PRODUCT MONOGRAPH

PrERYSOL®

(erythromycin 2% w/w, ethyl alcohol 75% w/w,
octinoxate 7.5% w/w, avobenzone 2% w/w)

TOPICAL GEL WITH SUNSCREENS

THERAPEUTIC CLASSIFICATION

TOPICAL ACNE THERAPY

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DATE OF REVISION:
January 30, 2014

Control Number: 170009

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ACTIONS AND CLINICAL PHARMACOLOGY

Erythromycin exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible bacteria and suppressing protein synthesis. Erythromycin is usually bacteriostatic but may be bactericidal in high concentrations or against highly susceptible organisms. The precise mechanism of action of erythromycin in the treatment of acne has not been established. Ethyl alcohol is a drying and peeling agent.

INDICATIONS AND CLINICAL USE

ERYSOL® (erythromycin 2%, ethyl alcohol 75%, octinoxate 7.5%, avobenzone 2%) Topical Gel with sunscreens is indicated in the treatment of inflammatory papular and pustular lesions of acne vulgaris.

ERYSOL® is not indicated for the treatment of cysts or nodules. It is not indicated for use in Grade IV acne.

CONTRAINDICATIONS

ERYSOL® (erythromycin 2%, ethyl alcohol 75%, octinoxate 7.5%, avobenzone 2%) Topical Gel with sunscreens is contraindicated in persons with a known sensitivity or allergy to erythromycin or any of the other ingredients.

WARNINGS

ERYSOL® (erythromycin 2%, ethyl alcohol 75%, octinoxate 7.5%, avobenzone 2%) Topical Gel with sunscreens is intended for external use only. Contact with the eyes, nostrils, mouth and other mucous membranes or areas of broken skin should be avoided because of its irritant effects.

Concomitant topical anti-acne therapy should be used with caution because a cumulative irritancy effect may occur, especially with preparations having peeling, desquamating or abrasive properties. If irritation or dermatitis occurs, ERYSOL® should be discontinued.

Clostridium Difficile-Associated Disease (CDAD): *Clostridium difficile* -associated disease (CDAD) has been reported with use of many antibacterial agents, including erythromycin. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *Clostridium difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases (see **ADVERSE REACTIONS**).

PRECAUTIONS

The use of preparations containing antibiotics such as ERYSOL (erythromycin 2%, ethyl alcohol 75%, octinoxate 7.5%, avobenzone 2%) Topical Gel with sunscreens may be associated with overgrowth of antibiotic resistant organisms, including those initially sensitive to the drug. If there has been no improvement after 6-8 weeks, or the condition becomes worse, the treatment should be discontinued.

Patients with poor tolerance of macrolide antibiotics or clindamycin may not tolerate ERYSOL®. Patients carrying strains of macrolide- or clindamycin-resistant bacteria may demonstrate resistance to ERYSOL®. If either of these should occur, ERYSOL® should be discontinued and alternate therapies should be considered.

Flammability: Due to the flammable nature of ERYSOL®, patients should avoid smoking or being near an open flame during application and immediately after use.

Special Populations

Pregnant women: There are no data on the effect of topical erythromycin on fertility in humans.

The safety of ERYSOL® during pregnancy has not been established. There are limited data on the use of topical erythromycin in pregnant women. Systemic exposure to erythromycin is very limited with topical application. Erythromycin

crosses the placental barrier. Topical erythromycin should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

Nursing Mothers: Percutaneous absorption of erythromycin is very limited; however, it is not known whether erythromycin is excreted in human milk after topical application. Erythromycin is excreted in human milk following oral and parenteral administration. Topical erythromycin should be used during lactation only if the expected benefit justifies the potential risk to the infant. If used during lactation, erythromycin should not be applied to the breast area to avoid accidental ingestion by the infant. Caution should be exercised whenever ERYSOL® is given to a nursing mother.

Pediatrics (< 12 years of age): Safety and effectiveness of topical erythromycin in children under the age of 12 have not been established.

Geriatrics: There are no specific recommendations for use in the elderly.

Patients with renal/hepatic impairment: No dosage adjustment is necessary. As there is very limited percutaneous absorption of erythromycin following topical application, renal/hepatic impairment is not expected to result in systemic exposure of clinical significance.

DRUG INTERACTIONS

Drug-Drug Interactions:

Clindamycin and erythromycin have been shown to be antagonistic in vitro.

ADVERSE REACTIONS

Adverse reactions very commonly reported in clinical trials with topical erythromycin preparations such as ERYSOL® (erythromycin 2%, ethyl alcohol 75%, octinoxate 7.5%, avobenzone 2%) Topical Gel with sunscreens include mild to

severe skin irritation symptoms including dryness especially on initiation of treatment, application site stinging, tenderness, application site erythema, and burning sensation.

Other adverse reactions reported include desquamation, scaling, coriaceousness, fissuring around the mouth, and oiliness.

There have been rare post-market reports of allergic reactions, diarrhea, abdominal discomfort, upper abdominal pain, rash, urticaria, pruritus, and facial edema. There have been very rare post-market reports of skin exfoliation.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Accidental ingestion of ERYSOL® (erythromycin 2%, ethyl alcohol 75%, octinoxate 7.5%, avobenzone 2%) Topical Gel with sunscreens could cause the same gastrointestinal adverse reactions as those seen with orally administered erythromycin (manifested by abdominal discomfort, cramping, diarrhea, or vomiting). The formulation contains a significant quantity of ethanol. Systemic absorption of this should be considered a possibility in the event of overdosage.

If ERYSOL® comes into contact with the eye, irrigate with copious amounts of water or irrigation solutions. If discomfort persists, consult a physician.

Excessive frequency of application may result in excessive dryness and scaling, pruritus, tenderness, erythema, desquamation and burning sensation. Discontinue use until condition subsides. Appropriate anti-inflammatory measures may be employed.

DOSAGE AND ADMINISTRATION

ERYSOL® (erythromycin 2%, ethyl alcohol 75%, octinoxate 7.5%, avobenzone 2%) Topical Gel with sunscreens should be applied in a thin film twice a day to areas affected by acne. These areas should be washed first with a mild soap, rinsed well, and patted dry, followed by application of the gel in a gentle rubbing motion, using fingertips to apply the medication. Wash hands thoroughly after application. Care should be taken to avoid eyes, nostrils, mouth and other mucous membranes as well as broken skin. Following application of ERYSOL®, the patient should be instructed to allow the skin to dry before applying cosmetics.

Ethyl alcohol contributes significantly to the efficacy of ERYSOL® due to its drying and peeling properties. Because ethyl alcohol is potentially irritating, the frequency of application may require adjustment to once a day.

Six to eight weeks of treatment may be required before a therapeutic effect is observed. Treatment may be continued for up to a maximum of 3 months. If there has been no improvement after 6 to 8 weeks, or if the condition becomes worse, treatment should be discontinued.

Missed Dose: If patients forget to take a dose of ERYSOL®, they should be instructed to apply the next dose at the usual time. Patients should be instructed to not apply a double dose to make up for forgotten doses.

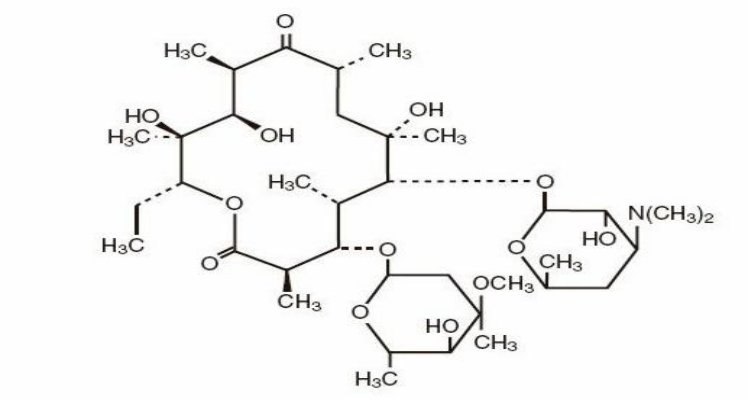
PHARMACEUTICAL INFORMATION

A. ERYTHROMYCIN

Proper Name: Erythromycin

Chemical Name: (3R*,4S*,5S*,6R*,7R*,9R*,11R*,12R*,13S*,14R*)-4-[(2,6-Dideoxy-3-C-methyl-3-0-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)-ß-D-xylo-hexopyranosyl]oxy] oxacyclotetradecane-2,10-dione.

Structural Formula:



Molecular Formula: $C_{37}H_{67}NO_{13}$ Molecular Weight: 733.94

Description: Erythromycin is a white or slightly yellow, odourless or practically odourless, crystalline powder. It is freely soluble in methanol, ethanol, acetone and chloroform. It is soluble in water at 2 mg/mL.

B. ETHYL ALCOHOL

Proper Name: Ethanol

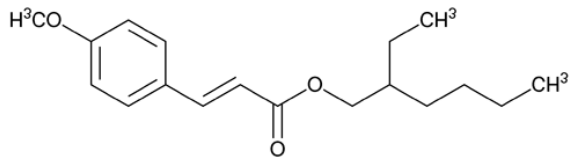
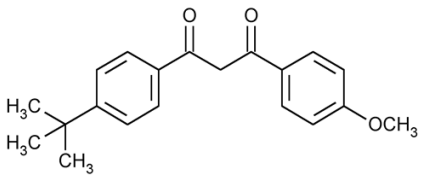
Chemical Name: Ethyl Alcohol

Structural Formula:

CH_3-CH_2-OH

Molecular Formula: C_2H_6O Molecular Weight: 46.07

Description: Clear colourless gel with characteristic odour.

C. SUNSCREEN DRUG SUBSTANCES	
Proper name: octinoxate	Proper name: avobenzone
Chemical name: 2-ethyl hexyl-P-methoxycinnamate	Chemical name: 1-(p-tert-butylphenyl)-3-(p-methoxyphenyl)-1,3-propanedione
Molecular formula: $C_{18}H_{26}O_3$	Molecular formula: $C_{20}H_{22}O_3$
Molecular Mass: 290.4 g/mol	Molecular Mass: 310.39 g/mol
Structural formula: 	Structural formula: 
Physicochemical properties: A pale yellow slightly oily practically odourless liquid.	Physicochemical properties: Off-white to yellow powder.

Composition: ERYSOL® Topical Gel with sunscreens is a clear gel containing erythromycin USP 2% w/w (20 mg/g) and ethyl

alcohol (75% w/w), with sunscreens octinoxate (7.5% w/w) and avobenzone (2% w/w). ERYSOL® also contains hydroxypropylcellulose, dioctyl malate, cyclomethicone, and isoarachidyl neopentanoate.

Storage: Store ERYSOL® Topical Gel between 15°C – 30°C. Keep container tightly closed when not in use. Contents are flammable. Keep away from fire, flame or heat. Do not leave ERYSOL® in direct sunlight.

AVAILABILITY

ERYSOL®: 25 g aluminium tubes with screw caps.

INFORMATION FOR THE CONSUMER

About this Medication

What ERYSOL® is and what it is used for:

Your physician has prescribed ERYSOL® (erythromycin 2% w/w, ethyl alcohol 75% w/w, octinoxate 7.5% w/w, avobenzone 2% w/w) Topical Gel with sunscreens to treat your acne. Erythromycin is one of the group of medicines called antibiotics. It works by fighting the bacteria that can cause the acne. ERYSOL® is not effective in most cases of severe acne.

When ERYSOL® should not be used:

ERYSOL® is not for use by children under the age of 12.

Do not use ERYSOL® if you cannot tolerate or have previously had a skin reaction or allergy to erythromycin or any of the other ingredients of ERYSOL®.

What the ingredients are:

ERYSOL® is a clear gel containing 2% erythromycin and 75% ethyl alcohol, with 7.5% octinoxate and 2% avobenzone as sunscreens. ERYSOL® also contains

hydroxypropylcellulose, dioctyl malate, cyclomethicone, and isoarachidyl neopentanoate.

Warnings and Precautions:

Before you use ERYSOL® your doctor needs to know if:

- you cannot tolerate or have previously had a skin reaction or allergy to erythromycin or any of the other ingredients of ERYSOL® (see What the ingredients are);
- you are pregnant or planning to become pregnant. If you do become pregnant during treatment with ERYSOL® tell your doctor;
- you are taking any other medicines, if you have taken any recently, or if you start taking a new one. This includes medicines bought without a prescription.
- you are breastfeeding. Your doctor will decide if you should use this product. If used during breastfeeding, do not apply ERYSOL® to the breast area to avoid accidental ingestion by the infant.
- Do not use ERYSOL® at the same time as clindamycin-containing acne medicines that are used on the skin. Do not use ERYSOL® at the same time as any other acne medications unless your doctor instructs you to do so.

If you experience symptoms such as severe diarrhea (bloody or watery) with or without fever, stomach cramps, abdominal pain, or tenderness, you may have *Clostridium difficile* colitis (bowel inflammation). If this occurs, stop taking ERYSOL® and contact a healthcare professional immediately.

FLAMMABLE: Due to the flammable nature of ERYSOL®, you should avoid smoking or being near an open flame while you're applying ERYSOL®, and immediately after you've used it.

Drug-Drug Interactions:

In test-tube studies, erythromycin and another antibiotic, called clindamycin, have been shown to work against each other.

Tell your doctor if you are using other acne or skin preparations including peeling agents (e.g., sulfur, resorcinol, salicylic acid) and abrasive agents as concomitant use with ERYSOL® may increase side effects such as skin irritation.

Proper Use of this Medication:

Usual dose:

1. First wash the affected areas with a mild soap (not medicated) and warm water, rinse well and gently pat dry.
2. Apply a thin film of ERYSOL® with your fingertips to the skin area affected by acne (not just each spot) and smooth in. Do not contact the eyes, mouth, nostrils and other mucous membranes, and rinse well with water if ERYSOL® is applied to these areas. If contact with eyes occurs, flush with water for at least 5 minutes. If discomfort persists, consult your doctor. Also do not contact irritated areas of skin such as cuts, grazes, sunburn or broken skin.
3. Use ERYSOL® twice daily. It can take six to eight weeks before you see the full benefit of ERYSOL®. If no improvements are seen in six to eight weeks or if the acne gets worse, stop using the medicine and talk to your doctor. Do not expect to see immediate improvement of your acne; but be patient and apply your medication as your doctor has directed. You should keep using the medicine according to your doctor's instructions up to a maximum of 3 months.
4. Apply the medication exactly as your doctor has told you to. Check with your doctor or pharmacist if you are not sure. Take care not to apply too much gel. Applying too much gel or applying it more frequently will not help your acne clear up more quickly and may cause additional irritation. If irritation is severe (severe dryness,

itching, tenderness, peeling, or burning), stop treatment and see your doctor.

5. ERYSOL® contains ingredients to help the antibiotic reach the bottom of your hair follicles where the acne starts. These ingredients keep the skin wet for a few minutes after applying it. Allow your face to dry completely before using any makeup.
6. Wash your hands thoroughly after using the medication.

Overdose

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

The product contains a large amount of alcohol (75%) which could be an important factor in treating a case of accidental oral ingestion of a large amount of ERYSOL®, particularly in a small child.

The ingredients of ERYSOL® are not expected to be harmful if swallowed in the small amounts normally applied to the face. If you do accidentally get ERYSOL® in your mouth, rinse at once with plenty of water. Seek medical advice if you swallow more than a small amount. You may get symptoms similar to when you take antibiotics by mouth (an upset stomach).

Missed Dose

If you forget to use ERYSOL®, don't apply a double dose to make up for forgotten doses. Apply the next dose at the usual time.

Side Effects and What to Do About Them

Like all medicines, ERYSOL® can cause side effects, but not everybody gets them. Stop using ERYSOL® and see a doctor straight away if you notice an allergic

reaction (such as swelling of your face, or hives), or if you develop severe or prolonged diarrhea.

The following side effects have been reported very commonly: redness, tenderness, dryness, skin irritation, burning sensation, stinging. Peeling was commonly reported. Other side effects include scaly skin, leathery appearance, cracks around the mouth, and oiliness.

Rare side effects include diarrhea, stomach pain, stomach discomfort, itching, rash, or swelling of the face. Tell your doctor or pharmacist if any of the side effects become severe or troublesome, or if you notice any side effects not listed here.

How to store ERYSOL®:

Store between 15°C – 30°C. Keep the container tightly closed when not in use. Contents are flammable. Keep ERYSOL® away from all sources of fire, flame and heat. Do not leave ERYSOL® in direct sunlight. Keep out of the sight and reach of children. ERYSOL® is available in 25 g tubes.

Do not use after the expiry date which is stated on the tube and outer carton. REMEMBER: ERYSOL® has been prescribed by your doctor for you; do not allow other people to use it as it may harm them even if their symptoms seem to be the same as yours.

MICROBIOLOGY

Erythromycin is a macrolide antibiotic which inhibits protein synthesis in susceptible organisms by reversibly binding to 50 S ribosomal subunits, thereby inhibiting translocation of aminoacyl transfer-RNA and inhibiting polypeptide synthesis.

Topical erythromycin is known to inhibit *in vitro* the growth of *Propionibacterium acnes* (*Corynebacterium acnes*), an anaerobe found in sebaceous glands and follicles.[1,2]

The *in vitro* susceptibility of *P. acnes* and related species to erythromycin[1] is shown in the following table:

Species	**No of Strains**	**Cumulative % of strains inhibited at MIC (mg/L)**				
		<0.02	0.04	0.1	0.2	0.4
P. acnes	38	37	95	100	--	--
P. granulosum	15	100	--	--	--	--
C. minutissimum	3	--	--	--	67	100
C. parvum	1	100	--	--	--	--

Applied topically, erythromycin suppresses *Propionibacterium acnes*, resident bacteria of sebaceous follicles thus reducing the *P. acnes* mediated hydrolysis of triglycerides to fatty acids and so decreasing fatty acid formation. This is thought to be one factor responsible for its effectiveness in reducing acne lesion counts.

Resistance and Cross-resistance

Continuous use of erythromycin for more than 8-12 weeks can increase the risk of development of erythromycin-resistant *P acnes*.

Cross-resistance can develop as a result of point mutations in the genes encoding the 23 S ribosomal RNA. As a result of these point mutations, most strains of *P acnes* that are resistant to erythromycin may be cross-resistant to

clindamycin. Studies show less common cross-resistance phenotypes against macrolides, lincosamide, and type B streptogramin.

In the clinical use of erythromycin[3], strains of *P. acnes* have been recovered which are resistant to erythromycin. These have been reported as developing in about 20% of subjects. The resistant organisms recovered were also resistant to clindamycin.

PHARMACOLOGY

Animal:

Specific studies on the animal pharmacology of ERYSOL® (erythromycin 2%, ethyl alcohol 75%, octinoxate 7.5%, avobenzone 2%) Topical Gel with sunscreens have not been conducted.

Pharmacokinetics:

Percutaneous absorption of erythromycin from topical applications is negligible. Serum levels were not detected after 2-month studies of topical 2% erythromycin use.

TOXICOLOGY

Animal Studies

Acute Toxicity:

Acute toxicity studies with ERYSOL® (erythromycin 2%, ethyl alcohol 75%, octinoxate 7.5%, avobenzone 2%) Topical Gel with sunscreens have not been conducted.

ERYTHROMYCIN

LD_{50} (mg/kg)		
ROUTE	MICE	RATS
I.V.	426	209
I.M.	394	--
P.O.	3112	9227

Subacute Toxicity:
In irritation studies in rabbits, topical application of erythromycin 2% in ethyl alcohol resulted in minimal to moderate dermal erythema and edema in both abraded and intact skin.

A chronic toxicity study with erythromycin base was performed in dogs and rats. Dogs were administered oral dosages ranging up to 100 mg/kg/day for a period up to 90 weeks. Rats were given up to 4 g/kg/day orally for a period up to 85 weeks.

A review of the clinical signs and symptoms, weight curves, clinical laboratory values and gross and microscopic findings showed no evidence of toxicity due to drug action in dogs and rats at the dose levels indicated.

Other:

Ocular irritation, sensitizing potential, phototoxicity, fertility and reproductive performance, and perinatal and postnatal studies with ERYSOL® have not been conducted.

Human Studies:

7-Day Cumulative Irritation Test:

In a study where ERYSOL® and the alcohol base gel were applied by occlusive patches to the skin of 23 volunteers for seven successive days, both test materials were graded as Class 3 irritant (possibly mild in normal use).

TERATOLOGY

ERYTHROMYCIN

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

Teratogenicity studies with ERYSOL® (erythromycin 2%, ethyl alcohol 75%, octinoxate 7.5%, avobenzone 2%) Topical Gel with sunscreens have not been conducted.

GENOTOXICITY

Genotoxicity studies have not been conducted with erythromycin base.

Erythromycin stearate was not mutagenic in a bacterial mutagenicity assay (*Salmonella typhimurium*) in the presence and absence of metabolic activation, and was not genotoxic in a chromosome aberration assay and a sister chromatid exchange assay in Chinese Hamster Ovary cells, in the presence and absence of metabolic activation. A small increase in mutation frequency of questionable biological relevance was observed in the mouse L5178Y lymphoma cell assay in the absence of metabolic activation.

CARCINOGENESIS

Carcinogenicity studies have not been conducted with erythromycin base.

Carcinogenicity studies in mice and rats with dietary administration of erythromycin stearate did not show evidence of tumorigenicity.

REFERENCES

1. Hoeffler V, Ko HL, and Pulverer G. Antimicrobial susceptibility of Propionibacterium acnes and related microbial species. Antimicrobial Agents and Chemotherapy 1976; 10: 387-394.
2. Wang WLL, Everett ED, Johnson M and Dean E. Susceptibility of Propionibacterium acnes to seventeen antibiotics. Antimicrobial Agents and Chemotherapy II. 1977; 171-173.
3. Crawford WW, Crawford IP, Stoughton RB and Cornell RC. Laboratory induction and clinical occurrence of combined clindamycin and erythromycin resistance in Corynebacterium acnes J of Invest Derm. 1979; 72:187-190.