.23
Structure:



Drug Class: antibacterial, antiacne

Indication: topical treatment of acne vulgaris

Clinical formulation: The product will be supplied as a single-use, dual-chambered pouch. One chamber will be filled with — benzoyl peroxide gel and the other with — erythromycin gel in equal quantities. The two gels will be mixed at the time of use by the patient to yield a gel with 3% erythromycin and 5% benzoyl peroxide. The final composition of the mixed gel is shown in the table below. Also shown in the table below is the formula for another dual chamber gel product that the sponsor has used in some of the early nonclinical studies.

Ingredient
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°
—
—

Route of administration: topical to the skin

Introduction and drug history:
Benzamycin is an approved product that has been marketed in the United States since 1985. The product is currently supplied to the pharmacist as two components that are then mixed by the pharmacist before dispensing the product to the patient. The new patient-mixed product has been evaluated in several phase 1 studies and in two multi-center phase 3 studies.

Studies reviewed within this submission:
The sponsor has submitted reports of 5 nonclinical studies. The results of these studies have been summarily described in a submission to — but the full reports have not been previously submitted or reviewed. Four of these studies have been conducted with the early dual chamber formulation. Only one (— was conducted with the to-be-marketed formulation. Four studies with Benzamycin gel were submitted previously to NDA 50-557.

13-Week Dermal Toxicity Study in Rats with Benzamycin Dual Chamber, Benzamycin Dual Chamber Vehicle and Benzamycin (Commercial), Study No: DL-PC-6026-9410(01)

13-Week Dermal Toxicity Study in Rabbits with Benzamycin Dual Chamber, Benzamycin Dual Chamber Vehicle and Benzamycin (Commercial), Study No: DL-PC-6026-9410(02)

28-Day Dermal Rabbit Study, Study No: DL-PC-6026-9725 [redacted] ML-DKL-3N11-98-249)

Dermal Sensitization Study in Guinea Pigs (Buehler's Technique Modified) of Benzamycin Dual Chamber (BDC) and Benzamycin Topical Gel, Study No: DL-PC-6026-9409

Primary Dermal Irritation Study in Rabbits, Study No: DL-PC-6026-9408

PHARMACOLOGY:

Summary of pharmacology:

Some of the efficacy of erythromycin and benzoyl peroxide against acne may be because both are active against *Propionibacterium acnes*. Some of the antiacne action of benzoyl peroxide has also been attributed to its peeling and comedolytic effects.

PHARMACOKINETICS/TOXICOKINETICS:

One *in vivo* human pharmacokinetic study and two *in vitro* studies were conducted with the dual chamber formulation. These studies will be reviewed by the biopharmaceutics reviewer. The sponsor claims that the *in vivo* studies showed that very little erythromycin was absorbed systemically after topical application of 0.8 or 2.4 grams of the dual chamber gel. Only one blood sample was greater than the lower limit of quantitation of 2 ng/ml.

An *in vitro* skin permeation study showed that approximately 95% of the erythromycin from either the dual chamber gel or the marketed Benzamycin gel was unabsorbed during a 24 hour exposure. Less than one percent of the applied erythromycin penetrated the skin to the receptor fluid. This study suggests that the two gels have similar absorption properties.

TOXICOLOGY:

Study Title: **13-Week Dermal Toxicity Study in Rats with Benzamycin Dual Chamber, Benzamycin Dual Chamber Vehicle and Benzamycin (Commercial)**

Study No: DL-PC-6026-9410(01)

Amendment #000, Vol. #6, and page #5-1-87

Conducting laboratory and location: [redacted]

Date of study initiation: 1 November 1994

GLP compliance: Yes

QA-Report: Yes

Methods:

Dosing:

- species/strain: rat / Sprague-Dawley Crl: CDBR
- #/sex/group or time point: 5/sex/group
- age: 6.5 weeks

- Body weights: There were no significant differences between the groups in body weight.
- Food consumption: There were no significant differences between the groups in food consumption.
- Ophthalmoscopy: No treatment related effects were observed.
- Hematology: There was a statistically significant decrease in the mean group monocyte count for group 5 females. However, the magnitude of this change was small and the value was within the historical control range.
- Clinical chemistry: There was a statistically significant decrease in the mean group globulin concentration in the group 5 females. However, the magnitude of this change was small and did not cause a significant change in the total protein concentration or the albumin/globulin ratio.
- Organ Weights: No significant differences in organ weights between treated and control groups were noted.
- Gross pathology: Gross pathological findings consisted of a prominent reticular pattern in the liver of one group 5 male, a pale area in one group 4 male liver and a dark area in one group 4 male liver, an enlarged kidney with dilated pelvis in one group 4 male, dark areas in the stomach of one male and one female in group 4, and a sore on the treated skin of one group 5 male.
- Histopathology: The only histopathologic finding apparently related to the treatment was acanthosis at the treatment site. The severity of the acanthosis was greater in the group 5 animals as is apparent in the following summary table for the incidence and severity of acanthosis at the treatment site.

Acanthosis severity	No. of animals affected									
	Male					Female				
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 1	Group 2	Group 3	Group 4	Group 5
None		1	1	1			1			
Minimal		1	1			1	2	1	1	
Slight	5	3	2	4	2	4	2	4	4	1
Moderate			1		2					4
Mod. severe					1					
Severe										

Key Study Findings: Topical treatment with either the commercial Benzamycin or the dual chamber formulation did not to produce any detectable systemic effects in the rat in this 13 week study. Both formulations and the vehicle produce acanthosis in the skin at the treated site. This acanthosis was similar in animals treated with the vehicle and with the low dose (20 µl/kg) of either Benzamycin formulation. The higher dose of the dual chamber formulation produced acanthosis of greater severity.

Study Title: **13-Week Dermal Toxicity Study in Rabbits with Benzamycin Dual Chamber, Benzamycin Dual Chamber Vehicle and Benzamycin (Commercial)**
Study No: DL-PC-6026-9410(02)
Amendment #000, Vol. #7, and page #5-2-1
Conducting laboratory and location:
Date of study initiation: 1 November 1994

- weight: males from 224 to 277 g, females from 160 to 186 g
- dosage groups in administered units:

Group	Treatment	Dose (µl/kg/dose)	No./sex
1	BDC vehicle	200	5
2	Benzamycin (commercial)	20	5
3	BDC (low)	10	5
4	BDC (mid)	20	5
5	BDC (high)	200	5

- Route, form: The gels were applied twice per day for 13 weeks at the dose noted in the above table to a clipped area of approximately 2x3 cm on the backs of the animals. The second daily application was made approximately 6 hours after the first. The high dose is considered to be ten times the expected clinical dose on a µl/kg basis. However, the concentration of benzoyl peroxide and erythromycin are the same as the clinical formulation: 5% benzoyl peroxide and 3% erythromycin.
- Lot and batch numbers:

  Benzamycin dual chamber gel [redacted] erythromycin gel component, [redacted] benzoyl peroxide component, [redacted] (concentrations before mixing)

  Benzamycin dual chamber vehicle: erythromycin gel vehicle, [redacted] benzoyl peroxide gel vehicle, [redacted]

  Benzamycin commercial product: [redacted]

Observations and times:

- Clinical signs: Clinical signs including dermal irritation were recorded daily.
- Body weights: Body weights were recorded weekly.
- Food consumption: Food consumption was recorded weekly.
- Ophthalmoscopy: Ophthalmoscopic examinations were conducted prior to treatment and during week 13.
- Hematology: Blood for hematologic analysis was collected prior to necropsy.
- Clinical chemistry: Blood for clinical chemistry was collected prior to necropsy.
- Gross pathology: All animals were subject to gross necropsies at the end of the study.
- Organs weighed: adrenals, kidneys, liver and testes with epididymides
- Histopathology: A select group of major tissues was examined in all animals from groups 1 and 5 (see table attached as appendix to this section). Gross lesions, treated and untreated skin, lungs, liver and kidneys were examined in all animals from groups 2, 3 and 4.

Results:

- Clinical signs: Crust was observed on the dorsal skin in 3/5 Group 5 males at least once and sometimes during several weeks. This appeared to be less common in other groups. Very slight erythema was noted at week 6 for one group 3 female, and one group 4 male. Very slight erythema was also noted at week 8 for one group 4 female, at week 7 for all group 5 males and two group 5 females. Generally, these signs lasted for 1 to 4 weeks although in one group 5 male they were seen at weeks 7-14. The dermal irritation had abated by the time of sacrifice in all animals except one group 5 male.

GLP compliance: Yes
QA-Report: Yes
Methods:
Dosing:

- species/strain: rabbit / Hra:(NZW)SPF
- #/sex/group or time point: 5/sex/group
- age: 3 months
- weight: males from 2123 to 2479 g and females from 2263 to 2634 g
- dosage groups in administered units:

Group	Treatment	Dose (µl/kg/dose)	No./sex
1	BDC vehicle	200	5
2	Benzamycin (commercial)	20	5
3	BDC (low)	10	5
4	BDC (mid)	20	5
5	BDC (high)	200	5

- route, form: The gels were applied twice per day for 13 weeks at the dose noted in the above table to a clipped area of approximately 6x6 cm on the backs of the animals. The second daily application was made approximately 6 hours after the first. The high dose is considered to be ten times the expected clinical dose on a µl/kg basis. However, the concentration of benzoyl peroxide and erythromycin are the same as the clinical formulation: 5% benzoyl peroxide and 3% erythromycin.
- Lot and batch numbers:

  Benzamycin dual chamber gel: [redacted] thromycin gel component, [redacted] and [redacted] benzoyl peroxide component, [redacted] (concentrations before mixing)

  Benzamycin dual chamber vehicle: erythromycin gel vehicle, [redacted] benzoyl peroxide gel vehicle, [redacted]

  Benzamycin commercial product: [redacted]

Observations and times:

- Clinical signs: Clinical signs including dermal irritation were recorded daily.
- Body weights: Body weights were recorded weekly.
- Food consumption: Food consumption was recorded weekly.
- Ophthalmoscopy: Ophthalmoscopic examinations were conducted prior to treatment and during week 13.
- Hematology: Blood for hematologic analysis was collected prior to necropsy.
- Clinical chemistry: Blood for clinical chemistry was collected prior to necropsy.
- Gross pathology: All animals were subject to gross necropsies at the end of the study.
- Organs weighed: adrenals, kidneys, liver with drained gall bladder and testes with epididymides
- Histopathology: A select group of major tissues was examined in all animals from groups 1 and 5 (see table attached as appendix to this section). Treated and untreated skin, lungs, liver and kidneys were examined in all animals from groups 2, 3 and 4.

Results:

- Clinical signs: Very slight erythema was noted at the treatment site in the following numbers of animals in each group: 1/5 males and 2/5 females in group 1, 5/5 males

and 5/5 females in group 2, 5/5 males and 5/5 females in group 3, 5/5 males and 4/5 females in group 4, and 5/5 males and 5/5 females in group 5.

Very slight edema was noted at the treatment site in the following numbers of animals in each group: 1/5 males and 1/5 females in group 1, 1/5 males and 3/5 females in group 2, 5/5 males and 3/5 females in group 3, 3/5 males and 2/5 females in group 4, and 1/5 males and 2/5 females in group 5.

- Body weights: There was a significantly greater mean body weight gain in group 4 females during week 1. This change seems unlikely to be related directly to the treatment.
- Food consumption: There was significantly lower food consumption for group 4 males at week 7. This change seems unlikely to be related directly to the treatment.
- Ophthalmoscopy: There were no ophthalmologic findings at the final examination.
- Hematology: There were statistically significant decreases in the mean platelet count in group 5 females and mean segmented neutrophil counts in group 2 and 4 females. The magnitude of these changes was small and no dose response was noted.
- Clinical chemistry: There was a statistically significant increase in the mean urea value for group 3 males. However, the magnitude of this change was small and no dose response was observed.
- Organ Weights: The mean absolute adrenal weight was significantly increased in the group 4 females. The magnitude of this increase was small and there was no increase in the adrenal to body weight ratio for this group. There was also no dose response for the adrenal weight change.
- Gross pathology: A dark area was noted on the skin of one male each in groups 2 and 4 and one female in group 2. The liver of one female in group 3 was noted as enlarged; however, the weight of this liver was similar to others from group 3 females.
- Histopathology: There was a dose related increase in the severity of dermal mononuclear cell infiltrates, acanthosis and hyperkeratosis in the Benzamycin dual chamber treated animals when compared to the vehicle treated animals. Animals treated with 20 µl/kg of the commercial Benzamycin formulation had similar severity of these findings as those animals treated with 10 and 20 µl/kg of the dual chamber formulation.

Key Study Findings: Topical treatment with either the commercial Benzamycin or the dual chamber formulation did not produce any detectable systemic effects in the rabbit in this 13 week study. Both formulations and the vehicle produce inflammation, acanthosis and hyperkeratosis in the skin of the treated site. These effects were similar in animals treated with the vehicle and with the lower doses of either Benzamycin formulation. The higher dose of the dual chamber formulation produced dermal effects of greater severity.

Study Title: **28-Day Dermal Rabbit Study**
Study No: DL-PC-6026-9725
Amendment #000, Vol. #8, and page #5-3-1
Conducting laboratory and location:
Date of study initiation: 7 May 1998

GLP compliance: Yes
QA-Report: Yes
Methods:
Dosing:

- species/strain: Rabbit / NZW
- #/sex/group or time point: 5/sex/group
- weight: mean=2.6 kg
- dosage groups in administered units:

Group	Treatment	Dose (µl/kg/dose)	No./sex
1	BDC vehicle	200	5
2	Benzamycin (commercial)	20	5
3	BDC (low)	10	5
4	BDC (mid)	20	5
5	BDC (high)	200	5
6	BDC degraded	200	5

Route, form: The gels were applied twice per day for 28 (females) or 30 (males) days at the dose noted in the above table to a clipped area of approximately 6x6 cm on the backs of the animals. The second daily application was made approximately 6 hours after the first. The high dose is considered to be ten times the expected clinical dose on a µl/kg basis. However, the concentration of benzoyl peroxide and erythromycin are the same as the clinical formulation: 5% benzoyl peroxide and 3% erythromycin. The degraded Benzamycin dual chamber test article is Benzamycin dual chamber product that was aged at 40°C and 75% relative humidity for two months.

Lot Numbers:

Benzamycin dual chamber gel (fresh and degraded): [redacted]

Benzamycin dual chamber vehicle: erythromycin gel vehicle, [redacted] benzoyl peroxide gel vehicle, [redacted]

Benzamycin commercial product: benzoyl peroxide component [redacted] erythromycin component: [redacted]

Observations and times:

- Clinical signs: Clinical signs including dermal irritation were recorded daily.
- Body weights: Body weights were recorded weekly.
- Food consumption: Food consumption was recorded qualitatively.
- Ophthalmoscopy: Ophthalmoscopic examinations were conducted prior to treatment and prior to necropsy.
- Hematology: Blood for hematologic analysis was collected in females on day 29 and in males on day 31.
- Clinical chemistry: Blood for clinical chemistry was collected in females on day 29 and in males on day 31.
- Gross pathology: All animals were subject to gross necropsies at the end of the study.
- Organs weighed: adrenals, epididymides, kidneys, liver, ovaries and testes
- Histopathology: Tissues was examined in all animals from groups 1, 5 and 6 (see table attached as appendix to this section). Gross lesions and skin sites were examined from all animals in all groups.

Results:

- Clinical signs: Very slight erythema was noted in all groups of males and in all groups of females except group 1. Two episodes of well-defined erythema were noted in group 5 and 6 females. All animals in groups 5 and 6 experienced some erythema whereas the other groups had at least some animals experiencing no erythema.
- Body weights: Group mean body weights for all groups were similar during all weeks of the study.
- Food consumption: Some animals in groups 1, 2, 3, and 4 were noted to have low food consumption at some point during the study.
- Ophthalmoscopy: There were no abnormal ophthalmic findings noted during the study.
- Hematology: White blood cells and absolute lymphocytes were statistically decreased in group 6 females.
- Clinical chemistry: Albumin was statistically increased in group 3 males. Chloride was statistically decreased in group 2 females and gamma glutamyltransferase was increased in group 4 females. All of these changes were of small magnitude and a dose-response was not apparent.
- Organ Weights: No significant differences in organ weights were noted.
- Gross pathology: Several group 5 and 6 males and females had crusting of the skin. Several animals in groups 3, 4 and 5 had red discoloration of the skin.
- Histopathology: Epidermal hyperplasia, hyperkeratosis and dermal inflammation occurred in all groups. The severity of these findings was greater in those groups receiving the higher dose of active ingredients. Two animals that had red skin discoloration as a gross observation also had microscopic evidence of dermal or skeletal muscle hemorrhage. Animals receiving the same dose of the commercial Benzamycin or the dual chamber formulation appeared to have similar incidence and severity of findings.

Key Study Findings: Topical treatment with commercial Benzamycin or the dual chamber formulation either fresh or degraded did not to produce any detectable systemic effects in the rabbit in this 28 day study. Both formulations and the vehicle produce inflammation, hyperplasia and hyperkeratosis in the skin of the treated site. These effects were similar in animals treated with the vehicle and with the lower doses of either Benzamycin formulation. The higher dose of the dual chamber formulation produced dermal effects of greater severity.

Overall Toxicology Summary:

The reviewed studies suggest that the topical application of the Benzamycin dual chamber gel does not produce systemic toxicity. Local effects such as inflammation and epidermal hyperplasia are observed. These effects are similar to those produced by the marketed Benzamycin gel. The effects appear to follow a dose response. The use of the degraded Benzamycin dual chamber gel did not produce any additional signs of toxicity.

Addendum list: Histopathology inventory table

Addendum 1
Histopathology Inventory for NDA #50-769

Study	13 week	13 week	28 day	
Species	Rat	Rabbit	Rabbit	
Adrenals	X*	X*	X*	
Aorta	X	X	X	
Bone Marrow smear	X	X	X	
Bone (femur)				
Brain	X	X	X	
Cecum	X	X	X	
Cervix				
Colon	X	X	X	
Duodenum	X	X	X	
Epididymis	X*	X*	X*	
Esophagus	X	X	X	
Eye				
Fallopian tube				
Gall bladder		X	X	
Gross lesions	X	X	X	
Harderian gland				
Heart	X	X	X	
Ileum	X	X	X	
Injection site	X	X	X	
Jejunum	X	X	X	
Kidneys	X*	X*	X*	
Lachrymal gland				
Larynx			X	
Liver	X*	X*	X*	
Lungs	X	X	X	
Lymph nodes, cervical				
Lymph nodes mandibular			X	
Lymph nodes, mesenteric	X	X	X	
Mammary Gland				
Nasal cavity				
Optic nerves				
Ovaries	X	X	X*	
Pancreas	X	X	X	
Parathyroid	X	X	X	
Peripheral nerve			X	
Pharynx			X	
Pituitary	X	X	X	
Prostate				
Rectum	X	X	X	
Salivary gland		X		
Sciatic nerve	X	X		
Seminal vesicles				
Skeletal muscle				
Skin	X	X	X	
Spinal cord				
Spleen	X	X	X	
Sternum			X	
Stomach	X	X	X	
Testes	X*	X*	X*	
Thymus	X	X	X	
Thyroid	X	X	X	
Tongue			X	
Trachea	X	X	X	
Urinary bladder	X	X	X	
Uterus	X	X	X	
Vagina				
Zymbal gland				

* organ weight obtained

CARCINOGENICITY:

No new carcinogenicity studies have been submitted in the current NDA. The carcinogenicity of benzoyl peroxide has been investigated in a number of studies; however, most of the studies have not been of two years duration and have not used daily application. In most studies, benzoyl peroxide applied alone did not produce skin tumors; however, in a study using SENCAR mice, benzoyl peroxide alone applied 2 times per week for 51 weeks produced skin tumors in 5 of 20 animals (Kurokawa et al., 1984). While the studies evaluating the carcinogenicity of benzoyl peroxide applied alone are limited, the studies clearly show that benzoyl peroxide is a tumor promoter and tumor progression agent in the skin in several animal models. The models in which benzoyl peroxide has shown activity include chemically or UV-initiated mice and hamsters. In one study conducted by the National Toxicology Program, benzoyl peroxide was shown to promote tumor formation initiated by dimethylbenzathracene or methyl-nitro-nitrosoguanidine in $B6C3F_1$, Swiss CD-1 and SENCAR mice (NTP TR 441, 1996). In this study the initiator was administered once and benzoyl peroxide was administered weekly for 52 weeks. Benzoyl peroxide by itself did not produce skin tumors in any strain in this study.

It has been argued that the tumor promoting ability of benzoyl peroxide in animal models is not relevant to humans (Binder et al., 1995; Kraus et al., 1995). Proponents of this view argue that induction of cellular proliferation is required in order for benzoyl peroxide to cause tumor promotion and that since this proliferation is not observed in humans, benzoyl peroxide is not a tumor promoter in humans. An alternative argument would be that benzoyl peroxide might be a tumor promoter in human skin if it were used at a high enough dose and duration. Also it is possible that other mechanisms may contribute to the tumor promoting ability of benzoyl peroxide. Several mechanisms have been proposed to explain the tumor promoting ability of benzoyl peroxide. Some of these mechanisms might occur even in the absence of cellular proliferation. A scientific consensus on which mechanisms are most relevant has not yet been established.

Human epidemiologic studies on the increased risk of skin cancer from benzoyl peroxide are limited in number and size but have not shown any association between benzoyl peroxide use and skin cancer. The largest and most relevant study was a retrospective study conducted in Canada, which examined acne treatments used by 966 facial skin cancer patients and 3864 age- and sex-matched controls over a period of 22 years. This study found no increased risk of skin cancer in individuals reporting benzoyl peroxide use for acne (Hogan et al., 1991).

The International Agency for Research on Cancer has reviewed the human and animal data on the carcinogenic potential of benzoyl peroxide (IARC monograph, 71:345-358, 1999). They concluded that there was limited evidence in animals and inadequate evidence in humans for the carcinogenicity of benzoyl peroxide. Overall, they concluded that benzoyl peroxide was not classifiable as to its carcinogenicity to humans.

In an evaluation of the safety of benzoyl peroxide in over-the-counter drug products, the agency stated in 1991 that the animal studies conducted were not adequate to evaluate the carcinogenicity of benzoyl peroxide (FR 56(102):37622, August 7, 1991). The agency was concerned that benzoyl peroxide might show complete carcinogenic effects with a long latency period since it possessed weak genotoxic potential. The Consumer Health Products Association

(CHPA, formerly the NDMA) is currently conducting two-year dermal carcinogenicity studies in rats and mice with a benzoyl peroxide carbopol gel formulation to help address this concern.

The ——— transgenic mouse model is considered by the Agency to be an acceptable alternative model for the evaluation of carcinogenicity. Studies with ——— mice are typically conducted using 20 weeks of treatment and compounds that are tumor promoters can be detected by this model. Benzoyl peroxide in acetone at doses of 5 and 10 mg administered twice per week induced skin tumors in ——— mice in a study with a total of 20 weeks of topical treatment (Spalding et al., 1993). This positive result should be included in the label.

In addition to studies in animals, several other studies have evaluated the impact of benzoyl peroxide treatment on intercellular communication in cultured cells. These assays are purported to identify nongenotoxic carcinogens. Results have been variable. Cases of decreased, increased or unchanged intercellular communication have been observed (for examples see Mikalson and Sanner, 1994; Jansen and Jongen, 1996 and Rivedal et al., 2000).

Long term (2 year) studies with erythromycin base and erythromycin ethylsuccinate at up to 0.25% of the diet have been conducted in rats. These studies did not provide evidence of tumorigenicity. In 1993 the FDA requested that this information be included in the Benzamycin package insert so that it would be consistent with topical erythromycin class labeling developed at that time. Long term (2 year) studies have also been conducted with erythromycin stearate in rats and mice with doses up to 1% and 0.5% of the diet, respectively (NTP TR 338, 1988). These studies were interpreted by the NTP review panel as showing no evidence of carcinogenic activity in rats or mice.

Photocarcinogenicity:
The sponsor notes that a photococarcinogenicity study of 5% benzoyl peroxide, sponsored by the CHPA, was ongoing at the time of previous meetings between the sponsor and the Agency. At these meetings it was recommended that the sponsor include the results of the CHPA photococarcinogenicity study on benzoyl peroxide in the label if benzoyl peroxide was photococarcinogenic. If this study did not demonstrate that benzoyl peroxide was photococarcinogenic then it was recommended that the sponsor conduct an evaluation of the photococarcinogenic potential of the drug product.

The sponsor states that they understand the results of the CHPA study to be negative. They would like to revisit the need for a photocarcinogenicity study in light of the CHPA results and in the context of the scientific consensus for appropriate photocarcinogenicity assessment.

The study sponsored by the CHPA did not detect any increase in UV-induced tumor formation in hairless mice treated with a 10% benzoyl peroxide carbopol gel. On the other hand, a different study submitted to the Division of Dermatologic and Dental Drugs Products under a different NDA showed that application of a 5% benzoyl peroxide gel increased UV-induced tumor formation in hairless mice. These studies were conducted by the same laboratory using similar protocols. One possibly critical difference between the two studies was in the order of drug application and light exposure. In the NMDA study drug was applied before radiation on Mon., Wed. and Fri. and after radiation on Tues. and Thurs. In the other study this order was reversed

- Doses employed: 0.5 ml of the Benzamycin dual chamber gel or of the commercial Benzamycin product were used for the induction and challenge phase
- Route of Administration: Material was applied to the backs of the animals using an occlusive patch (Hilltop Chamber) after hair was removed by clipping. For the induction phase, the material was applied for 6 hours, once a week for three weeks. Thirteen days after the last induction dose a challenge dose was applied using an occlusive patch to a clipped naïve site. This dose was left in place for 6 hours. A rechallenge dose was applied in the same manner as the challenge dose six days after the challenge application.
- Lot and batch numbers:

  Benzamycin dual chamber gel: erythromycin gel component, [redacted], benzoyl peroxide component, [redacted]

  Benzamycin dual chamber vehicle: erythromycin gel vehicle, [redacted], benzoyl peroxide gel vehicle, [redacted]

  Benzamycin commercial product: [redacted]

- Rationale: intended clinical route of application is topical to the skin
- Number of animals/sex/dosing group:

The following groups were employed in the current study.

Group No.	Treatment	No. of animals/sex	Treatment phases
1	BDC gel vehicle	5	Challenge only
2	BDC gel	10	Induction and Challenge
3	Commercial Benzamycin gel	10	Induction and Challenge
4	Positive control (DNCB)	2	Induction and Challenge

- Observations:

  Application sites were scored for erythema, edema and other cutaneous reactions according the method of Draize, 24 hours after induction applications and 24, 48 and 72 hours after challenge and rechallenge applications.

- Results:

  One male in group 2 had to be euthanized during the study. 2 of 19 animals exhibited well-defined erythema and 2 animals exhibited very slight edema after rechallenge with the dual chamber Benzamycin gel. The remaining animals exhibited very slight erythema after rechallenge with the dual chamber Benzamycin gel. 2 of 20 animals exhibited well-defined erythema after rechallenge with the commercial Benzamycin gel. Eight of the remaining animals exhibited very slight erythema after rechallenge with the commercial Benzamycin gel. No reaction was seen in the vehicle control animals. All four animals treated with DNCB had a positive reaction.

Key Study Findings: The report concludes that both the dual chamber formulation and the commercially available formulation have a weak sensitizing potential in the guinea pig model.

REPRODUCTIVE TOXICOLOGY:

No reproductive toxicity studies of Benzamycin or of benzoyl peroxide alone have been conducted.

The current label of Benzamycin contains a description of long term (2-year) studies that were conducted with up to 0.25% erythromycin in the diet. In these studies, animals were bred and there was no evidence of effect on fertility of the males and females and no evidence of teratogenicity or other adverse effect on reproduction.

According to Shepard's Catalog of Teratogenic Agents, Takaya (1965) gave 10 to 25 mg per kg subcutaneously to rats on days 6-10 and found no increase in defects or decrease in fetal weight.

According to TERIS – The Teratogen Information System, no increase in the frequency of malformations was observed among the offspring of rats treated with <1-12 times the maximum human dose of erythromycin or among the offspring of mice treated with 25 times the maximum human dose of erythromycin during pregnancy (Takaya, 1965; Moriguchi et al., 1972a, b).

GENETIC TOXICOLOGY:

The genotoxicity of benzoyl peroxide has been evaluated in a number of studies. The results of these studies have sometimes been positive and sometimes negative. Many of the bacterial assays conducted with benzoyl peroxide did not use strains of Salmonella sensitive to oxidative types of DNA damage such as the TA102 and TA104 strains. Consequently, these studies may have underestimated the mutagenic potential of benzoyl peroxide. Genotoxic effects have been observed with benzoyl peroxide in other *in vitro* models. For example, increases in sister chromatid exchanges have been reported in CHO or V79 cells (Jarventaus et al., 1984; Swierenga, et al., 1987). Two studies in *E. coli* have reported an increase in the SOS response after benzoyl peroxide treatment (Matula et al., 1987; Eder et al., 1989). Benzoyl peroxide can break down to form benzoyloxyl and phenyl radicals and *in vitro* studies with DNA have shown that these radicals can form DNA adducts (Hazlewood and Davies, 1996). Benzoyl peroxide is clearly capable of causing DNA strand breaks and oxidative DNA damage in cell cultures (for eg. see Hazlewood and Davies, 1996; Kawanishi et al., 1999). In 1991 the agency reviewed the genotoxicity of benzoyl peroxide and concluded that it possessed genotoxic potential (FR 56(102):37622, August 7, 1991). The studies conducted since then continue to indicate that benzoyl peroxide can cause DNA damage.

The genotoxicity of erythromycin stearate was evaluated by the NTP and is reported in Technical report No. 338, 1988. Erythromycin stearate was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535 or TA1537 with or without S9 microsomes from male Sprague-Dawley rat or Syrian hamster liver. Erythromycin stearate demonstrated equivocal mutagenicity in the mouse L5178Y lymphoma cell assay because in the absence of S9 increases in forward mutations were observed, but only at concentrations at or just below those that caused precipitation. No mutations were observed in the presence of F344 rat liver S9 microsomes at concentrations that did not cause precipitation. Erythromycin stearate did not cause any increase in sister chromatid exchanges or chromosomal aberrations in CHO cells in the presence or absence of rat liver S9 microsomes. Overall, the report concluded that erythromycin stearate appeared to be nonmutagenic.

SPECIAL TOXICOLOGY STUDIES:

General Comments: The drug is a topical gel and so a primary dermal irritation study was conducted.

Study Title: **Primary Dermal Irritation Study in Rabbits**
Study No: DL-PC-6026-9408
Amendment #000, Vol. #6, and page #5-1-36
Conducting laboratory and location: [redacted]
Date of study initiation: 20 October 1994
GLP compliance: No
QA-Report: No

Methods: The backs of three male and three female Hra:(NZW) SPF/HRP rabbits were shaved free of hair 24 hours before dosing. The animals were approximately 3 months old and weighed approximately 2200 g.

Dosing: Six sites were marked on each animal and test articles were applied in the following pattern. Site 1) Benzamycin dual chamber (dorsal-left); Site 2) Benzamycin dual chamber (dorsal-left); Site 3) Benzamycin dual chamber vehicle (dorsal-left); Site 4) commercial Benzamycin (dorsal-right); Site 5) 4) commercial Benzamycin (dorsal-right); and Site 6) untreated (dorsal-right). Sites 2 and 5 in all animals were abraded and site 3 was abraded in two males and one female before test article application. A 0.5 ml aliquot of the appropriate formulation was applied to the designated treatment site, covered with gauze and a nonabsorbent binder. After 24 hours of exposure excess material was removed.

Drug, lot#:

Benzamycin dual chamber gel: erythromycin gel component, [redacted]
benzoyl peroxide component, [redacted]

Benzamycin dual chamber vehicle: erythromycin gel vehicle, [redacted]
benzoyl peroxide gel vehicle, [redacted]

Benzamycin commercial product: lot# not specified

Formulation/vehicle: gel containing erythromycin at 3% and benzoyl peroxide at 5% final concentration.

Observations and times:
Rabbits were observed for mortality and moribundity twice daily. Skin reaction was evaluated according to the method of Draize at 30 to 60 minutes after removal of the gauze and then daily thereafter for 13 days. Body weights were recorded prior to treatment and at termination on day 14.

Results:
Very slight edema was noted on one animal for three days beginning 72 hours after patch removal at the Benzamycin dual chamber abraded site. Slight epidermal scaling was noted on

one animal at the Benzamycin dual chamber abraded and intact sites and at the commercial Benzamycin abraded site 6-9 days after patch removal. Slight erythema was observed on this same animal at the commercial Benzamycin abraded site 30-60 minutes after patch removal.

Summary:

Key finding(s): Both Benzamycin dual chamber formulation and the commercial Benzamycin product demonstrated very slight irritation potential in this study. The dual chamber vehicle was not irritating.

OVERALL SUMMARY AND EVALUATION:

The toxicity produced by the new dual chamber Benzamycin gel is similar to that produced by the approved Benzamycin product. This is not surprising since they contain the same concentration of active ingredients and similar excipients. The pharmacokinetic studies conducted with the new and old formulation show that absorption of the two products is similar. Consequently, no new systemic toxicity is anticipated from the new formulation. The local toxicity of the new formulation is also similar to that of the marketed product. No new toxicity was noted when degraded dual chamber Benzamycin gel was used in the 28 day rabbit toxicity study. Both the new dual chamber gel and the marketed product appear to have weak sensitizing potential when tested in the guinea pig. This is consistent with literature reports of benzoyl peroxide as a human sensitizer.

Communication Review:

Labeling Review (NDA):

Considering all of the available data, it seems reasonable to state in the label of benzoyl peroxide drugs that it is a tumor promoter and progression agent in animal models of skin cancer. In addition, since the FDA considers the Tg.AC model as a valid alternative model for the evaluation of carcinogenicity, it also seems reasonable to describe the results of the study conducted with benzoyl peroxide in this model. Rather than describing the mixed results of photocarcinogenicity studies conducted to date, it may be adequate to include a statement in the label about the tumor promoting capability of benzoyl peroxide together with a warning to avoid exposing benzoyl peroxide treated skin to sunlight. This warning is justified regardless of the outcome of animal photococarcinogenicity studies with benzoyl peroxide since repeated treatment of human skin with benzoyl peroxide can reduce the minimal erythema dose and since sun-exposed human skin is expected to contain UV-initiated cells. If the results of the CHPA sponsored dermal carcinogenicity studies are made public and are considered adequate then this information may be incorporated into the label in the future. The genotoxicity of benzoyl peroxide has been demonstrated in several studies and the ability of benzoyl peroxide to cause DNA strand breaks and oxidative DNA damage is established. Therefore, it seems reasonable to include a statement in the label about this. Information on the genotoxicity and carcinogenicity of erythromycin stearate is available from studies conducted by the NTP and it is reasonable to include this information in the label. The following paragraphs contain possible wording for the Carcinogenesis, Mutagenesis and Fertility section of the label. The sponsor's proposed label is shown for comparison.

Pages have been redacted in full from this document

Reason:

_____ b(2) 'low'

__X__ b(4) CCI DRAFT LABELING

_____ b(4) TS

_____ b(5) Deliberative Process: Attorney Client and Attorney Work Product Privilege

_____ b(6) Personal Privacy

_____ b(7) Law Enforcement Records

[redacted]

The wording proposed by the sponsor for the Pregnancy: Teratogenic Effects: Pregnancy Category section of the label is acceptable from a pharm/tox perspective. This wording is reproduced below.

[redacted]

Conclusions:
Benzamycin in the dual chamber formulation is unlikely to produce toxicity different from the approved Benzamycin product. Animal studies are not adequate to evaluate the complete carcinogenicity of topically applied benzoyl peroxide at this time. It is clear that benzoyl peroxide is a tumor promoter and progression agent in animal models of skin cancer. The results of photocarcinogenicity studies of benzoyl peroxide are mixed. To date, epidemiologic studies have not indicated an increase in skin tumors in humans using benzoyl peroxide for acne. Erythromycin has been nonmutagenic and noncarcinogenic in the studies conducted to date. The application is approvable with suggested labeling changes.

RECOMMENDATIONS:
The application is approvable with changes to the proposed label as outlined above.

/S/

Paul C. Brown, Ph.D.
Reviewing Pharmacologist
cc:
NDA 50-769
HFD-340
HFD-540
HFD-540/Pharm/Brown
HFD-540/TL/Jacobs
HFD-540/MO/Vaughan
HFD-540/Chem/Vidra
HFD-540/PM/Cross

Concurrence Only:
HFD-540/DD/Wilkin /S/

HFD-540/TL/Jacobs /S/

Draft date (# of drafts): August 18, 2000 (1st draft)
August 28, 2000 (2nd draft)
August 30, 2000 (3rd draft)

Appendix: List of References Cited in Review

List of References Cited in Review

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FR 56(102):37622, August 7, 1991

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Division of Dermatologic and Dental Drug Products (HFD-540)

Pharmacology/Toxicology Checklist for NDA Forward Planning Meeting

Meeting Date: 3/2/00, 1:00 pm
Reviewer: Paul C. Brown
NDA Number: 50-769
Sponsor: Dermik Laboratories
Product Name: Benzamycin
Drug Substance(s): erythromycin 3% and benzoyl peroxide 5%
Indication: Acne vulgaris
Route of Administration: topical to the skin
Date CDER Received: 1/27/00
User Fee Due Date (if filed): 11/27/00
Expected Date of Draft Review (if filed): May 2000

(1) Does the pharmacology/toxicology section of the NDA appear to be organized in a manner that would allow a substantive review to be completed?
Yes

(2) Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner to enable a timely and substantive review?
Yes

(3) Is the pharmacology/toxicology section of the NDA sufficiently legible to permit a substantive review to be completed?
Yes

(4) Based upon a cursory review, does the presentation of data appear to be appropriate (consider tables, graphs, completeness of study reports, inclusion of individual animal data, appropriateness of data analysis, etc.)?
Yes

(5) Are all necessary nonclinical studies completed and submitted in this NDA?
Yes

(6) Please itemize the pivotal nonclinical studies included in the NDA and indicate any important nonclinical studies that were omitted.

Since this application is for a product which is essentially a reformulation of an already approved product much of the pharmacology and toxicology information is in the form of a review of the literature and of studies previously submitted to the Benzamycin® Topical Gel NDA.

Five studies are included in the current NDA.

Four studies were conducted with an earlier slightly different "dual chamber" formulation:
1. Primary dermal irritation in rabbits
2. Guinea pig sensitization
3. 13-week dermal toxicity in rats
4. 13-week dermal toxicity in rabbits

One study is a "bridging" study utilizing the current "dual chamber" formulation.
5. 28-day dermal toxicity in rabbits

(7) Based upon a cursory review, do the pivotal nonclinical studies appear to have been adequately designed (e.g., appropriate numbers of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?
Yes

(8) As appropriate, were the test materials utilized in the pivotal nonclinical studies identical to the drug product or drug substance proposed for commercial use (including impurity profiles)? If not, or if this matter is unclear, please comment.
Yes, see #6 above

(9) Based upon a cursory review, do the excipients appear to have been adequately qualified?
Yes

(10) Was the route of administration used in the nonclinical studies the same as the intended clinical route of administration?
Yes

(11) Has proposed draft labeling been submitted?
Yes

(12) From a pharmacology/toxicology perspective, should this NDA be filed? If not, or if you have additional concerns, please

indicate your recommendations in the form of draft comments that may be transmitted to the sponsor.
Yes

/S/
Reviewing Pharmacologist

2/24/00
Date Signed

/S/
Pharmacology Team Leader

2/24/00
Date Signed