

**CENTER FOR DRUG
EVALUATION AND RESEARCH**

Approval Package for:

APPLICATION NUMBER:

65-009

Trade Name: E Glades

Generic Name: Erythromycin Topical Gel, USP, 2%

Sponsor: Glades Pharmaceuticals, Inc.

Approval Date: March 18, 2002

**CENTER FOR DRUG EVALUATION
AND RESEARCH**

**APPLICATION NUMBER:
65-009**

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**CENTER FOR DRUG
EVALUATION AND RESEARCH**

APPLICATION NUMBER:

65-009

APPROVAL LETTER

MAR 18 2002

Glades Pharmaceuticals, Inc.
Attention: William A. Carr, Jr.
Route 145
Oak Hill, NY 12460

Dear Sir: .

This is in reference to your abbreviated new drug application dated February 2, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for E-Glades (Erythromycin Topical Gel, USP), 2%. We note that this product is subject to the exception provisions of Section 125(d)(2) of Title I of the Food and Drug Administration Modernization Act of 1997.

Reference is also made to your amendment dated January 9, 2002.

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 E-Glades (Erythromycin Topical Gel, USP), 2%, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Erygel[®] of Allergan Herbert, Div. of Allergan, Inc.).

Under Section 506A of the Act, 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 and 314.98. 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 that 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-40). 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-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

^

JSI

' Gary Buehler 3/18/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

65-009

Final Printed Labeling

Actual size
1-13/16" x 1-1/8" x 4-15/16"

099480



E•Glades
(Erythromycin
Topical Gel, USP) 2%

84660
Rev. 0199

NDC 59366-2767-2

E•Glades
(Erythromycin
Topical Gel, USP) 2%

**FOR DERMATOLOGIC
USE ONLY-
NOT FOR OPHTHALMIC
USE.**

Rx only

50 g



GLADES

Each gram of Erythromycin Topical Gel, USP contains 20 mg of erythromycin with SD 40-2 alcohol 84% v/v, propylene glycol, and hydroxypropyl cellulose.

Usual Dosage:
Apply sparingly as a thin film to affected area(s) once or twice a day after the skin is thoroughly cleansed and patted dry. Spread the medication lightly rather than rubbing it in. The hands should be washed after application. See package insert for full prescribing information.

NDC 59366-2767-2

E•Glades
(Erythromycin
Topical Gel, USP) 2%

**FOR DERMATOLOGIC
USE ONLY-
NOT FOR OPHTHALMIC
USE.**

Rx only

MAR 18 2002

APPROVED

50 g



GLADES



3 59366 27672 8



084660

PMS 206

PMS 354

Black

MAR60

65-009

3/18/02

NOTE:
FLAMMABLE.
Keep away from heat and flame.
Keep bottle tightly closed. Store between 15° and 25°C (59° and 77°F). Keep this and all drugs out of the reach of children.

Manufactured by
Stiefel Laboratories, Inc.
Coral Gables, FL 33134
for
Glades Pharmaceuticals, Inc.
Coral Gables, FL 33134

Questions? Please call
1-888-4GLADES
1-888-445-2337

Stock No. 2767-2

MAR60

Actual Size
1-1/8" x 2-3/4"

front label

back label

NDC 59366-2767-2

E•Glades
(Erythromycin
Topical Gel, USP) 2%

FOR DERMATOLOGIC
USE ONLY.
NOT FOR OPHTHALMIC
USE.

Rx only

MAR 18 2002

APPROVED

50 g

85724



GLADES

Each gram of Erythromycin Topical Gel, USP contains 20 mg of erythromycin with SD 40-2 alcohol 84% v/v, propylene glycol, and hydroxypropyl cellulose.

Usual Dosage: Apply sparingly as a thin film to affected area(s) once or twice a day after the skin is thoroughly cleansed and patted dry. Spread the medication lightly rather than rubbing it in. The hands should be washed after application.

See package insert for full prescribing information.

NOTE: FLAMMABLE. Keep away from heat and flame.

Keep bottle tightly closed. Store between 15° and 25°C (59° and 77°F). Keep this and all drugs out of the reach of children.

Manufactured by
Stiefel Laboratories, Inc.
Coral Gables, FL 33134
for Glades Pharmaceuticals, Inc.
Coral Gables, FL 33134

Questions? Please call
1-888-4GLADES
1-888-445-2337
Stock No. 2767-2
86375 Rev. 0199



PMS 354



Black



PMS 206



Black

PRECAUTIONS:

General: For topical use only; not for ophthalmic use. Concomitant topical acne therapy should be used with caution since 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 E+Glades should receive the following information 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-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% 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 in pediatric patients have not been established.

ADVERSE REACTIONS: In controlled clinical trials the incidence of burning associated with Erythromycin Topical Gel was approximately 25%. The following additional 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. A generalized urticarial reaction, possibly related to the use of erythromycin, which required systemic steroid therapy has been reported.

DOSAGE AND ADMINISTRATION: Erythromycin Topical Gel should be applied sparingly as a thin film to affected area(s) once or twice a day after the skin is thoroughly cleansed and patted dry. The hands should be washed after application. 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. There are no data directly comparing the safety and efficacy of b.i.d. versus q.d. dosing.

HOW SUPPLIED: E+Glades (Erythromycin Topical Gel, USP) 2% is supplied in a plastic bottle containing 50 g (NDC 59366-2767-2).

Note: FLAMMABLE. Keep away from heat and flame. Keep bottle tightly closed. Store and dispense in original container. Keep this and all drugs out of the reach of children. Store between 15° and 25°C (59° and 77°F).

Manufactured by Stiefel Laboratories, Inc., Coral Gables, FL 33134

for Glades Pharmaceuticals, Inc., Coral Gables, FL 33134

Questions? Please call 1-888-4GLADES

1-888-445-2337

86784

Rev. 0101



GLADES

E•Glades

(Erythromycin Topical Gel, USP) 2%

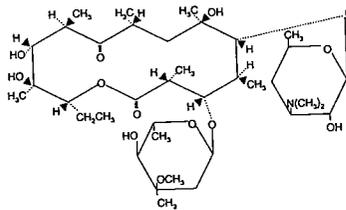
For Dermatologic Use Only-
Not for Ophthalmic Use.

MAR 18 2002
APPROVED

Rx only

DESCRIPTION: E•Glades (Erythromycin Topical Gel, USP) 2% contains erythromycin ((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-hexa-methyl-6-[[3,4,6-trideoxy-3-(dimethylamino)- β -D-xylo-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione), for topical dermatological 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 $C_{27}H_{47}NO_{13}$. It has the following structural formula:



Erythromycin has the molecular weight of 733.94. It is a white or slightly yellow, odorless or practically odorless, bitter crystalline powder. Erythromycin is very soluble in very polar organic solvents such as alcohols, acetone, chloroform, acetonitrile and ethyl acetate. It is moderately soluble in less polar solvents such as ether, dichloroethylene and amyl acetate. It is slightly soluble in nonpolar solvents such as hexane. It is very poorly soluble in water.

Each gram of Erythromycin Topical Gel, USP contains 20 mg of erythromycin with SD 40-2 alcohol 84% v/v, propylene glycol, and hydroxypropyl cellulose.

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 50S 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: E•Glades is indicated for the topical treatment of acne vulgaris.

CONTRAINDICATIONS: E•Glades 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.



**CENTER FOR DRUG
EVALUATION AND RESEARCH**

APPLICATION NUMBER:

65-009

CHEMISTRY REVIEW(S)

DW

1. CHEMIST'S REVIEW NO. #1

2. ANDA #65-009

3. NAME AND ADDRESS OF APPLICANT

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

4. LEGAL BASIS FOR SUBMISSION

21 CFR §452.510e

Reference drug: Erygel® (Erythromycin Topical Gel USP) 2%
manufactured by Allergan Herbert.

No statement regarding expired patent or marketing
exclusivity is provided.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

E◇Glades (Proposed)

7. NONPROPRIETARY NAME

Erythromycin Topical Gel USP, 2%

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Original submission: 2/2/98
Amendment 3/25/98 to "Refuse to File" letter 3/11/98
FDA acknowledgment: 4/1/98

10. PHARMACOLOGICAL CATEGORY

Antibacterial

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

ANDA's # _____ and _____
See DMF list under #37

13. DOSAGE FORM

Topical gel

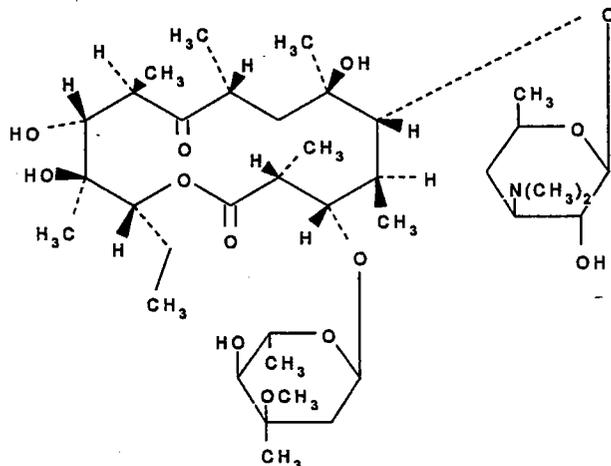
14. POTENCY

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

16. RECORDS AND REPORTS

N/A

17. COMMENTS

[Empty box for comments]

[]

Status Summary for #65-009:

Labeling: Under review
EER: Acceptable 6/15/98
Sample: Not requested (USP drug)
Bio: Under review

Attachment:

- A. Stability protocol for Erythromycin Base (from Y-008).
- B. Impurity Profile of Erythromycin Base /
- C. Evaluation of assay for Erythromycin Base as a Stability Indicating Assay /

18. CONCLUSIONS AND RECOMMENDATIONS

Not approvable (MAJOR)

19. REVIEWER:

Maria C. Shih

DATE COMPLETED:

8/31/98

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commercial

information

1. CHEMIST'S REVIEW NO. #2 (revised)

2. ANDA #65-009

3. NAME AND ADDRESS OF APPLICANT

Glades Pharmaceuticals, Inc.
(Stiefel Laboratories, Inc.)
Attention: William A. Carr, Jr.
Agent for Glades Pharmaceuticals
Route 145
Oak Hill, NY 12460

4. LEGAL BASIS FOR SUBMISSION

21 CFR §452.510e

Reference drug: Erygel® (Erythromycin Topical Gel USP) 2%
manufactured by Allergan Herbert.

No statement regarding expired patent or marketing
exclusivity is provided.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

E◇Glades

7. NONPROPRIETARY NAME

Erythromycin Topical Gel USP, 2%

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Original submission: 2/2/98

Amendment 3/25/98 to "Refuse to File" letter 3/11/98

FDA acknowledgment: 4/1/98

Amendment 4/28/99 to labeling letter 12/1/98

Amendment 7/9/99 to N/A (MAJOR) letter 9/22/98

10. PHARMACOLOGICAL CATEGORY

Antibacterial

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

See DMF list under #37

13. DOSAGE FORM

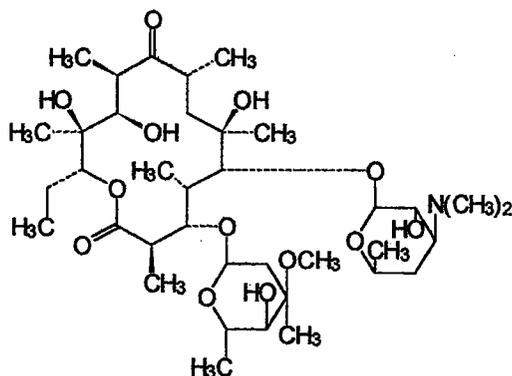
Topical gel

14. POTENCY

2%

15. CHEMICAL NAME AND STRUCTURE

Erythromycin. (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-xyllo-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione. C₃₇H₆₇NO₁₃. 733.94. 114-07-8. Antibacterial.



16. RECORDS AND REPORTS

N/A

17. COMMENTS

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commercial

information

APPEARS THIS WAY
ON ORIGINAL

Status Summary for #65-009:

DMF: _____
Labeling: Acceptable 10/2099
EER: Acceptable 10/22/99
Sample: Not requested (USP drug)
Bio: Acceptable (10/14/98)

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable (MAJOR AMENDMENT)

19. REVIEWER: Maria C. Shih DATE COMPLETED: 10/13/99 (Revised 10/25/99)

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commercial

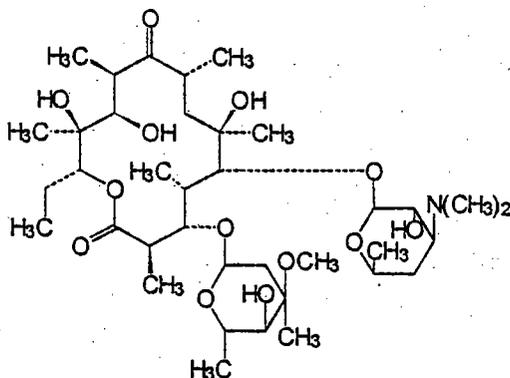
information

1. CHEMIST'S REVIEW NO. #3
2. ANDA #65-009
3. NAME AND ADDRESS OF APPLICANT
Glades Pharmaceuticals, Inc.
(Stiefel Laboratories, Inc.)
Attention: William A. Carr, Jr.
Agent for Glades Pharmaceuticals
Route 145
Oak Hill, NY 12460
4. LEGAL BASIS FOR SUBMISSION
Reference drug: Erygel® (Erythromycin Topical Gel USP) 2%
manufactured by Allergan Herbert.

No statement regarding expired patent or marketing
exclusivity is provided.
5. SUPPLEMENT(s)
N/A
6. PROPRIETARY NAME
E◇Glades
7. NONPROPRIETARY NAME
Erythromycin Topical Gel USP, 2%
8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:
Original submission: 2/2/98
Amendment 3/25/98 to "Refuse to File" letter 3/11/98
FDA acknowledgment: 4/1/98
Amendment 4/28/99 to labeling letter 12/1/98
Amendment 7/9/99 to N/A (MAJOR) letter 9/22/98
Amendment 8/8/00 to N/A (MAJOR) letter 11/9/99
10. PHARMACOLOGICAL CATEGORY
Antibacterial
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)
See DMF list under #37
13. DOSAGE FORM
Topical gel
14. POTENCY
2%

15. CHEMICAL NAME AND STRUCTURE

Erythromycin. (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-xyllo-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione. C₃₇H₆₇NO₁₃. 733.94. 114-07-8. Antibacterial.



16. RECORDS AND REPORTS

N/A

17. COMMENTS

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information

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commercial

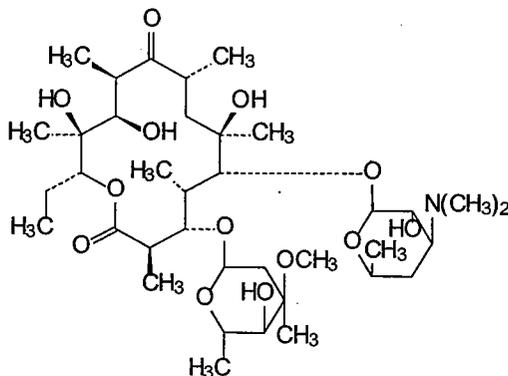
information

1. CHEMIST'S REVIEW NO. #4
2. ANDA #65-009
3. NAME AND ADDRESS OF APPLICANT
Glades Pharmaceuticals, Inc.
(Stiefel Laboratories, Inc.)
Attention: William A. Carr, Jr.
Agent for Glades Pharmaceuticals
Route 145
Oak Hill, NY 12460
4. LEGAL BASIS FOR SUBMISSION
Reference drug: Erygel® (Erythromycin Topical Gel USP) 2%
manufactured by Allergan Herbert.

No statement regarding expired patent or marketing
exclusivity is provided.
5. SUPPLEMENT(s)
N/A
6. PROPRIETARY NAME
E◇Glades
7. NONPROPRIETARY NAME
Erythromycin Topical Gel USP, 2%
8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:
Original submission: 2/2/98
Amendment 3/25/98 to "Refuse to File" letter 3/11/98
FDA acknowledgment: 4/1/98
Amendment 4/28/99 to labeling letter 12/1/98
Amendment 7/9/99 to N/A (MAJOR) letter 9/22/98
Amendment 8/8/00 to N/A (MAJOR) letter 11/9/99
Amendment 3/14/01 to N/A (MINOR) letter 1/8/01
10. PHARMACOLOGICAL CATEGORY
Antibacterial
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)
See DMF list under #37
13. DOSAGE FORM
Topical gel
14. POTENCY
2%

15. CHEMICAL NAME AND STRUCTURE

Erythromycin. (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-xyllo-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione. C₃₇H₆₇NO₁₃. 733.94. 114-07-8. Antibacterial.



16. RECORDS AND REPORTS

N/A

17. COMMENTS

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17

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commercial

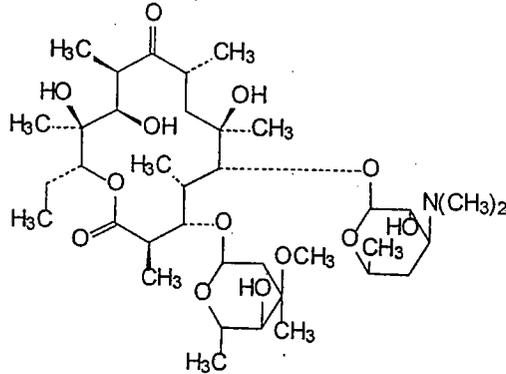
information

1. CHEMIST'S REVIEW NO. #5 (revised)
2. ANDA #65-009
3. NAME AND ADDRESS OF APPLICANT
Glades Pharmaceuticals, Inc.
(Stiefel Laboratories, Inc.)
Attention: William A. Carr, Jr.
Agent for Glades Pharmaceuticals
Route 145
Oak Hill, NY 12460
4. LEGAL BASIS FOR SUBMISSION
Reference drug: Erygel® (Erythromycin Topical Gel USP) 2%
manufactured by Allergan Herbert.

No statement regarding expired patent or marketing
exclusivity is provided.
5. SUPPLEMENT(s)
N/A
6. PROPRIETARY NAME
E◇Glades
7. NONPROPRIETARY NAME
Erythromycin Topical Gel USP, 2%
8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:
Original submission: 2/2/98
Amendment 3/25/98 to "Refuse to File" letter 3/11/98
FDA acknowledgment: 4/1/98
Amendment 4/28/99 to labeling letter 12/1/98
Amendment 7/9/99 to N/A (MAJOR) letter 9/22/98
Amendment 8/8/00 to N/A (MAJOR) letter 11/9/99
Amendment 3/14/01 to N/A (MINOR) letter 1/8/01
Amendment 7/26/01 to N/A (MINOR) letter 4/24/01
10. PHARMACOLOGICAL CATEGORY
Antibacterial
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)
See DMF list under #37
13. DOSAGE FORM
Topical gel
14. POTENCY
2%

15. CHEMICAL NAME AND STRUCTURE

Erythromycin. (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-xyl-oxacyclotetradecane-2,10-dione. C₃₇H₆₇NO₁₃. 733.94. 114-07-8. Antibacterial.



16. RECORDS AND REPORTS
N/A

17. COMMENTS



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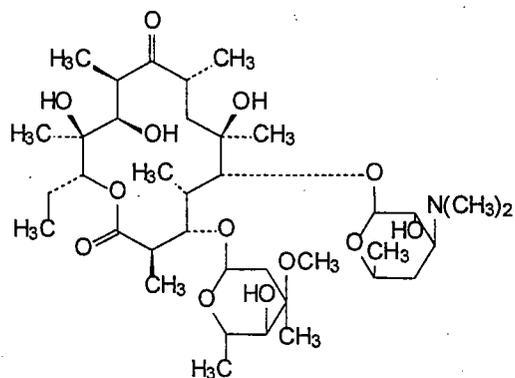
information

1. CHEMIST'S REVIEW NO. #6
2. ANDA #65-009
3. NAME AND ADDRESS OF APPLICANT
Glades Pharmaceuticals, Inc.
(Stiefel Laboratories, Inc.)
Attention: William A. Carr, Jr.
Agent for Glades Pharmaceuticals
Route 145
Oak Hill, NY 12460
4. LEGAL BASIS FOR SUBMISSION
Reference drug: Erygel® (Erythromycin Topical Gel USP) 2%
manufactured by Allergan Herbert.

No statement regarding expired patent or marketing
exclusivity is provided.
5. SUPPLEMENT(s) N/A
6. PROPRIETARY NAME
E◇Glades
7. NONPROPRIETARY NAME
Erythromycin Topical Gel USP, 2%
8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
9. AMENDMENTS AND OTHER DATES:
Original submission: 2/2/98
Amendment 3/25/98 to "Refuse to File" letter 3/11/98
FDA acknowledgment: 4/1/98
Amendment 4/28/99 to labeling letter 12/1/98
Amendment 7/9/99 to N/A (MAJOR) letter 9/22/98
Amendment 8/8/00 to N/A (MAJOR) letter 11/9/99
Amendment 3/14/01 to N/A (MINOR) letter 1/8/01
Amendment 7/26/01 to N/A (MINOR) letter 4/24/01
Amendment 1/9/02 to N/A (MINOR) letter 11/16/01
10. PHARMACOLOGICAL CATEGORY
Antibacterial
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)
See DMF list under #37
13. DOSAGE FORM
Topical gel
14. POTENCY
2%

15. CHEMICAL NAME AND STRUCTURE

Erythromycin. (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. C₃₇H₆₇NO₁₃. 733.94. 114-07-8. Antibacterial.



16. RECORDS AND REPORTS N/A

17. COMMENTS

[Empty space for comments]

(A)

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Status Summary for #65-009:

DMF:

Labeling: Acceptable (1/18/02)

EER: Acceptable (10/10/01)

Sample: Not requested (USP drug)

Bio: Acceptable (10/14/98)

18. CONCLUSIONS AND RECOMMENDATIONS

Approval recommended

19. REVIEWER:

Maria C. Shih

DATE COMPLETED:

3/5/02

**APPEARS THIS WAY
ON ORIGINAL**

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21

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**CENTER FOR DRUG
EVALUATION AND RESEARCH**

APPLICATION NUMBER:

65-009

BIOEQUIVALENCE REVIEW

4
APR 24 2001

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-009

APPLICANT: Glades Pharmaceuticals

DRUG PRODUCT: 2% Erythromycin Gel

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

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/s/

Dale P. Conner, Pharm. D.

Director

Division of Bioequivalence

Office of Generic Drugs

Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
VISION OF BIOEQUIVALENCE

65-009

SPONSOR: Glades Pharmaceuticals Inc.

& DOSAGE FORM : Erythromycin 2% gel

STRENGTH : 2%

TYPE: Study-waiver

SUMMARY :

-
1. Formulation for topical use.
 2. AT rated drug product.
 3. Route of administration and end use identical to the reference labeling.

For reasons 1, 2 and 3 the in-vivo bioequivalence study waiver granted.

PRIMARY REVIEWER : Pradeep M. Sathe, Ph.D. BRANCH : II

INITIAL : PS DATE : 9/15/98

Team Leader : S.G.Nerurkar, Ph.D. BRANCH : II

INITIAL : IS DATE : 9/15/1998

DIRECTOR : Dale Conner, Pharm.D.
DIVISION OF BIOEQUIVALENCE

INITIAL : DC DATE : 10/14/98

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL : _____ DATE : _____

APPEARS THIS WAY
ON ORIGINAL

Erythromycin
2% W/W Topical Gel

~~ANDA # 65-009~~

Reviewer: Pradeep M. Sathe
WP #65009W.398

Glades Pharmaceuticals
Coral Gables, FL-33134
Submission Date:

~~March 25, 1998~~

61
Hopes

REVIEW OF A BIO-STUDY WAIVER REQUEST

Background:

The firm is requesting a waiver of the in vivo bioavailability requirement for their 2% erythromycin topical gel, packaged in 30 and 50 g bottles based upon 21 CFR 320.22(b)(2). Currently, the 'Orange Book' lists the erythromycin gel products with the 'AT' category. Allergan-Herberts' Erygel^R Topical gel is listed by the orange book as the innovator formulation. The firm's original application (filed under Stiefel's name) of the same strength formulation packaged in tubes was approved by the Agency on Jan. 29, 1993. Though, the active ingredient, route of administration and dosage form of the firm's current formulation is same as the earlier approved product, the firm has modified the composition of the current formulation with respect to the inactive ingredients. The firm's modified formulation now has propylene glycol as an additional excipient. In 1991, the Division approved a Erythromycin 2% Gel formulation by Glaxo Welcome (ANDA owner in 1991 was Fulton Pharma-Cal Inc.) which had propylene glycol of similar strength. The Glaxo formulation was approved based on the consultative review opinion of the Director of the Anti-infective Drug Products. Table 1 lists, the composition of the test, reference and the approved Galxo-Welcome products. Attachment I provides composition of the firm's original approved formulation. Attachment II gives the Division of Anti-infective Drug products' opinion on the issue and Attachment III provides OGD medical officers opinion regarding the ingredients used for denaturing alcohol.

* Note: The application was originally filed by Stiefel Laboratories. Before the review was finalised the Division was informed that "all rights pending to ANDA 65-009 have been transferred to Glades Pharmaceuticals" (Attachment IV).

Table I. The Composition of Erythromycin Gel 2%

<u>Erythromycin Gel 2%</u> <u>(Test)</u>			Firm's modified product	<u>Erygel^R</u> <u>2%,</u> <u>(Ref.)</u>	Glaxo's Engel ^R 2%, Generic
Ingredient	~~~~~	50 gm bottle	Percent	Percent	Percent
*Erythromycin	~~~~~	1.05g	~~~~~	2.0	2.0
Hydroxypropyl Cellulose	~~~~~	~~~~~	~~~~~	~~~~~	~~~~~
SDA 40-2, Ethyl Alcohol	~~~~~	~~~~~	~~~~~	~~~~~	~~~~~
Propylene Glycol	~~~~~	~~~~~	~~~~~	~~~~~	~~~~~
~~~~~			~~~~~		
~~~~~			~~~~~		
Total	~~~~~	50 g	~~~~~	~~~~~	~~~~~

*

Comments:

- a. The ~~50 g~~ and 50 g container test products are exactly dose proportional with respect to the active and inactive ingredients.
- b. The excipients _____ are added as _____. They are _____
- c. The modified test product has different excipients (as propylene glycol) compared to the reference

APPEARS THIS WAY
ON ORIGINAL

product, however the modified test product is similar to the already approved generic product by Glaxo which was granted a waiver of biostudy and was deemed bioequivalent to the reference drug product by the Agency (see attachment V , the letter dated August 23 1991).

Recommendation:

The request for waiver of the in-vivo bioavailability requirement for Erythromycin Gel 2% manufactured by Glades Pharmaceuticals (packaged in — and 50 g plastic bottles) is granted.

ISI 9/15/98

Pradeep M. Sathe, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED S Nerurkar
FT INITIALED S Nerurkar

ISI *h*

Date: 10/9/1998

Concur: *ISI*

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence.

cc: ANDA # 65-009 original, HFD-650 (Director), Division File,
HFD-655 (Sathe), Drug File.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-009

APPLICANT: Glades Pharmaceuticals

DRUG PRODUCT: 2% Erythromycin Gel

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

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA-65009
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Reviewer

X:\NEW\FIRMSAM\GLADES\65009W.398
Printed in final on 09/15/98

Endorsements: (Final with Dates)
HFD-655/ Reviewer (P.Sathe) *PS 9/15/98*
HFD-655/ Bio team Leader (S.Nerurkar)
HFD-650/ D. Conner *DC 10/14/98*

AN 9/15/98

BIOEQUIVALENCY - ACCEPTABLE

submission date: March 25, 1998

1. WAIVER (WAI)

Strengths: 2% Erythromycin Gel
Outcome: AC

Outcome Decisions: AC - Acceptable

WinBio Comments: Product deemed bioequivalent, waiver granted.

**APPEARS THIS WAY
ON ORIGINAL**

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

65-009

**ADMINISTRATIVE
DOCUMENTS**

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 65-009

Date of Submission: March 14, 2001

Applicant's Name: Glades Pharmaceuticals

Established Name: E♦Glades (Erythromycin Topical Gel USP, 2%) – 50g

Labeling Deficiencies:

1. GENERAL COMMENT

Your proposed proprietary name "E♦Glades" has been forwarded to the Office of Post-Marketing Drug Risk Assessment for review. We will inform of their response once available.

2. CONTAINER: 50 g

Qualify the percentage of your alcohol. We refer you to 21 CFR 201.10(d)(2).

3. INSERT:

a. General Comments

i. Please note, we do not consider photo copied labeling as final print. Your previous submission was not photo copied and was acceptable as final print.

ii. DESCRIPTION

We refer you to comment (2) under CONTAINER.

We will not ask for the final printed labeling until we receive comments from OPDRA about your proposed proprietary name.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes, http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

ISI



William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 65-009

Date of Submission: July 26, 2001

Applicant's Name: Glades Pharmaceuticals

Established Name: E♦Glades (Erythromycin Topical Gel USP, 2%) – 50g

Labeling Deficiencies:

1. GENERAL COMMENT

Your proposed proprietary name "E♦Glades" was not found to be objectionable by the Office of Post-Marketing Drug Risk Assessment.

2. INSERT:

a. See comment under CONTAINER.

b. Delete the text, ' _____ ' and ' _____ '. We consider this text promotional in tone. Please refer to 21 CFR 201.56(b).

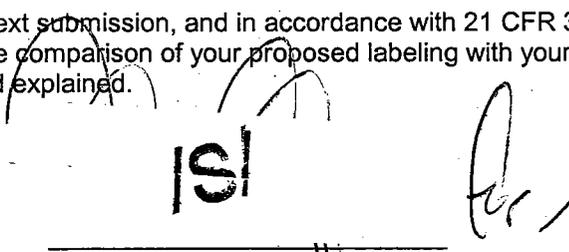
Please revise your insert labeling, as instructed above. Submit twelve copies of final printed container labels, carton labeling and insert labeling.

Submit twelve copies of final printed container labels, carton labeling and package insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes, http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ERYTHROMYCIN 2% GEL

AN ISSUE FOR 4 DDs MEETING

1. Currently erythromycin is marketed as i) DR capsule, ii) topical gel, iii) topical lotion and iv) ophthalmic ointment. All these dosage forms were approved post 1962.

According to November 17, 1994 policy memo regarding Interim Inactive Ingredients Policy:

a) Pre-1962 topical products forms receive waiver of biostudy requirement and post-1962 topical dosage forms do not receive waiver of biostudy.

b) The generic topical products are also required to be Q1 and Q2 same as the reference listed drug (RLD).

2. The first Generic erythromycin gel from Glaxo was approved in 1991. It received a waiver of biostudy requirement. It was not Q1 and Q2 same to the RLD. It has AT rating in the Orange Book. The Glaxo's product was approved on the basis of the Agency clinician's recommendation. There is also a internal memo (dated September 30, 1994) stating that granting waiver of biostudy requirement for erythromycin gels/ointment should be continued even though they are post 1962 drugs.

3. Subsequently two more gels were approved in 1993 and 1997 without a biostudy. These gels were Q1 and Q2 same as the RLD (Erygel from Allergan Herbert).

4. Recently we received an ANDA for a third generic erythromycin gel from Glade. The firm is requesting a waiver of biostudy requirement. However, the gel is not Q1 and Q2 same to the RLD. The Glade's ANDA raises following questions.

i) The November 17, 1994 policy memo does not invalidate exemptions granted for erythromycin gels and ointments. This exception still holds in 1998. It should be noted that two requirements (pre-1962 drug and Q&Q same) were exempted for Glaxo's ANDA. While in case of other two ANDAs only one requirement (pre-1962) was exempted. Therefore, it is necessary to decide whether only one requirement (pre-1962) or both requirements (pre-1962 and Q&Q sameness) are still exempt

ii) Glaxo's gel was deemed bioequivalent to RLD and is listed as AT in the Orange Book. Therefore, if we grant a waiver of biostudy to Glade's gel we need to deem it bioequivalent to the RLD. Is it possible to grant a waiver of biostudy and not to include a statement in the review that deems Glade's gel bioequivalent to the RLD ?

MEMO TO THE FILE

To: ANDA 65-009, Erythromycin Topical Gel USP, 2%
(Stiefel Laboratories, Inc.)

From: Sandra T. Middleton

Date: March 27, 1998

Subject: _____

I spoke with Dr. Fanning regarding the Stiefel claim to use of _____ solely as _____. Stiefel stated that the incorporation of _____ is exclusively related to the use of Alcohol SD 40-2, which is _____

Dr. Fanning acknowledges that _____ making process. She also suggests that I speak with Chemistry regarding the use of _____ and that we should consult Chemistry.

I spoke with John Harrison and Richard Adams on March 26, 1998, regarding the use of _____. They did not foresee any problem with the use of _____

The Regulatory Support Staff will acknowledge the application based on the above conversations.

FROM THE DESK OF...

SAUNDRA T. MIDDLETON
CONSUMER SAFETY OFFICER
CDER\FDA\OGD\DLPS
7500 STANDISH PLACE
ROCKVILLE MD 20855

301-827-5862
Fax: 301-594-1174

Dr. Fanning! RCM 10/22/99

SD-40

Cover Letter, FDA 356b, etc

Regulatory Statement

Agreement between Consumer/ANDA

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

65-009

CORRESPONDENCE



Research in Dermatology

STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX. 518-239-6341

January 9, 2002

N/AM

ORIG AMENDMENT

Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

RE: **MINOR AMENDMENT**
ANDA 65-009
E◇Glades (Erythromycin
Topical Gel, USP) 2%

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application for E◇Glades (Erythromycin Topical Gel, USP) 2%.

Reference is also made to FDA's 16 November 2001 not approvable communication specific to subject application.

We are here responding to FDA's 16 November communication via this Minor Amendment to the ANDA.

Our response is numerically keyed to FDA's comments for ease of review. Additional supporting data, referenced by tab and by page, is also included in this submission as required.

A. Chemistry Deficiencies:

FDA Comment

[Redacted area containing the FDA comment]

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FID
1/14/02
[Handwritten initials]

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Research in Dermatology

STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX. 518-239-6341

July 26, 2001

Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
ORIG AMENDMENT
N/AM

RE: **MINOR AMENDMENT**
ANDA 65-009
E◇Glades (Erythromycin
Topical Gel, USP) 2%

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application for E◇Glades (Erythromycin Topical Gel, USP) 2%.

Reference is also made to FDA's 24 April 2001 not approvable communication specific to subject application.

We are here responding to FDA's 24 April communication via this Minor Amendment to the ANDA.

Our response is numerically keyed to FDA's comments for ease of review. Additional supporting data, referenced by tab and by page, is also included in this submission as required.

Chemistry Deficiencies:

FDA Comment

[]

Official Response

We have received notification from the holder of DMF # _____ that
to the DMF dated June 29, 2001 (see Tab 1).

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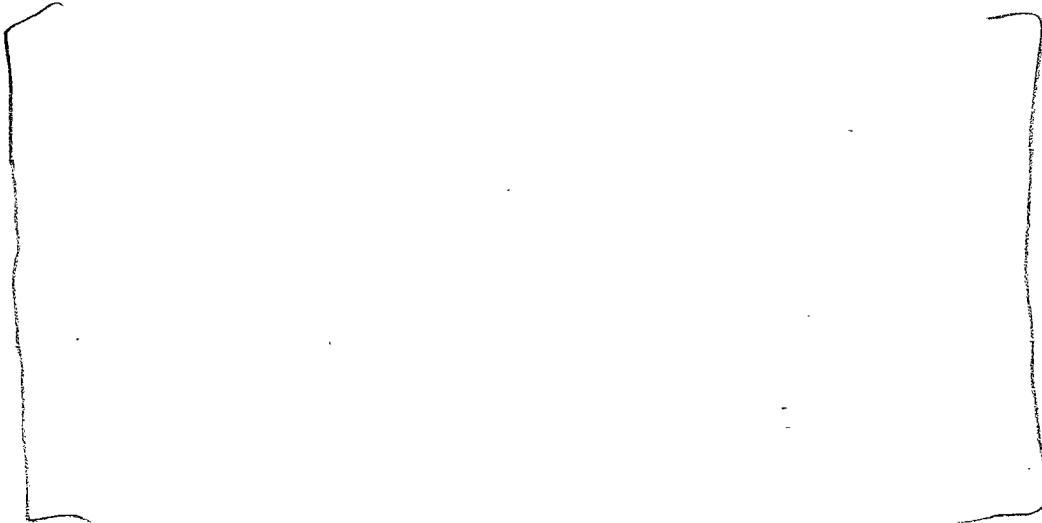
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Stiefel Response



Specifications have been established for _____ based upon observed data.

FDA Comment

7.

_____ Does it affect potency? Please comment.

Stiefel Response

We believe the _____ - which is also observed in the EmGel/Glaxo product - may contribute to the observed _____

Labeling Deficiencies

We have revised our labeling to qualify the percentage of alcohol in accordance with the provisions of 21 CFR 201.10(d)(2), as requested. Please find enclosed draft labeling specific to the referenced revision. (Tab 8)

Also enclosed, please find a side-by-side comparison of the proposed labeling to our last submission with all differences annotated and explained.

We here acknowledge that our proposed proprietary name "EØGlades" has been forwarded to the Office of Post-Marketing Drug Risk Assessment for review. We will, upon FDA's request, submit final printed labeling following receipt of OPDRA's comments regarding our proposed proprietary name.

We also here confirm that we will routinely monitor the labeling review branch website for approved revisions made to the reference listed drug.

MINOR AMENDMENT to ANDA 65-009
E Δ Glades (Erythromycin Topical Gel, USP) 2%

July 26, 2001
Page 6 of 6

Bioequivalency Comments

We acknowledge that the Division of Bioequivalency has completed its review and has no further questions at this time.

We look forward to your timely review.

Sincerely,
STIEFEL LABORATORIES, INC.

Mary Jane Carr for
William A. Carr, Jr.
Agent, Glades Pharmaceuticals, Inc.

WAC:mjc

**APPEARS THIS WAY
ON ORIGINAL**



Research in Dermatology

STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX. 518-239-6341

March 14, 2001

Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N/AM
FPL

RE: MINOR AMENDMENT
ANDA 65-009
E◇Glades (Erythromycin
Topical Gel, USP) 2%

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application for E◇Glades (Erythromycin Topical Gel, USP) 2%.

Reference is also made to FDA's 8 January 2001 not approvable communication specific to subject application.

We are here responding to FDA's 8 January communication via this Minor Amendment to the ANDA.

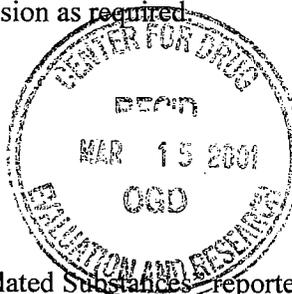
Our response is numerically keyed to FDA's comments for ease of review. Additional supporting data, referenced by tab and by page, is also included in this submission as required.

Chemistry Deficiencies:

Regarding the release specifications for the product:

FDA Comment

1. Based upon a summary of your results for the "Related Substances" reported on the submitted COA's on pages 27-8, 55-57, and 99-101, the proposed specifications should be tightened to be more consistent with the analytical



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Handwritten initials and date: *AS* 3/20/01

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Stiefel Response (Tab 5)

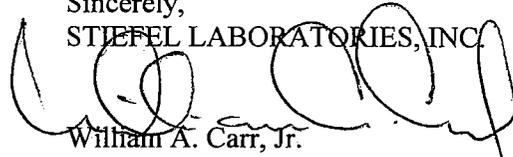
We here confirm that the _____ product is withdrawn from this application. ✓

We have revised our labels (insert) to reflect the 50 gram product, as requested.

Container and carton labeling will reflect final printed labeling provided at pages 015 and 017 of our April 28, 1999 Major Amendment to the ANDA specific to the 50 gram product.

We look forward to your timely review of this submission.

Sincerely,
STIEFEL LABORATORIES, INC.



William A. Carr, Jr.
Agent, Glades Pharmaceuticals, Inc.

WAC:mjc



Research in Dermatology

STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX. 518-239-6341

August 8, 2000

Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

AC
ANDA ORG AMENDMENT

RE: MAJOR AMENDMENT
ANDA 65-009
E◇Glades (Erythromycin
Topical Gel, USP) 2%

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application for E◇Glades (Erythromycin Topical Gel, USP) 2%.

Reference is also made to FDA's 8 November 1999 not approvable communication specific to subject application.

We are here responding to FDA's 8 November communication via this Major Amendment to the ANDA.

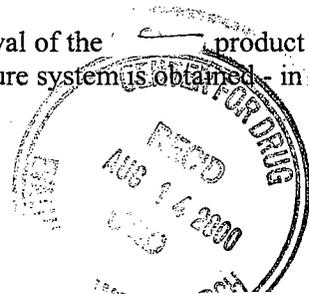
Our response is numerically keyed to FDA's comments for ease of review. Additional supporting data, referenced by tab and by page, is also included in this submission as required.

Please note that this response includes a request for the withdrawal of the product from the ANDA – with re-submission, if an acceptable container-closure system is obtained, in accordance with the provisions of 21 CFR 314.70.

Chemistry Deficiencies:

FDA Comment

[]



001

CORPORATE OFFICES: 255 ALHAMBRA CIRCLE, CORAL GABLES, FLORIDA 33134

ATLANTA, GEORGIA • RENO, NEVADA • ROCKVILLE, MARYLAND • BAYAMON, PUERTO RICO • BUENOS AIRES, ARGENTINA • CASTLE HILL, NSW, AUSTRALIA • BRUXELLES, BELGIUM • SAO PAULO, BRAZIL • MONTREAL, CANAD
SANTIAGO, CHILE • BOGOTA, COLOMBIA • CAIRO, EGYPT • PARIS, FRANCE • OFFENBACH/MAIN, GERMANY • ATHENS, GREECE • KOWLOON, HONG KONG • AMSTERDAM, HOLLAND • DUBLIN & SLIGO, IRELAND • MILAN, ITAL
TOKYO, JAPAN • SEOUL, KOREA • MEXICO CITY, MEXICO • CASABLANCA, MOROCCO • LAHORE, PAKISTAN • LIMA, PERU • MANILA, PHILIPPINES • WARSAU, POLAND • AMADORA, PORTUGAL • JURONG, SINGAPORE
JOHANNESBURG, SOUTH AFRICA • MADRID, SPAIN • ZURICH, SWITZERLAND • TAIPEI, TAIWAN • BANGKOK, THAILAND • HIGH WYCOMBE/BUCKS & SLOUGH/BERKS, UK • CARACAS, VENEZUELA

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Research in Dermatology

STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX. 518-239-6341

July 9, 1999

Director
Office of Generic Drugs
Center for Drug Evaluation
and Research
U.S. Food and Drug Administration
Metropark North II
7500 Standish Place
Rockville, MD 20855

NDA ORIG AMENDMENT

N/A/C

RE: MAJOR AMENDMENT
ANDA 65-009
EØGlades
(Erythromycin Topical Gel, USP) 2%

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application for EØGlades (Erythromycin Topical Gel, USP) 2%.

Reference is also made to FDA's 22 September 1998 not approvable communication specific to subject application.

We are here responding to FDA's 22 September communication via this MAJOR AMENDMENT to the ANDA.

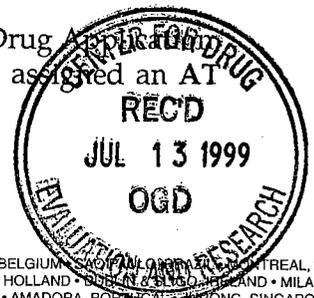
Our response is numerically keyed to FDA's comments for ease of review. Additional supporting data, referenced by page and by tab, is also included in this submission as required.

We recognize the reference listed drug for subject product, as established by the Food and Drug Administration in the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), is Erygel®/Allergan Herbert and we have met all applicable comparative requirements specific to the reference listed drug.

We also recognize established FDA policies and procedures allow for variation in excipients for topical dosage forms.

In this regard, Emgel® (erythromycin) 2% Topical Gel; Abbreviated Antibiotic Drug Application AADA, 63-107; was approved by FDA on August 23, 1991 and subsequently assigned an AT rating of therapeutical equivalence to the reference listed drug, Erygel®.

001



CORPORATE OFFICES: 255 ALHAMBRA CIRCLE, CORAL GABLES, FLORIDA 33134

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Our product has been formulated to duplicate the Emgel® product in accordance with the provisions provided under FDA's Inactive Ingredient policy statement issued during November 1994.

Available information also suggests that Emgel® (erythromycin) 2% Topical Gel utilizes an _____ in the formulation (please find enclosed - freedom of information document for AADA 63-107, and assay data generated). (TAB 1)

In light of the above, we believe a duplication of the Emgel® product, to include _____, is fully justified and are accordingly here proposing _____ erythromycin drug substance _____ in subject formulation.

Enclosed please find associated documents specific to Master Formula (MF) _____ to include applicable formulation pages and manufacturing log sheet. (TAB 1).

We believe an _____ is fully justified for MF# _____ referenced above.

Chemistry Deficiencies:

FDA Comment

1. For the composition statement on page 58, the following information is needed:
 - a. Designation of the qualitative grade for each of the ingredients.
 - b. Specify the unit of measurement for each ingredient after the quoted quantity.

Stiefel Response

Please find enclosed a revised composition statement which explicitly designates the qualitative grade and unit of measurement for each ingredient utilized, as requested. (TAB 2)

Please note that the referenced composition statement is specific to MF# _____ referenced at TAB 1 above.

FDA Comment

2. Regarding the Certificate of Analysis (page 116) from the new drug substance _____
 - a. The manufacturing site should be indicated on the COA since two _____
 - b. The requirements for each testing item should be stated.
 - c. All specifications need to be updated according to the current USP compendia.

- d. Please submit a Certificate of Analysis from a more recent batch which meet the revised specifications.

Stiefel Response

Please find enclosed a current _____ Certificate of Analysis for erythromycin drug substance which has been updated to specifically include site of manufacture and requirements for each testing item.

Also please note that current certificate(s) of analysis are inclusive of all USP testing requirements specified in the current USP monograph. (TAB 3)

FDA Comment

3. Regarding your specifications for the _____ (page 118):
- a. Please establish the limits for erythromycin potency and for "Related Substances" by the _____ assay method.
 - b. It is suggested that you establish a range for the particle size distribution in the release testing protocol.
 - c. We note that the test for _____ is not performed in the submitted COAs (pages 130-133). You may delete this test item if a rationale is provided for why it is not necessary.

Stiefel Response

_____ and Specifications for Erythromycin, USP have been revised to include limits for assay potency and related substances by _____ methodology in accordance with the current USP23/NF18 (USP23/NF18; Supplement 10).

Please find enclosed revised _____ and Specifications for Erythromycin, USP, to include a copy of the USP/NF specific to the referenced revision. (TAB 4)

Please note that referenced _____ and Specifications will be further updated to reflect all revisions in future USP/NF supplements, as required.

As noted previously, testing for erythromycin drug substance is performed in accordance with the current USP/NF.

We recognize the particle size distribution of the drug substance may substantially effect specific dosage forms, such as suspensions. However, subject product dosage form is a gel in which the erythromycin drug substance is solubilized in a formulation consisting of alcohol _____ and propylene glycol _____.

In light of the solubility characteristics of the drug substance in the proposed formulation, determination of particle size distribution, in our view, will not substantially enhance the rather rigid testing parameters already established for the drug substance and for the finished drug product.

Specific to point 3.c., referenced COAs are specific to erythromycin _____ which was released on 03-May-1996. The USP testing requirement for _____ became official on November 15, 1996 (USP23/NF18; Supplement 5), subsequent to the issuance of the May 1996 release. All testing performed on or after November 15, 1996 is inclusive of the _____ test requirement.

FDA Comment

4. The Certificate of Analysis for Alcohol SDA-40-2 from _____ does not provide specifications for each test item. Please clarify.

Stiefel Response

Please find enclosed a current Aaper Certificate of Analysis which has been updated to to include specifications for each test item, as requested. (TAB 5)

FDA Comment

5. Please confirm the maximum production batch size is to be ? _____

Stiefel Response

We here confirm that the maximum production batch size for E0Glades (Erythromycin Topical Gel, USP) 2% is _____, which is specific to MF#444. Manufacturing formula and manufacturing log sheet specific to commercial production operations are included at TAB 1 referenced above.

FDA Comment

6. Regarding your specifications for the finished product (pages 240 and 492):
- Requirements for "Description" and "Viscosity" should be provided.
 - Limits for all _____ assays (potency and Related Substances) need to be established.
 - Do you test pH for the product at release?
 - Please provide the rationale for the proposed ethanol limit.

Stiefel Response

Requirements for "Description" are included on the Release Packaged Product Tests and Specifications document included at page 474 of our February 2, 1998 ANDA submission. Referenced Release Packaged Product Tests and Specifications are utilized in conjunction with the above referenced Certificate(s) of Analysis (pp. 240 and 492).

Finished product must meet pre-established specifications as identified on the Release Packaged Product Tests and Specifications. Results specific to Description are reported as either Passes or Fails on the batch specific Certificate of Analysis due to the rather

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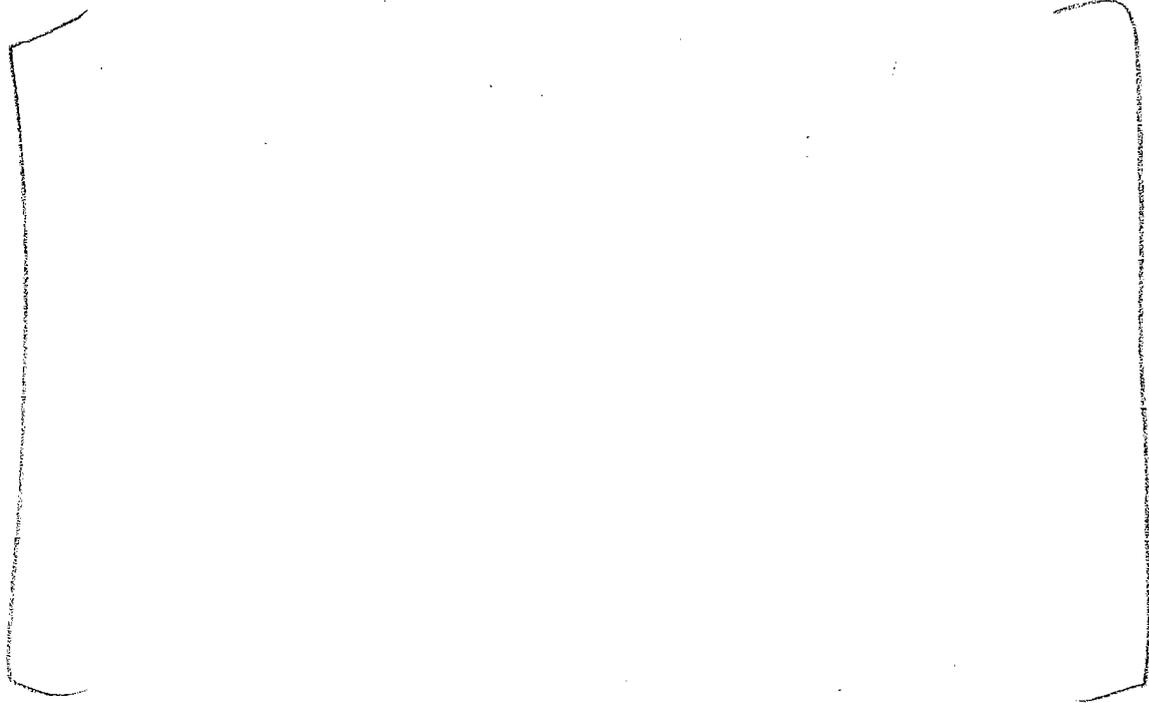
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- c. On page 589 you note that _____ has been observed for the duration of the stability study. Please comment on this finding. Have you observed the same phenomenon with Glaxo's product EmGel?

Stiefel Response

Designation of storage position is detailed in Standard Operating Procedure SOP 'SRI 100H' (please refer to pages 571-573 of our original submission) "...as to allow intimate contact of the product with the container and the product contact surfaces of the closure, where applicable.". Specific to Erythromycin Topical Gel a horizontal storage position will be utilized. Storage specific information has been incorporated on the proposed stability protocol, as requested. (TAB 8)



It is important to note that the proposed container system, to our knowledge, is identical to that utilized by Glaxo.

In addition to all of the above, updated (reprocessed) long-term stability data, specific to MFSRI359, is also here enclosed. (TAB 9)

We look forward to your timely review.

Sincerely,
STIEFEL LABORATORIES, INC.

William A. Carr, Jr.
Agent, Glades Pharmaceuticals, Inc.

WAC:mjc



Research in Dermatology

STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL: 518-239-6901 • FAX: 518-239-6341

April 28, 1999

Director
Office of Generic Drugs
Center for Drug Evaluation
and Research
U.S. Food and Drug Administration
Metropark North II
7500 Standish Place
Rockville, MD 20855

FPL
MAJOR ORIG AMENDMENT
Ac

RE: MAJOR AMENDMENT
ANDA 65-009
EØGlades
(Erythromycin Topical Gel, USP) 2%

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application for EØGlades (Erythromycin Topical Gel, USP) 2%.

Reference is also made to FDA's 1 December 1998 not approvable communication specific to labeling deficiencies noted in subject application.

We are here responding to FDA's 1 December communication via this MAJOR AMENDMENT to the ANDA.

Enclosed please find final printed labeling, revised in accordance with FDA's comments.

Also provided please find a side-by-side comparison of our proposed labeling to the last submission, with all differences annotated and explained.

This submission is complete in one (1) volume, not including additional copies which are also included as required.

Sincerely,
STIEFEL LABORATORIES, INC.

William A. Carr, Jr.
Agent, Glades Pharmaceuticals, Inc

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APR 29 1999

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CORPORATE OFFICES: 255 ALHAMBRA CIRCLE, CORAL GABLES, FLORIDA 33134

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Attachment IV

STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX 518-239-6041

September 4, 1998

Director
Office of Generic Drugs
Center for Drug Evaluation
and Research
U.S. Food and Drug Administration
Metropark North II
7500 Standish Place
Rockville, MD 20855

RE: Pending ANDA 65-009
E0Glades
(Erythromycin Topical Gel) 2%

Dear Sir/Madam:

This letter will confirm that all rights to pending ANDA 65-009 E0Glades (Erythromycin Topical Gel) 2% have been transferred to:

Glades Pharmaceuticals
255 Alhambra Circle
Coral Gables, FL 33134

Sincerely,
STIEFEL LABORATORIES, INC.

William A. Carr, Jr.
Vice President

CORPORATE OFFICES: 2801 PONCE DE LEON BOULEVARD, CORAL GABLES, FLORIDA 33134

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ANDA 65-009

Stiefel Laboratories, Inc.
Attention: William Carr, Jr.
Route 145
Oak Hill New York, 12460

APR 1 - 1998

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Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letter dated March 11, 1998, and your amendment dated March 25, 1998.

NAME OF DRUG: Erythromycin Topical Gel USP, 2%

DATE OF APPLICATION: February 2, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 27, 1998

We will correspond with you further after we have had the opportunity to review your application.

Please identify any communications concerning this application with the number shown above.

Should you have questions concerning this application contact:

Mark Anderson
Project Manager
(301) 827-5849

Sincerely yours,

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Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research



Research in Dermatology

STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX. 518-239-6341

March 25, 1998

Director
Office of Generic Drugs
Center for Drug Evaluation
and Research
U.S. Food and Drug Administration
Metropark North II
7500 Standish Place
Rockville, MD 20855

NDA ORIG AMENDMENT
N/AC

RE: ANDA 65-009
EϕGlades
(Erythromycin Topical Gel, USP) 2%

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application for EϕGlades (Erythromycin Topical Gel, USP) 2%, ANDA 65-009, submitted 2 February 1998.

Reference is also made to FDA's 11 March 1998 Refusal to File communication specific to the above referenced ANDA.

We are here requesting a reversal of FDA's 11 March decision based upon the following information.

Our response is keyed to FDA's comments for ease of review. Additional supporting information is included as required.

FDA Comment

MAR 27 1998

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FDA Comment

You have failed to provide the source and certificate of analysis (COA) for the inactive ingredients. Please note that sources and COAs must be provided for all inactives listed.

Stiefel Response

_____ of the alcohol utilized in the finished product. The _____ alcohol, SD 40-2 Alcohol, is _____. A Certificate of Analysis is provided specific to SD 40-2 Alcohol which is inclusive of a quantitative determination of _____ and _____ (see Volume 1 of 2, page 155).

FDA Comment

In addition, please submit a reprocessing statement per OGD Policy and Procedure Guide #23-90 and 21 CFR 211.115.

Stiefel Response

A reprocessing statement is included at Volume 1 of 2, page 210 which specifically states that EϕGlades (Erythromycin Topical Gel, USP) 2% will not be reprocessed unless individual, batch specific approval is received from FDA.

We look forward to your timely review of this request.

Sincerely,
STIEFEL LABORATORIES, INC.



William A. Carr, Jr.
Vice President

WAC:mjt

ANDA 65-009

Stiefel Laboratories, Inc.
Attention: William Carr, Jr.
Route 145
Oak Hill New York, 12460

MAR 11 1998



Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated February 2, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Erythromycin Topical Gel USP, 2%.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

The information to demonstrate safety should include, but is not limited to: (a) examples of approved drug products administered by the same route of administration which contain the same inactive ingredients and that are within the same concentration range, (b) a description of the purpose of the inactive ingredients when different inactive ingredients are included in the proposed drug product, and (c) a comparison of the physical and chemical properties



Research in Dermatology

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STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX. 518-239-6341

February 2, 1998

Director
Office of Generic Drugs
Center for Drug Evaluation
and Research
U.S. Food and Drug Administration
Metropark North II
7500 Standish Place
Rockville, MD 20855

Dear Sir/Madam:

We are here submitting an Abbreviated Antibiotic Drug Application for E0Glades (Erythromycin Topical Gel, USP) 2% in accordance with the provisions of 21 CFR 314.94(c).

Please direct all communications concerning this application to:

Mr. William A. Carr, Jr.
Vice President
Stiefel Laboratories, Inc.
Route 145
Oak Hill, NY 12460

This submission is complete in two (2) volumes, not including additional copies which are also included as required.

Sincerely,
STIEFEL LABORATORIES, INC.

William A. Carr, Jr.
Vice President

WAC:mjt

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