CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 064127

Trade Name: ERYTHROMYCIN TOPICAL SOLUTION USP 2%

Generic Name: Erythromycin Topical Solution USP 2%

Sponsor : Stiefel Laboratories, Inc.

Approval Date: February 14, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 064127

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Bioequivalence Review(s)	X			
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 064127

APPROVAL LETTER

AADA 64-127

FEB 14 1997

~~FEB 10 1997~~

Stiefel Laboratories, Inc.
Attention: William A. Carr, Jr.
Route 145
Oak Hill, NY 12460

FEB 14 1997

Dear Sir:

This is in reference to your abbreviated antibiotic application dated March 22, 1994, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for Erythromycin Topical Solution USP, 2%.

Reference is also made to your amendments of December 6, 1996, and January 30, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your product to be bioequivalent and therefore therapeutically equivalent to the listed drug (T-Stat® 2% Topical Solution by Westwood Squibb Pharmaceuticals).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 064127

FINAL PRINTED LABELING

Actual Size
1-5/8" x 1-5/8" x 4-15/16"

086812

NDC 0145-2478-02

Erythromycin Topical Solution USP, 2%

For External Use.

Avoid contact with eyes.

CAUTION: Federal law prohibits dispensing without prescription.

60 mL

STIEFEL

To use enclosed applicator:
a. Remove cap and discard.
b. Firmly press applicator into bottle.
c. Seal firmly by tightening domed cap.

Instructions for use:
a. Wash skin with soap and water and pat dry.
b. Apply enough solution to thoroughly wet the affected area(s) twice a day, avoiding eyes and mouth. If medication accidentally enters eyes, rinse thoroughly with tap water and see a physician if pain or burning persists.
c. When using the "dab-o-matic" applicator top, use a dabbing motion of the tip, rather than a rolling action. If the tip becomes dry, invert bottle and depress several times until it becomes moist.
d. Close bottle tightly after each use.
e. Contains alcohol. Do not use near open flame.

STIEFEL®

Stiefel Laboratories, Inc.
Coral Gables, FL 33134

Stock No. 2478-2

86812
Rev. 1293

NDC 0145-2478-02

Erythromycin Topical Solution USP, 2%

For External Use.

Avoid contact with eyes.

CAUTION: Federal law prohibits dispensing without prescription.

60 mL

STIEFEL

Lot

Exp.

See package insert for complete product information.

Store at controlled room temperature 15°-30°C (59°-86°F)

Each mL contains 20 mg erythromycin in a vehicle consisting of 68.5% alcohol (denatured with *tert*-butyl alcohol and denatonium benzoate), propylene glycol and citric acid to adjust pH.

3 0145-2478-02 8

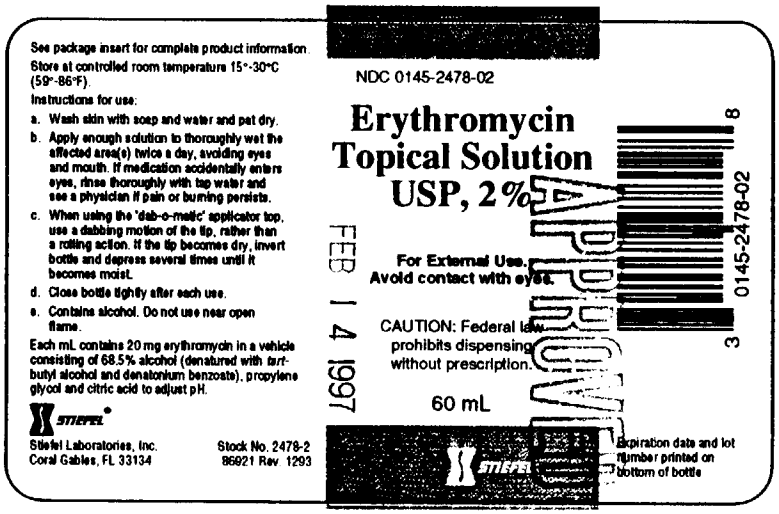
MY-1094

e

x 4"

9

4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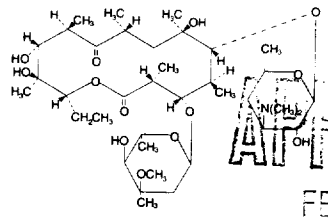
Stiefel Laboratories, Inc.
Coral Gables, FL 33134
Stock No. 2478-2
86921 Rev. 1293
NDC 0145-2478-02
Erythromycin Topical Solution USP, 2%
For External Use.
Avoid contact with eyes.
CAUTION: Federal law prohibits dispensing without prescription.
60 mL
FEB 14 1997
APPROVED
8 0145-2478-02 3
Expiration date and lot number printed on bottom of bottle

100%

Erythromycin Topical Solution USP, 2%

For Dermatologic Use Only
Not for Ophthalmic Use

DESCRIPTION:
Erythromycin Topical Solution USP, 2% contains erythromycin, USP for topical dermatologic use. Erythromycin is a macrolide antibiotic produced from a strain of *Saccaropolyspora erythraea* (formerly *Streptomyces erythreus).* It is a base and readily forms salts with acids.
Chemically, erythromycin is $C_{37}H_{67}NO_{13}$. It has the following structural formula:



The chemical name for erythromycin is (3*R**,4*S**,5*S**,6*R**,7*R**,9*R**,11*R**,12*R**,13*S**,14*R**)-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.
Erythromycin has the molecular weight of 733.94. It is a white or slightly yellow, crystalline powder. It is odorless or practically odorless. Slightly soluble in water; soluble in alcohol, in chloroform, and in ether.
Each mL of Erythromycin Topical Solution USP contains 20 mg erythromycin, USP in a vehicle of 68.5% alcohol (denatured with *tert*-butyl alcohol and denatonium benzoate), propylene glycol and citric acid to adjust pH.

CLINICAL PHARMACOLOGY:
The exact mechanism by which erythromycin reduces lesions of acne vulgaris is not fully known: however, the effect appears to be due in part to the antibacterial activity of the drug.

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

INDICATIONS AND USAGE:
Erythromycin Topical Solution USP is indicated for the topical treatment of acne vulgaris.

CONTRAINDICATIONS:
Erythromycin Topical Solution USP is contraindicated in those individuals who have shown hypersensitivity to any of its components.

WARNINGS:
Pseudomembranous colitis has been reported with nearly all antibacterial agents, including erythromycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS:

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

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

Avoid contact with eyes and all mucous membranes.

Information for Patients: Patients using Erythromycin Topical Solution USP should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with eyes, nose, mouth, and all mucous membranes.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. Patients should not use any other topical acne medication unless otherwise directed by their physician.
4. Patients should report to their physician any signs of local adverse reactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No animal studies have been performed to evaluate the carcinogenic and mutagenic potential or effects on fertility of topical erythromycin. However, long-term (2-year) oral studies in rats with erythromycin ethylsuccinate 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.

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

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed. Erythromycin has been reported to cross the placental barrier in humans, but fetal plasma levels are generally low.

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

Pediatric use: Safety and effectiveness of this product in pediatric patients have not been established.

ADVERSE REACTIONS:

The following local adverse reactions have been reported occasionally: peeling, dryness, itching, erythema, and oiliness. Irritation of the eyes and tenderness of the skin have also been reported with topical use of erythromycin. Generalized urticarial reactions, possibly related to the use of erythromycin, which required systemic steroid therapy have been reported.

DOSAGE AND ADMINISTRATION:

a. Wash skin with soap and water and pat dry.
b. Apply enough solution to thoroughly wet the affected area(s) twice a day, avoiding eyes and mouth. If medication accidentally enters eyes, rinse thoroughly with tap water and see a physician if pain or burning persists.
c. When using the "dab-o-matic" applicator top, use a dabbing motion of the tip, rather than a rolling action. If the tip becomes dry, invert bottle and depress several times until it becomes moist.
d. Close bottle tightly after each use.
e. Contains alcohol. Do not use near open flame.

HOW SUPPLIED:

Erythromycin Topical Solution USP is available in the following size:
60 mL applicator bottle- NDC 0145-2478-02.

Keep container tightly closed.
Store at controlled room temperature 15°-30°C (59°-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

STIEFEL®

Stiefel Laboratories, Inc.
Coral Gables, FL 33134

83369 Rev. 1096

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 064127

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 3

2. AADA# 64-127

3. NAME AND ADDRESS OF APPLICANT

Manufacturing Facility:
August C. Stiefel Research Institute, Inc.
Rte 145
Oak Hill, NY 12460

Corporate Offices:
Stiefel Labs
255 Alhambra Circle
Suite 1000
Coral Gables
Florida 33134

4. AF NUMBER
N/A N/A

5. SUPPLEMENT(s)

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Erythromycin

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

1.	Original submission	3/22/94
2.	Fax communication: proposed responses to deficiency letter.	9/16/94
3.	Telecon re: proposed response to deficiency letter.	9/21/94
4.	Telecons to discuss prospective response to deficiency letter.	10/24/95, 12/6/95
5.	Major amendment	5/24/96
*6.	Minor amendment	12/6/96
7.	Telephone amendment to add pH and wtl oss specs	1/30/97

FDA:

1.	Acknowledgment letter	4/20/94

2.	Bio review: biowaiver request granted.	8/22/94
3.	Labelling review #1	6/29/94
4.	Chem. Review No. 1	8/31/94
5.	Deficiency letter #1	8/31/94
6.	Labelling review #2	6/11/96
7.	Labelling review #3 - acceptable	12/17/96
8.	Sample analyses - acceptable	11/13/96
9.	EER - acceptable	11/14/96

***Amendment being reviewed**

10. PHARMACOLOGICAL CATEGORY
Antibiotic

11. HOW DISPENSED
2% topical solution:
60 mL/container

12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

13. DOSAGE FORM
Topical solution

14. POTENCY
2%

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 064127

BIOEQUIVALENCE REVIEW(S)

NDA #64-127

AUG 22 1994

Erythromycin
2% Topical Solution
Form 6, #64-127
Reviewer: J. Lee
64127W.394

Stiefel Laboratories, Inc.
Coral Gables, Florida
Submission date:
March 22, 1994

Review of a Request for Waiver

The sponsor has submitted an application for erythromycin 2% topical solution and has requested a waiver of evidence of in-vivo bioavailability under 21 CFR 320.22 (b)(3)(i).

Section 320.22 (b)(3)(i) states that the Agency may waive in-vivo requirements for a drug product if the product (i) is a solution for application to the skin, an oral solution, elixir, syrup, tincture, or similar other solubilized form.

There are also parts (b)(3)(ii) and (b)(3)(iii) which were not cited by the sponsor:

> (ii) contains an active drug ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full NDA; and
>
> (iii) contains no inactive ingredient or other change in formulation from the drug product . . . that may significantly affect absorption of the active drug ingredient or active moiety.

The drug product is used for the topical control of acne vulgaris and is Coded AT in the Therapeutic Equivalence List.

Listed below is a formulation comparison of the sponsor's product vs the brand product, T-stat® (Westwood-Squibb).

	Stiefel per ml	T-stat per ml
Erythromycin (as the base)	2.1%	2%
Alcohol	(b)4 - Confidential Business	
Propylene Glycol		
Denatonium Benzoate		
Citric acid (to adj. pH)		

Comment:

1. The sponsor has cited A/T/S Topical Solution (Hoechst-Roussel) as the reference product. The sponsor should be informed that T-stat topical solution (Westwood-Squibb) should be used as the reference listed product.

2. The test formulation contains no inactive ingredients that would significantly affect the absorption of the active moiety.

Recommendation:

1. The Division of Bioequivalence finds that the information submitted by Stiefel Labs demonstrates that erythromycin 2% topical solution falls under 21 CFR 320.22 (b)(3)(i)(ii)(iii) of Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of an in-vivo bioavailability study be granted. Stiefel's erythromycin 2% topical solution is deemed bioequivalent to T-stat® 2% topical solution manufactured by Westwood-Squibb.

2. Comment #1 should be transmitted to the company.

/S/ 6/30/94
J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED RPATNIAK
FT INITIALED RPATNAIK

/S/

Concur: /S/ Date: 8/22/94

Ramakant Mhatre, Ph.D.
Acting Director, Division of Bioequivalence

JLee/jl/05-27-94

cc: NDA #64-127 (original, duplicate), HFD-630, HFD-600 (Hare), HFD-655 (Patnaik, Lee), HFD-130 (JAllen), HFD-344 (Vish), Drug File, Division File