AADA 64-184

SEP 30 1997

Altana Inc.
Attention: Virginia Carman
60 Baylis Road
Melville, NY 11747

Dear Madam:

This is in reference to your abbreviated antibiotic application dated August 20, 1996, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for Erythromycin Topical Gel USP, 2%.

Reference is also made to your amendments dated March 21, August 19, and September 18, 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 Erythromycin Topical Gel USP, 2%, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Erygel® Topical Gel 2%, of Allergan-Herbert) .

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.

Post-marketing 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 changes 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 Drug 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

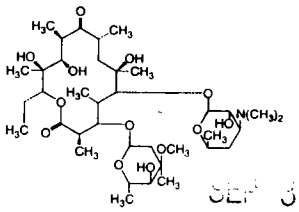
fougera®

Erythromycin Topical Gel USP, 2%

For Dermatologic Use Only **Not for Ophthalmic Use**

DESCRIPTION:

Erythromycin Topical Gel contains erythromycin 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: (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. It has the following structural formula:



SEP 30 1997

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

Erythromycin is a white or slightly yellow crystalline powder that is very soluble in water, freely soluble in alcohols, acetone, chloroform, acetonitrile, ethyl acetate, and moderately soluble in ether, ethylene dichloride and amyl acetate.

Each gram of Erythromycin Topical Gel 2% contains: Active Ingredient: erythromycin USP, 2% (20 mg/g). Inactive Ingredients: alcohol USP, 92% and hydroxypropyl cellulose NF.

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 Gel is indicated for the topical treatment of acne vulgaris.

CONTRAINDICATIONS:

Erythromycin Topical Gel 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 ther-

apy 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 Gel 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, 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 years) 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% of 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 Mothers: 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 most common adverse reaction reported with Erythromycin Topical Gel was burning.

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:

Apply sparingly as a thin film to affected area(s) once or twice a day after the skin is thoroughly cleansed and patted dry. If there has been no improvement after 6 to 8 weeks, or if the condition becomes worse, treatment should be discontinued, and the physician should be reconsulted. Spread the medication lightly rather than rubbing it in. The hands should be washed after application. There are no data directly comparing the safety and efficacy of b.i.d. versus q.d. dosing.

HOW SUPPLIED:

Erythromycin Topical Gel USP, 2% is supplied as follows:

30 gram tubes - NDC 0168-0216-30 60 gram tubes - NDC 0168-0216-60

NOTE: FLAMMABLE. Keep away from heat and flame.

Store and dispense in original container.

Keep tube tightly closed.

Store between 15° and 25°C (59° and 77°F).

Caution: Federal law prohibits dispensing without prescription.

E. FOUGERA & CO.
a division of Altana Inc.
MELVILLE, NY 11747

I2216
#153
R2/97

℞

IX4254
R2/97
#153

NDC 0168-0216-60

fougera®

ERYTHROMYCIN TOPICAL GEL USP, 2%

FOR DERMATOLOGIC USE ONLY.
NOT FOR OPHTHALMIC USE.

60 grams

CAUTION: Federal law prohibits dispensing without prescription

ERYTHROMYCIN TOPICAL GEL USP, 2%

USUAL DOSAGE: See package insert for complete prescribing information.

Active Ingredient: erythromycin, USP 2% (20 mg/g).
Inactive Ingredients: alcohol USP, 92% and hydroxypropyl cellulose NF.

E. FOUGERA & CO.
a division of Altana Inc.
MELVILLE, NEW YORK 11747

NOTE: FLAMMABLE. Keep away from heat and flame.

Keep tube tightly closed.

Store between
15° and 25°C (59° and 77°F).

Keep this and all drugs out of the reach of children.

NDC 0168-0216-60

fougera®

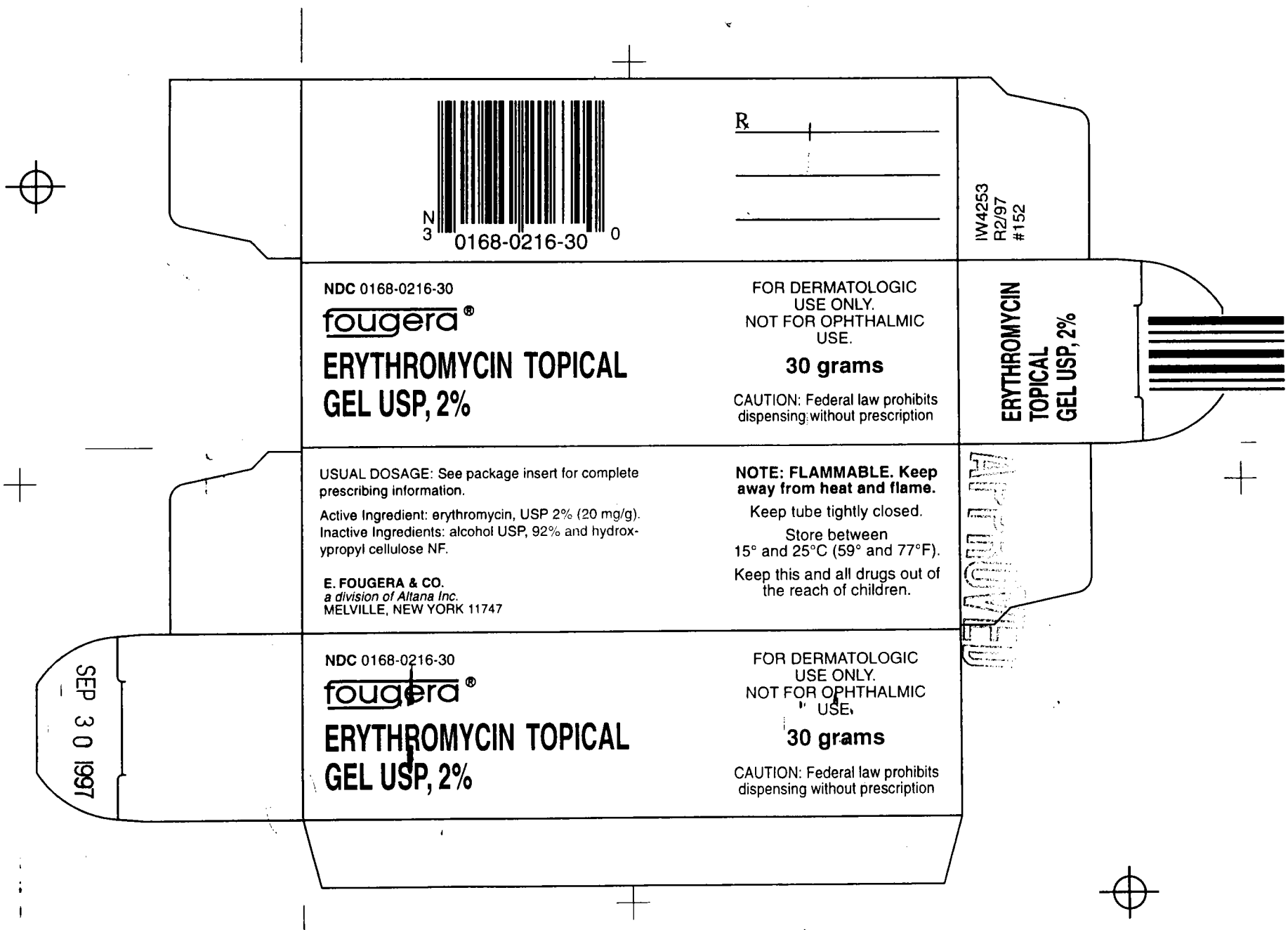
ERYTHROMYCIN TOPICAL GEL USP, 2%

FOR DERMATOLOGIC USE ONLY.
NOT FOR OPHTHALMIC USE.

60 grams

CAUTION: Federal law prohibits dispensing without prescription

PS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3 0168-0216-30 0
℞
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R2/97
#152
NDC 0168-0216-30
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MELVILLE, NEW YORK 11747
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SEP 3 0 1997
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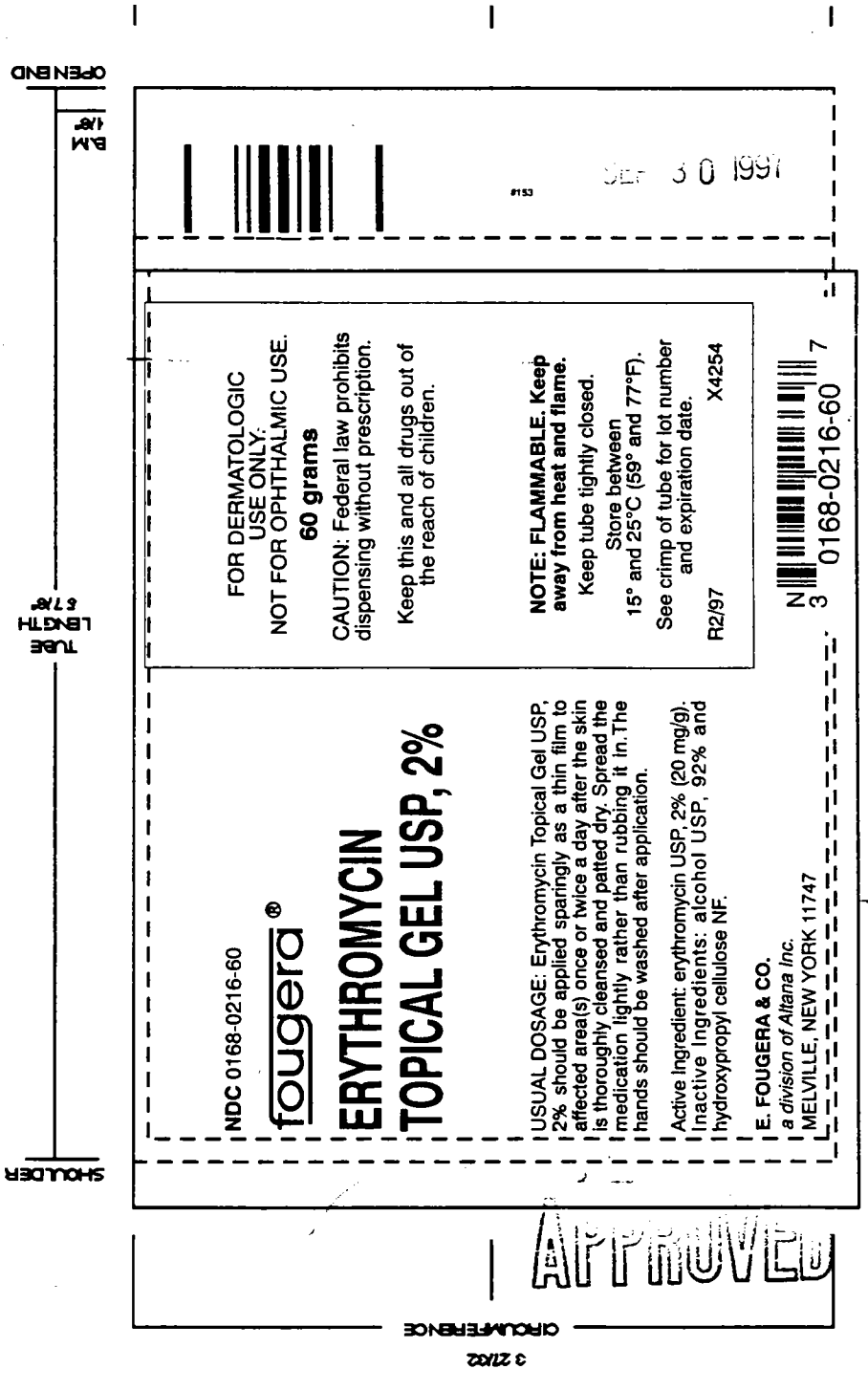
AADA 64-184

Erythromycin Topical Gel USP, 2%

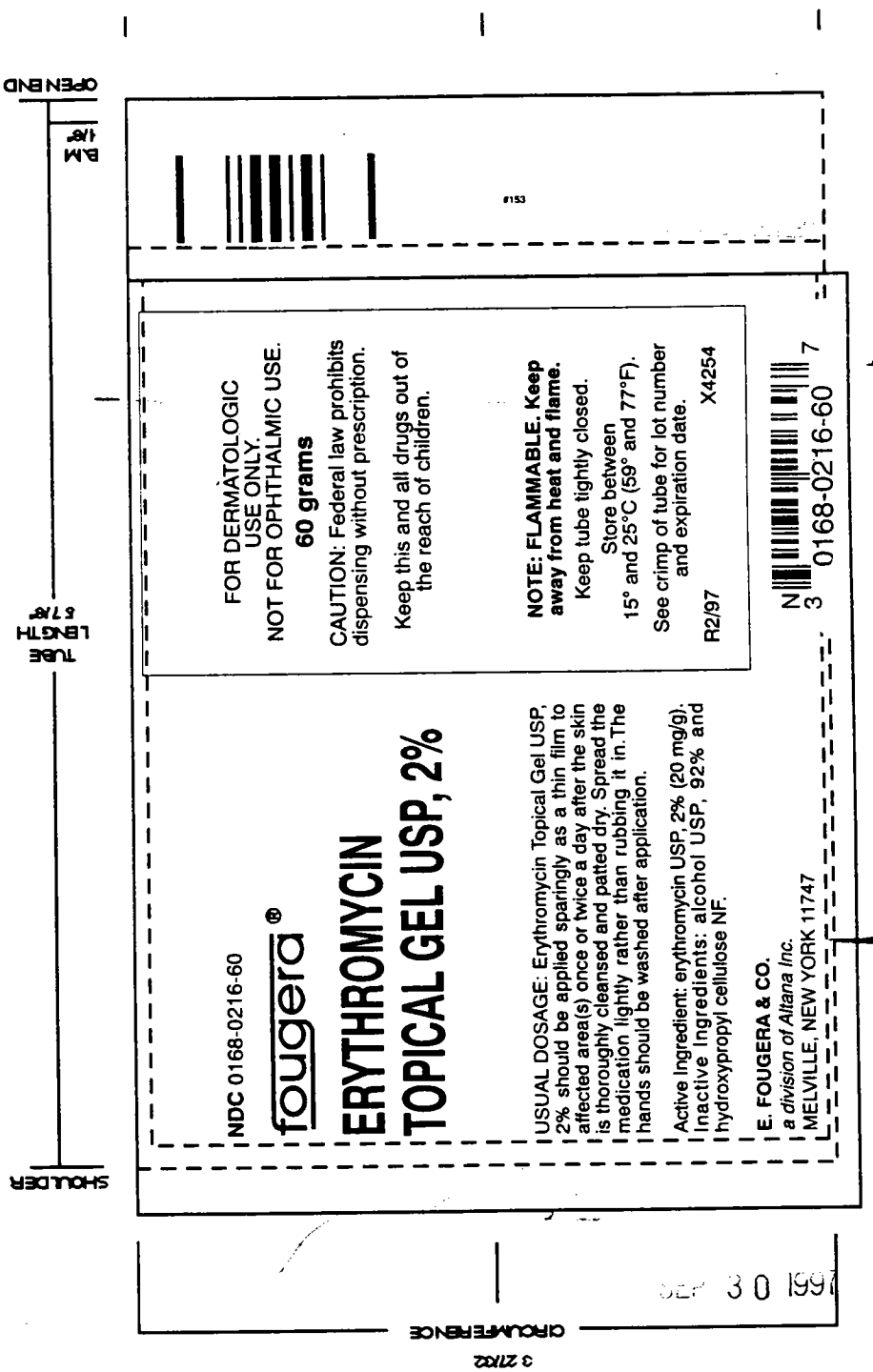
Container Label



AADA 64-184

Erythromycin Topical Gel USP, 2%

Container Label



1. CHEMIST'S REVIEW NO. #3

2. AADA #64-184

3. NAME AND ADDRESS OF APPLICANT

Altana Inc.
Attention: Steven W. Brown, R. Ph.
60 Baylis Road
Melville, NY 11747

Telephone: 516-454-7677
Fax: 516-454-6389

4. LEGAL BASIS FOR SUBMISSION
21 CFR §452.510e

Reference drug: Erygel® (Erythromycin Topical Gel USP) 2% manufactured by Allergan Herbert. Signed certification is provided (page 5) stating that all listed patents in the U.S. have expired.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Erythromycin Topical Gel USP, 2%

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

9. AMENDMENTS AND OTHER DATES:

Original Submission: 8/20/96
Acknowledgment: 11/4/96
Amendment 3/21/97 to N/A letter (MAJOR) 12/31/96
Amendment 8/19/97 to N/A letter (FACSIMILE) 7/22/97
Telephone Amdt.

10. PHARMACOLOGICAL CATEGORY
Antibacterial

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

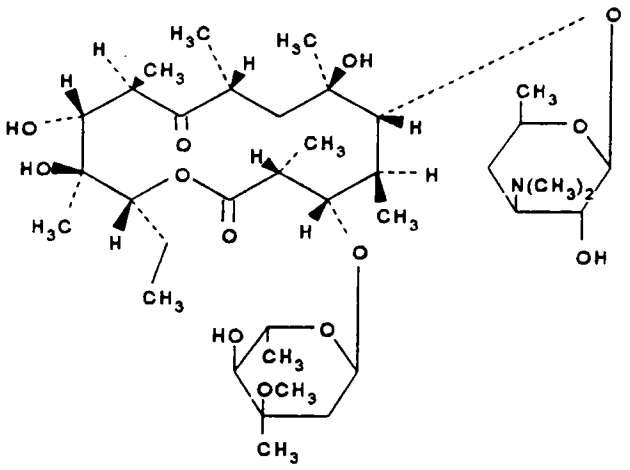
13. DOSAGE FORM
Topical gel

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

In Amendment 8/19/97 Firm answers N/A letter 7/22/97 in order:

Q2. Data upon which your proposed release and stability limits for related substances and degradation products are based. We suggest you supply data obtained by using the to test your product and those similar products already in the marketplace.

A2. In Attachment 3 Firm presents a copy of the of products already in the marketplace: products from Allergan, Glaxo and Glades and total impurities). Based on the various data, Firm has tightened the stability specifications for and total impurities .

Q3. Have you tried to identify some of the related substances and degradation products observed from the submitted What is the impurity with a

A3. Firm has tried to identify the related substances, impurities and degradation products by comparing and of their gel with those of marketed products, and by reference to information in publications. Results are presented in Attachment 4. The impurity with a is postulated to be or, possibly,

Comment:

Other manufacturers of erythromycin topical dosage forms are using high performance liquid chromatography for controlling the related substances, impurities and degradants in the bulk drug substance and their dosage form products. The HPLC analytical methodology is well known and has been the subject of numerous publications (e.g. "Liquid Chromatography of Erythromycin A and Related Substances on Poly(styrene-divinylbenzene", *Chromatographia* Vol. 32, No. 3-4, August 1991, pp 162-167, 1991, Hoogmartens, *et.al.*; "High Performance Liquid Chromatographic Analysis of Erythromycin", *J. Liq. Chrom.*, Vol.19, No. 14, pp.2329-2348 (M.M. Nasr and T.J. Tschappier); *European Pharmacopeia*, 1995 pp 179/2 - 179/4; *Pharmacopeial Forum*, Vol. 21, No.2, pp 315-317; *Pharmacopeial Forum,* Vol. 22, No. 6, pp 3132-3134). Please commit to adopting a HPLC method for identifying and controlling the quantities of erythromycin related substances, impurities and degradants within one year following the approval of this application.

Response: Firm commits to do so.

18. CONCLUSIONS AND RECOMMENDATIONS

Approval recommended.

19. REVIEWER: DATE COMPLETED:

Maria C. Shih 9/3/97

AADA 64-184

JAN 23 1997

Altana Inc.
Attention: Steven W. Brown, R.Ph.
60 Baylis Road
Melville NY 11747

Dear Sir:

Reference is made to your abbreviated antibiotic application submitted pursuant to Section 507 of the Federal Food, Drug and Cosmetic Act for Erythromycin Topical Gel USP, 2%.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JAN 17 1997

Erythromycin
2% Topical Gel USP
ANDA **#64-184**
Reviewer: Z.Z. Wahba
File #64184w.896

Altana Inc.
Melville, NY
Submission Date:
August 21, 1996

REVIEW OF WAIVER REQUEST OF BIOEQUIVALENCE STUDY REQUIREMENT FOR A TOPICAL GEL

BACKGROUND

The firm has requested a waiver of the in vivo bioavailability requirement for its test product Erythromycin Topical Gel USP 2% based upon 21 CFR 320.22 since the active ingredient, route of administration and dosage form is the same as the reference listed product, Allergan-Herbert's Erygel® Topical Gel 2% (NDA #50-617).

FORMULATION

The comparative formulations of the test and reference products are as follows:

INGREDIENT	TEST Amount %	REFERENCE Amount %
Erythromycin USP	[a]2.2% (20 mg/g)	2.0% (20 mg/g)
Hydrxypropyl cellulose		
Alcohol USP		
Alcohol USP		
Total	100%	100%

[a]The test product contains a 10% overage of the labeled amount of erythromycin USP.

[b]The labeling of the reference listed drug (Erygel®) states that the product contains "alcohol 92%". This is presumed to represent 92% v/v pure ethanol at 15.56 °C, per USP and Federal regulations. The proposed drug contains 95.05% w/w alcohol USP. Alcohol USP contains between 92.3-93.8% w/w ethanol at 15.56 °C (or any temperature). Therefore, the proposed drug product contains 89.16% w/w ethanol, which equates to 92% v/v. (The information was reported in vol. B1.1, page #10 and 14-15)

COMMENTS

1. The test drug product contains an active ingredient in the same concentration and dosage form as the currently approved reference product, Allergan-Herbert's Erygel® (NDA #50-617).

2. Using Hydroxypropyl Cellulose and Alcohol at the concentrations that are provided in statement of chemical composition fall in the acceptable range of the inactive ingredient guide.

4. The drug product is classified "AT" in the list of the "Approved Drug Products with Therapeutic Equivalence Evaluations".

5. The waiver of in vivo bioequivalence study requirements should be granted based on 21 CFR section 320.22(b)(3) of the Bioavailability/Bioequivalence Regulations.

RECOMMENDATION

The Division of Bioequivalence agrees that the information submitted by Altana Inc. for its drug product, Erythromycin Topical Gel USP 2%, falls under 21 CFR section 320.22(b)(3) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the drug is granted. From the Bioequivalence point of view, the Division of Bioequivalence deems Erythromycin Topical Gel USP 2%, manufactured by Altana Inc. to be bioequivalent to the reference listed drug Allergan-Herbert's Erygel® Topical Gel 2%.

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE 1/14/97

Concur: _____ Date: 1/17/97
Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

cc: ANDA# 64-184, original, HFD-604 (Hare), HFD-658 (Mhatre, Wahba), Drug File
ZZWahba/121396/011397/wp64184w.896