CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 064126

Trade Name : ERYTHROMYCIN PLEDGETS USP 2%

Generic Name: Erythromycin Pledgets USP 2%

Sponsor : Stiefel Laboratories, Inc.

Approval Date: July 3, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 064126

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 064126

APPROVAL LETTER

AADA 64-126

JUL 3 1996

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

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 Pledgets USP, 2% (jar of 60s).

Reference is also made to your amendment dated April 3, 1996.

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 Erythromycin Pledgets USP, 2% to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Erycette® Topical Solution (Pledgets), 2% of R.W. Johnson Pharmaceutical Research Institute.

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,

(b)4 - Confidential Business 7/3/96

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

CENTER FOR DRUG EVALUATION AND RESEARCH

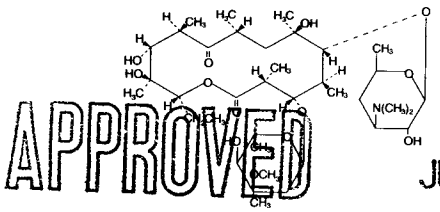
APPLICATION NUMBER 064126

FINAL PRINTED LABELING

Erythromycin Pledgets USP, 2%

For Dermatologic Use Only-
Not for Ophthalmic Use-

DESCRIPTION:
Erythromycin Pledgets USP, 2% contain 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, slightly soluble in water, soluble in alcohol, in chloroform, and in ether. It is odorless or practically odorless. It has a pH range between 8.0 and 10.5 in a methanol and water solution prepared by diluting 1 volume of a methanol solution, containing 40 mg per mL, with 19 volumes of water.
Each mL of expressible liquid contains 20 mg erythromycin in a base of alcohol (68.5%) (denatured with *tert*-butyl alcohol and denatonium benzoate), propylene glycol and citric acid to adjust pH. Each pledget is filled to contain 0.8 mL of erythromycin topical solution.

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, and lincomycin, chloramphenicol, and clindamycin.

INDICATIONS AND USAGE:
Erythromycin Pledgets are indicated for the topical treatment of acne vulgaris.

CONTRAINDICATIONS:
Erythromycin Pledgets are 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 Pledgets 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 the 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, and 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:

The erythromycin pledget should be rubbed over the affected area twice a day after skin is thoroughly washed with warm water and soap and patted dry. Acne lesions on the face, neck, shoulder, chest, and back may be treated in this manner. Additional pledgets may be used, if needed. Each pledget should be used once and discarded. Close jar tightly after each use.

HOW SUPPLIED:

Erythromycin Pledgets USP, 2% are available in a plastic jar containing 60 pledgets - NDC 0145-2478-50.

Each pledget is filled to contain 0.8 mL of erythromycin topical solution.

Keep jar tightly closed.

Store at controlled room temperature between 15° and 30°C (59° and 86°F).

CAUTION: Federal law prohibits dispensing without prescription.

STIEFEL®

Stiefel Laboratories, Inc.
Coral Gables, FL 33134

85435 Rev. 1294

086825

NDC 0145-2478-50

Erythromycin Pledgets USP, 2%

60 pledgets

APPROVED

JUL 3 1996

NDC 0145-2478-50

Erythromycin Pledgets USP, 2%

For External Use.
Avoid contact with eyes.

CAUTION: Federal law prohibits dispensing without prescription.

60 pledgets

STIEFEL®

Instructions for use:

1. Wash affected area with warm water and soap and then pat dry.
2. Use pledget to apply to affected areas twice a day. Keep pledget away from eyes, nose, mouth and other mucous membranes. If medication accidentally enters eyes, rinse thoroughly with tap water. Additional pledgets may be used, if needed. Each pledget should be used once and discarded.
3. Close jar tightly after each use.

Stiefel Laboratories, Inc.
Coral Gables, FL 33134

Stock No.
2478-5

86825
Rev. 1293

2

[redacted]

PMS 282

OVERALL VARNISH

ACTUAL SIZE
'8" X 2-3/8" X 2-13/16"

NDC 0145-2478-50

Erythromycin Pledgets USP, 2%

For External Use.
Avoid contact with eyes.

CAUTION: Federal law prohibits dispensing without prescription.

60 pledgets

STIEFEL®

3 0145-2478-50 9

Usual Dosage: See package insert for complete product information.

Keep jar tightly closed. Keep out of the reach of children.

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

Each mL of expressible liquid contains 20 mg of erythromycin in a base of alcohol (68.5%) (denatured with *tert*-butyl alcohol and denatonium benzoate), propylene glycol and citric acid to adjust pH. Each pledget is filled to contain 0.8 mL of Erythromycin Topical Solution.

086825

Erythromycin Pads Label – 60's

ACTUAL SIZE

6" x 1.5"

PMS 282 Black

Usual Dosage: See package insert for complete product information.

Keep jar tightly closed. Keep out of the reach of children. Store at controlled room temperature, 15°-30°C (59°-86°F).

Instructions for use:

1. Wash affected area with warm water and soap and then pat dry.
2. Use pledget to apply to affected areas twice a day. Keep pledget away from eyes, nose, mouth and other mucous membranes. If medication accidentally enters eyes, rinse thoroughly with tap water. Additional pledgets may be used, if needed. Each pledget should be used once and discarded.
3. Close jar tightly after each use.

NDC 0145-2478-50

Erythromycin Pledgets USP, 2%

For External Use.

Avoid contact with eyes.

CAUTION: Federal law prohibits dispensing without prescription.

60 pledgets

STIEFEL®

Each mL of expressible liquid contains 20 mg erythromycin in a base of alcohol (68.5%) (denatured with *tert*-butyl alcohol and denatonium benzoate), propylene glycol and citric acid to adjust pH. Each pledget is filled to contain 0.8 mL of Erythromycin Topical Solution.

Expiration Date and Lot Number on bottom of jar.

APPROVED

JUL 3 1996

Stiefel Laboratories, Inc.
Coral Gables, FL 33134

Stock No. 2478-5
86934 Rev. 1293

100%

Erythromycin Pads Label – 60's

ACTUAL SIZE

6" x 1.5"

PMS 282 Black

Usual Dosage: See package insert for complete product information.

Keep jar tightly closed. Keep out of the reach of children. Store at controlled room temperature, 15°-30°C (59°-86°F).

Instructions for use:

1. Wash affected area with warm water and soap and then pat dry.
2. Use pledget to apply to affected areas twice a day. Keep pledget away from eyes, nose, mouth and other mucous membranes. If medication accidentally enters eyes, rinse thoroughly with tap water. Additional pledgets may be used, if needed. Each pledget should be used once and discarded.
3. Close jar tightly after each use.

NDC 0145-2478-50

Erythromycin Pledgets USP, 2%

For External Use.
Avoid contact with eyes.

CAUTION: Federal law prohibits dispensing without prescription.

60 pledgets

STIEFEL® JUL 3 1996

Each mL of expressible liquid contains 20 mg erythromycin in a base of alcohol (68.5%) (denatured with *tert*-butyl alcohol and denatonium benzoate), propylene glycol and citric acid to adjust pH. Each pledget is filled to contain 0.8 mL of Erythromycin Topical Solution.

Expiration Date and Lot Number printed on bottom of jar.

APPROVED

Stiefel Laboratories, Inc.
Coral Gables, FL 33134

Stock No. 2478-5
86934 Rev. 1293

100%

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 064126

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 4

2. AADA# 64-126

3. NAME AND ADDRESS OF APPLICANT

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

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

4. AF NUMBER
N/A

5. SUPPLEMENT(s)
N/A

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.	12/6/94
	3.	Telecon re: proposed response to deficiency letter.	12/16/94
	4.	Major amendment	1/23/95
	5.	Telecon to discuss prospective response to deficiency letter.	10/24/95
	6.	Major amendment	12/5/95
	7.	Fax re: turbidimetric assay	11/27/95
	8.	Telecon re: fax	12/6/95
*	9.	Minor amendment	4/3/96

***Subject of current review**

FDA:

1.	Acknowledgement letter	4/20/94
2.	Bio review: biowaiver request granted.	11/29/94
3.	Labeling review	10/25/94
4.	Chem. Review No. 1	11/21/94
5.	Deficiency letter #1	11/29/94
6.	Chem. Rev. #2	5/25/95
7.	Deficiency letter #2	7/25/95
8.	Labeling Rev. #2	6/15/95
9.	Telecon re : plate/turb assays	12/6/95
10.	Telecon noting that amendment should have been major rather than minor	12/14/95
11.	EER update request	12/21/95
12.	Labeling Rev. #3: acceptable in draft	1/30/96
13.	Chem. Rev. #3	2/29/96
14.	Deficiency letter #3	3/14/96
15.	Acceptable EER	3/14/96

10. PHARMACOLOGICAL CATEGORY
Antibiotic

11. HOW DISPENSED
Pledgets saturated with 2% erythromycin solution

12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

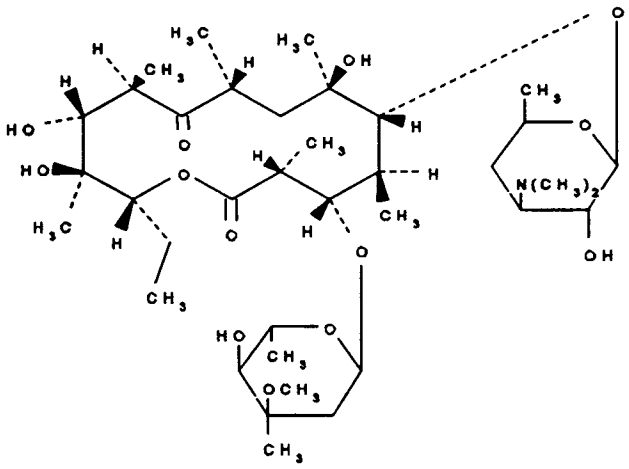
13. DOSAGE FORM
Topical solution

14. POTENCY
2%

15. CHEMICAL NAME AND STRUCTURE

Erythromycin USP

$C_{37}H_{67}NO_{13}$; M.W. = 733.94



(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)-ß-*D*-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione. CAS [114-07-8]

16. RECORDS AND REPORTS

N/A

17. COMMENTS

A. **Synopsis of First Three Review Cycles:**

The exhibit batch prepared in support of the original application was unacceptable for several reasons detailed in the earlier review, although the firm continued attempts to justify the unacceptable stability results presented in the original submission through two cycles. For the response to our deficiency letter of 7/25/95, the firm prepared a new exhibit batch and generated requisite supporting data on this batch.

The firm attributed the poor stability of the earlier batch to low pH and reduced the amount of citric acid used to adjust the pH from 0.04% to 0.005%, an eight-fold reduction. Aside from the amount of citric acid used to adjust the pH, the remaining components and composition are identical, and the manufacturing process has not changed. The new exhibit batch (Manufacturing lot #A0724) was [redacted] and this lot was shipped in its entirety to the contract packager (became package lot #A0917).

The firm now assays for the important process-related substances/degradants but no specifications have been set. The firm commits to monitoring for these substances and to setting specifications at some point when sufficient experience and data have been collected.

B. Fourth Cycle - Minor Amendment Response:

Following the major amendment which was reviewed the second cycle, there remained but minor deficiencies. These are listed below along a summary of the firm's response:

Deficiency #1

1. Although you indicate that the stability of this drug product is likely related to pH, and the pH of the exhibit batch is controlled within a very narrow range (Batch A0724, page 31 of the December 5, 1995 submission), the instruction for this procedure as presented for the proposed production batch log on page 21 is much less specific. Please discuss.

Response:

The firm agreed with this point and revised that step in the manufacturing instructions to include appropriate in-process-testing for pH. A pH Test and Specification was also added. the revised batch record and tests and Specification was provided (Attachment 1).

Acceptable

Deficiency #2

2. The stability protocol and stability data reporting sheets are generally adequate for the 25°C±2°C/60% R.H. studies but details regarding the additional studies are not included in either case:

   a. Please incorporate details of these studies in the protocol and stability data reporting forms and present the study results/protocols separately for each study.

   b. Although you indicate in the protocol for the 25°C study the stations and tests to be performed, several appear to be missing, *e.g.* "Assay and Minimum Volume" was not found for any of the stations.

Response:

The requested additional details were provided and the section describing "Storage Conditions" was correspondingly expanded as were the respective protocols. The Stability Reports were also revised to include all stations and tests. These revisions are found in Attachment 2.

Acceptable

Deficiency #3:

3. We acknowledge your commitment to establish Specifications for related substances in the antibiotic drug substance and drug product based upon your methods development work with (b)4 This commitment should also include Specifications for degradants in the stability program. Also, please provide any additional available results to date.

Response:

The firm provided a commitment to monitor and establish specifications for (b)4 - Confidential Business and for any other degradants that may be identified during the ongoing methods development. The results will be communicated to FDA on an annual or more frequent basis via supplementation of the approved application.

Additional (b)4 results to date were provided in Attachment 2.

Acceptable

C. **Process Summary:**

(b)3 - Other Statutes

The product for marketing under this application is as individually wrapped pledgets; these are then placed into cartons of 30, 48, or 60. Alternatively, the individually wrapped pledgets may be placed, three at a time, into an envelope, and then 20 of these envelopes are packaged in a carton thus offering 60 pledgets in this configuration.

D. **EER, Bio, Labeling, Sample Analysis, Other:**

An **acceptable EER** was received 3/15/96.

The firm has requested a **biowaiver, approved 11/29/94.**

A labeling review **Approval Summary** was published **4/16/96.**

Sample Analysis pending

18. CONCLUSIONS AND RECOMMENDATIONS
This application is approvable pending receipt of **acceptable sample analyses.**

19. REVIEWER: R. C. Adams
DATE COMPLETED: 4/26/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 064126

BIOEQUIVALENCE REVIEW(S)

NOV 2 9 1994

OW

Erythromycin Pledgets USP
2%
AADA #64-126
Reviewer: Moo Park
Filename: 64126W.394

Stiefel Laboratories
Oak Hill, NY
Submission Date:
March 22, 1994

Review of a Waiver Request

I. Objective

Review of Stiefel's request for a waiver of in vivo bioequivalence study requirements for its Erythromycin Pledgets USP, 2%. The reference product is Ortho-McNeil Pharmaceutical's Erycette[R] Pledgets, 2%.

Erythromycin Pledgets are suitable absorbent pads impregnated with Erythromycin Topical Solution.

II. Comments

1. The test and reference products contain 2% erythromycin in almost identical solvent systems containing alcohol, propylene glycol and citric acid. The formulation of the test product (2% solution part only) is shown below:

Formulation of Stiefel's Test Product

Ingredient	Amount, % W/W
Erythromycin, USP	2.4
S.D. Alcohol 40 B	(b)4 -
Propylene Glycol	onfidenti
Citric Acid	Business

2. The firm did not include the component used as the absorbent pad as a part of the formulation. This component should be handled as an inactive ingredient.

3. The name of the test product causes a confusion. The USP maintains separate monographs for the pledgets and solution. However, Stiefel did not use the USP name 'Erythromycin Pledgets'.

4. Review Chemist should be alerted to Comments #2 and 3.

5. A waiver is granted.

III. Recommendation

The Division of Bioequivalence agrees that the information submitted by Stiefel Pharmaceutical demonstrate that Erythromycin Pledgets, 2%, falls under 21 CFR Section 320.22 (b) of the Bioavailability/ Bioequivalence Regulations. The waiver of in vivo bioequivalence study for Stiefel's Erythromycin Pledgets, 2%, is granted. Stiefel's Erythromycin Pledgets, 2%, is deemed bioequivalent to Ortho-McNeil Pharmaceutical's Erycette[R] Pledgets, 2%.

The firm should be informed of the recommendation.

/S/

Moo Park, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE

/S/ 11/29/94

Ramakant M. Mhatre, Ph.D.
Branch Chief, Review Branch III
Division of Bioequivalence

cc: AADA #64-126 (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-658 (Mhatre, Park), Drug File, Division File