PRODUCT MONOGRAPH

PrBENZAMYCIN®
Erythromycin and Benzoyl Peroxide
Topical Gel, USP

Acne Therapy

Bausch Health, Canada Inc.
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Canada

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Topical Gel, USP

ACTION AND CLINICAL PHARMACOLOGY

Erythromycin is a bacteriostatic macrolide antibiotic but may be bactericidal in high concentrations. Although the mechanism by which erythromycin acts in reducing inflammatory lesions of acne vulgaris is not fully elucidated, it is presumably due to its antibiotic action. It inhibits the growth of *Propionibacterium acnes* on the surface of the skin and reduces the concentration of free fatty acids in the sebum.

Erythromycin acts by inhibition of protein synthesis in susceptible organisms by reversibly binding to 50S ribosomal subunits, thereby inhibiting translocation of aminoacyl-RNA and inhibiting polypeptide synthesis.

Benzoyl peroxide is an agent which has been shown to be effective against *Propionibacterium acnes*, an anaerobe found in sebaceous follicles and comedones. The antibacterial action of benzoyl peroxide is believed to be due to the release of active oxygen. Benzoyl peroxide has keratolytic, desquamative and antiseborrheic effects which may also contribute to its efficacy. Benzoyl peroxide has been shown to be absorbed by the skin where it is converted to benzoic acid. Approximately 5% of the metabolite is excreted unchanged in the urine.

INDICATIONS AND CLINICAL USE

BENZAMYCIN (erythromycin and benzoyl peroxide topical gel, USP) is indicated for the topical treatment of moderate acne vulgaris characterized by comedones, inflammatory papules/pustules, with or without an occasional cyst or nodule (Grade II to III*). BENZAMYCIN is not indicated for the treatment of cystic acne (Grade IV*).

BENZAMYCIN contains an antibacterial ingredient, erythromycin. To reduce the risk of development of drug-resistant bacteria and maintain the effectiveness of erythromycin, BENZAMYCIN should only be used for the authorized indication and clinical use.

CONTRAINDICATIONS

BENZAMYCIN (erythromycin and benzoyl peroxide topical gel, USP) is contraindicated in those patients with a history of hypersensitivity to erythromycin, benzoyl peroxide or any of the ingredients in the preparation (see PHARMACEUTICAL INFORMATION - Composition).

WARNINGS

For external use only.

Not for ophthalmic use. Avoid contact with eyes, nose, lips, mouth and other mucous membranes. If contact occurs, rinse thoroughly with water.

BENZAMYCIN (erythromycin and benzoyl peroxide topical gel, USP) contains drying and peeling agents that are potential irritants. Therefore, reduction in frequency of application may be necessary to avoid excessive irritation. If severe irritation develops, discontinue use and institute appropriate therapy. Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with peeling, desquamating or abrasive agents.

Susceptibility/Resistance

Development of Drug-Resistant Bacteria
Prescribing BENZAMYCIN in the absence of the authorized indications is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Potential for Microbial Overgrowth
Prolonged use of BENZAMYCIN Topical Gel may result in overgrowth of non-susceptible organisms including fungi. If this should occur, administration of BENZAMYCIN (erythromycin and benzoyl peroxide) topical gel should be discontinued and appropriate measures taken.

P. acnes resistance to clindamycin has been documented. Resistance to clindamycin is often associated with resistance to erythromycin. If this should occur, therapy with BENZAMYCIN topical Gel should be discontinued and alternative therapy should be initiated.

PRECAUTIONS

Use in Pregnancy
The safety of BENZAMYCIN in pregnancy has not been established, nor have any animal reproduction studies been conducted with BENZAMYCIN. It is also not known whether BENZAMYCIN can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. BENZAMYCIN should be given to a pregnant woman only if clearly needed.

Use during Lactation
It is not known whether BENZAMYCIN is excreted in human milk after topical application. However, erythromycin is excreted in human milk following oral and parenteral administration. Therefore, caution should be exercised when erythromycin is administered to a nursing woman.

Use in Children
The safety and effectiveness of BENZAMYCIN in children below the age of 12 years have not been established.

Drug Interactions
Antagonism has been demonstrated *in vitro* between erythromycin, lincomycin, chloramphenicol and clindamycin. Therefore erythromycin, lincomycin, chloramphenicol and clindamycin should not be used concomitantly with BENZAMYCIN, although no studies have been conducted testing for antagonism of BENZAMYCIN with these antibiotics.

ADVERSE REACTIONS

Local irritation reactions such as irritation of the skin including: peeling, itching, burning sensation, erythema, inflammation of the face, eyes and nose, irritation of the eyes, skin discoloration, oiliness, tenderness of the skin, pruritus and edema may occur while using BENZAMYCIN (erythromycin and benzoyl peroxide topical gel, USP).

In clinical trials conducted with BENZAMYCIN, 5 of 155 patients experienced adverse reactions. Four of the adverse reactions were dryness, and one was an urticarial reaction which responded to symptomatic treatment.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Acute overdosage with the topical use of BENZAMYCIN (erythromycin and benzoyl peroxide topical gel, USP) is unlikely. In the event of accidental ingestion, appropriate intervention should be initiated.

DOSAGE AND ADMINISTRATION

BENZAMYCIN (erythromycin and benzoyl peroxide topical gel, USP) should be applied as a thin layer to affected areas twice daily, morning and evening, or as directed by physician. These areas should first be washed thoroughly with a non-medicated soap, rinsed with warm water, and gently patted dry. Improvement has been seen as early as two weeks, although in certain cases six to ten weeks of treatment may be required for best results.

PHARMACEUTICAL INFORMATION

Drug Substance

1. ERYTHROMYCIN

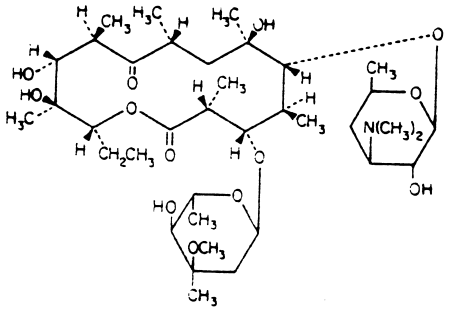
Proper Name: Erythromycin

Chemical Name: (3R*,4S*,5S*,6R*,7R*,9R*,11R*,12R*,13S*,14R*)-4-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)-oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-oxacyclotetradecane-2,10-dione.

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

Molecular Weight: 733.94 g/mol

Structural Formula:



Physicochemical Properties

Description: Erythromycin is a white or slightly yellow, crystalline powder. It is odorless or practically odorless. Erythromycin is slightly soluble in water, and soluble in alcohol, chloroform and ether.

2. BENZOYL PEROXIDE

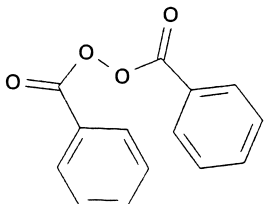
Proper Name: Hydrous benzoyl peroxide

Chemical Name: Benzoyl peroxide

Molecular Formula: $C_{14}H_{10}O_4$

Molecular Weight: 242.23 g/mol

Structural Formula:



Physicochemical Properties

Description: Benzoyl peroxide is a white granular powder, having a characteristic odour. It is sparingly soluble in water and in alcohol; and is soluble in acetone, chloroform and ether.

Composition
When dispensed, BENZAMYCIN (erythromycin and benzoyl peroxide topical gel, USP) contains 3% (30 mg/g) erythromycin and 5% (50 mg/g) benzoyl peroxide. Inactive ingredients include Alcohol, Carbomer, Docusate Sodium, Lemon Fragrance, Methyl Salicylate, Purified Water and Sodium Hydroxide.

Compounding Directions
BENZAMYCIN is supplied to the pharmacist in a package containing 40 g of benzoyl peroxide gel and 1.6 g of active erythromycin powder in a plastic vial (46.6 g net weight, as dispensed). **Prior to dispensing, tap the vial of erythromycin until all powder flows freely. For BENZAMYCIN 46.6 g (net weight, as dispensed), add 6 mL of ethyl alcohol (70%) to the erythromycin vial (to the mark) and immediately shake to completely dissolve the powder**. Add this solution to the gel and stir until homogeneous in appearance (1 - 1½ minutes).

Stability and Storage Recommendations
Prior to dispensing, the package containing one jar of benzoyl peroxide gel (40 g) and one plastic vial of active erythromycin powder (1.6 g) should be stored at room temperature (15° to 25°C). Following compounding (see Compounding Directions), BENZAMYCIN should be stored under refrigeration (2° to 8°C). Do not freeze. A 3-month expiration date is to be placed on the label.

AVAILABILITY OF DOSAGE FORMS

BENZAMYCIN (erythromycin and benzoyl peroxide topical gel, USP), is available in a 46.6 g net weight package size (as dispensed) and is supplied to the pharmacist as a carton containing 40 g of benzoyl peroxide gel and 1.6 g active erythromycin in a plastic vial (see PHARMACEUTICAL INFORMATION - Compounding Directions).

MICROBIOLOGY

Minimum inhibitory concentrations (MIC) of erythromycin as well as benzoyl peroxide for *P. acnes* have been reported in the literature as follows:

	MIC (mcg / mL)		
	P. acnes	*S. aureus*	*S. pyogenes*
Erythromycin [1,2]	0.05 - 0.4	0.006 - >100	≥0.024 - 0.05
Benzoyl Peroxide[3]	100 - 800	NA	NA
NA = not available			

PHARMACOLOGY

Clinical pharmacology studies have not been conducted with BENZAMYCIN (erythromycin and benzoyl peroxide topical gel, USP).

TOXICOLOGY

Animal Toxicology

Acute Toxicity
An oral, acute toxicity study was conducted with erythromycin and benzoyl peroxide topical gel in Swiss Webster mice. Groups of ten male and ten female animals were administered either 10, 12.6, 15.9, 20, 25.2, 31.8 or 40 mL/kg erythromycin and benzoyl peroxide topical gel as a single dose by gavage and were observed for 14 days. The estimated LD_{50} was found to be between 31.8 and 40 mL/kg (30.8 to 38.8 g/kg). The principal pharmacological effect observed was that of CNS depression, manifested by ataxia, decreased motor activity and loss of righting reflex. These effects were dose-related, and characteristic of alcohol intoxication (alcohol is an excipient in the erythromycin and benzoyl peroxide topical gel formulation).

Irritation Potential
Eye irritation tests were performed in albino rabbits. Erythromycin and benzoyl peroxide topical gel 0.1 mL was instilled in the right eye of three animals and was found to produce a conjunctival irritation that cleared by the seventh day post-treatment.

Another group of researchers conducted tests in albino rabbits (3M/3F) for eye irritation and primary irritation of the skin. For the eye irritation study, six animals received 0.1 mL of

erythromycin and benzoyl peroxide topical gel, instilled in the right eye. Observations were made at 24, 48 and 72 hours and 7 days post-treatment. Erythromycin and benzoyl peroxide topical gel was irritating to all the animals, with various degrees of irritation for the iris in two animals, and various degrees of irritation for the conjunctiva (redness and chemosis) in all animals. This irritation cleared by the seventh day post-treatment. These results show that erythromycin/ benzoyl peroxide gel is an irritant to the rabbit eye. In the skin irritation study, 0.5 mL of erythromycin and benzoyl peroxide topical gel was applied to one-inch square areas of intact and abraded skin of 6 animals (3M/3F). Following 24 hours exposure to erythromycin and benzoyl peroxide topical gel, the reactions of the skin were evaluated. No positive reaction was noted on the intact skin, and a minimal response was noted in 2 animals on the abraded skin. At 72 hours post-application, no irritation was noted at any site. These results indicate that erythromycin and benzoyl peroxide topical gel may be characterized as a very mild irritant.

Sensitization Potential
The sensitization potential of erythromycin and benzoyl peroxide topical gel was investigated using male guinea pigs. Eight animals received 10 intracutaneous injections of a 0.1% suspension of erythromycin and benzoyl peroxide topical gel in physiological saline. These injections were administered every other day, with the first injection being 0.05 mL, and the remaining injections being 0.1 mL. Two weeks following the final injection, a challenge injection of 0.05 mL erythromycin and benzoyl peroxide topical gel (0.1% suspension) was administered. It was found that the average response to the challenge injection was not greater than the average response for each animal to the initial injections. Thus, based on the result of this experiment, erythromycin and benzoyl peroxide topical gel is non-sensitizing to guinea pigs.

Carcinogenesis, Mutagenesis and Impairment of Fertility
No animal studies have been performed to evaluate the carcinogenic and mutagenic potential or effects on fertility of erythromycin and benzoyl peroxide topical gel. However, long-term (2-year) oral studies in rats with erythromycin ethyl succinate and erythromycin base did not provide evidence of tumorigenicity. There was no apparent effect on male or female fertility in rats fed erythromycin base at levels up to 0.25% of diet. Although the matter remains controversial in the literature, benzoyl peroxide has not been proven to be carcinogenic or mutagenic. There is no evidence that benzoyl peroxide has teratogenic or reproductive toxic effects.

Human Toxicology

Irritation Potential
In a 21-day cumulative irritation study with 27 evaluable volunteers, 0.2 mL of BENZAMYCIN, a 5% alcohol-based benzoyl peroxide, a 5% water-based benzoyl peroxide, and an alcohol vehicle were applied under occlusion for five consecutive days per week for three weeks. Irritancy was assessed on a five-point scale. The mean cumulative irritancy score for BENZAMYCIN was 7.9 ± 6.9 compared to 14.6 ± 6.8 for the alcohol-based benzoyl peroxide, 12.0 ± 7.9 for the water-based benzoyl peroxide, and 14.5 ± 7.1 for the alcohol vehicle.

Contact-sensitization Potential
The contact-sensitization potential of erythromycin and benzoyl peroxide topical gel was determined in 25 subjects (14M/11F). During the induction phase, 0.3g of erythromycin and benzoyl peroxide topical gel was applied to the forearm of the volunteers five times, once every 48 hours. Following a 10-day rest period, a challenge patch of the gel was applied. At 48 and 72 hours post-challenge, observations were made for a sensitization reaction (erythema, edema, vesiculation). No instances of contact-sensitization were noted under the experimental conditions in these evaluations.

Phototoxicity Potential
Ten female volunteers participated in a study designed to determine the phototoxic potential of erythromycin and benzoyl peroxide topical gel. 5µL of the test material was applied to duplicate skin sites on the backs of the subjects, and then covered. Six hours later, one site on each volunteer was uncovered and irradiated immediately with long wave ultraviolet light and visible light. The reactions were graded immediately, 24 and 48 hours post-irradiation. No instances of a phototoxic reaction (wheal-and-flare response or intense erythema and edema) were noted at any time point. Erythromycin and benzoyl peroxide topical gel is not considered to be phototoxic under these experimental conditions.

Photocontact Allergenic Potential
The photocontact allergenic potential of erythromycin and benzoyl peroxide topical gel was investigated in 25 volunteers with no history of phototoxicity (1M/24F). During the induction phase of the study, 10µL/cm^2 of the gel was applied to various skin sites over the mid-back of the subjects. Twenty-four hours later the patches were then removed, and the sites were exposed to three minimal erythema doses from a xenon solar simulator (UVA and UVB). The sites were irradiated again 48 hours later, and then two times per week for a total of 6 exposures. Ten days after the last induction exposure, the subjects were challenged by applying 5mcL/cm^2 of the gel to a skin site and exposing it to 4 joules/cm^2 of long ultraviolet light 24 hours later. The sites were examined 48 and 72 hours post-irradiation. At 48 hours, 10 patients exhibited a reaction to erythromycin - benzoyl peroxide. However, the same intensity of reaction was noted for the same individuals for patches of skin exposed to erythromycin and benzoyl peroxide topical gel but not irradiated with UVA light. At 72 hours, 2 additional subjects exhibited a reaction to erythromycin and benzoyl peroxide topical gel, both at irradiated and non-irradiated sites. When the gel base (placebo) was tested in the same manner, no reaction was observed in any volunteer. Although a high rate of primary contact reactions and contact sensitization reactions was observed under these experimental conditions, there was no detectable evidence that erythromycin and benzoyl peroxide topical gel has photoallergenic potential.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

PrBENZAMYCIN®
Erythromycin and Benzoyl Peroxide
Topical Gel, USP

Read this carefully before you start taking **BENZAMYCIN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **BENZAMYCIN**.

What is BENZAMYCIN used for?
- BENZAMYCIN is applied to the skin in a thin layer and helps to treat acne.
- BENZAMYCIN contains an antibacterial ingredient called erythromycin, and it should be used exactly as directed by your healthcare professional. Misuse or overuse of BENZAMYCIN could lead to the growth of bacteria that will not be killed by erythromycin. This means that BENZAMYCIN or other medicines that contain erythromycin may not work for you in the future. Do not share your medicine.

How does BENZAMYCIN work?
BENZAMYCIN is a mixture of two acne medications: erythromycin and benzoyl peroxide. They both work by fighting the bacteria that can cause the acne. Benzoyl peroxide also is a peeling agent; it helps to remove the external layer of the skin.

What are the ingredients in BENZAMYCIN?
Medicinal ingredients: Erythromycin 3% (30 mg/g) and Benzoyl Peroxide 5% (50 mg/g)
Non-medicinal ingredients: Alcohol, Carbomer, Docusate Sodium, Lemon Fragrance, Methyl Salicylate, Purified Water and Sodium Hydroxide.

BENZAMYCIN comes in the following dosage forms:
Topical gel

Do not use BENZAMYCIN if:
- You know you have an allergy to erythromycin, benzoyl peroxide or any of the ingredients of this preparation. See "What are the ingredients in BENZAMYCIN?" above.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take BENZAMYCIN. Talk about any health conditions or problems you may have, including if:
- You are pregnant or planning to become pregnant. It is not known if BENZAMYCIN may harm your unborn baby.
- You are breastfeeding or plan to breastfeed. BENZAMYCIN may pass through your milk and may harm your baby. Talk to your doctor about how to feed your baby while taking BENZAMYCIN.

Other warnings you should know about:

- You might experience slight stinging and/or redness when you start taking BENZAMYCIN. If excessive irritation or dryness occurs, stop taking BENZAMYCIN and consult your doctor.
- Do not use any other acne medication unless directed to do so by your doctor.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with BENZAMYCIN:

- Lincomycin
- Chloramphenicol
- Clindamycin

How to take BENZAMYCIN:

BENZAMYCIN should only be applied to your skin.

- Before to apply BENZAMYCIN, wash affected areas with a mild, non-irritating soap, rinse with warm water, and then gently pat dry.
- Apply BENZAMYCIN to affected areas in a thin layer.
- Wash your hands after application.
- Although you may see improvement as early as two weeks, continue to take BENZAMYCIN as directed by your doctor. In certain cases, six to ten weeks of treatment may be required for best results.
- Do not over-apply BENZAMYCIN. Using too much BENZAMYCIN will not speed up treatment but may irritate your skin.
- BENZAMYCIN is for external use only. Avoid contact with the eyes, nose, lips, mouth and other mucous membranes. If contact occurs, rinse well with water. If soreness or redness develops contact your doctor.

Usual dose:

Adults and children 12 years and older, apply a thin layer twice a day, morning and evening, or as directed by your doctor to affected areas.

Overdose:

If you think you have taken too much BENZAMYCIN, particularly by accidental oral ingestion, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to use BENZAMYCIN, you should wait for the next dose at the usual time. You should not double the dose to make up the forgotten dose.

What are possible side effects from using BENZAMYCIN?

These are not all the possible side effects you may feel when taking BENZAMYCIN. If you experience any side effects not listed here, contact your healthcare professional.

During the use of BENZAMYCIN Gel, you may notice some skin irritation such as peeling, itching, burning sensation, and erythema (redness of the skin); skin discoloration, unusual sensitivity of the skin and inflammation of the face, eyes and nose.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store this medication in your refrigerator. Do not freeze.
- Keep out of reach and sight of children.
- If after 3 months from the time your prescription was filled you have not used up the BENZAMYCIN, discard it and obtain a fresh supply.

If you want more information about BENZAMYCIN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); by contacting the sponsor: Bausch Health, Canada Inc. , 2150 St-Elzéar Blvd. West, Laval, (Quebec) H7L 4A8; or by calling 1-800-361-4261.

This leaflet was prepared by: Bausch Health, Canada Inc.

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