CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 201587

Name: Mupirocin Cream USP, 2%

Sponsor: Glenmark Generics Inc., USA

Approval Date: January 24, 2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201587

CONTENTS

Reviews / Information Included in this Review	
Approval Letter	**X**
Other Action Letters	
Labeling	**X**
Labeling Review(s)	**X**
Medical Review(s)	
Chemistry Review(s)	**X**
Pharm/Tox Review(s)	
Statistical Review(s)	**X**
Microbiology Review(s)	
Bioequivalence Review(s)	**X**
Other Review(s)	**X**
Administrative & Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201587

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 201587

Glenmark Generics Inc., USA
U.S. Agent for: Glenmark Generics Ltd.
Attention: William R. McIntyre, Ph.D.
Executive Vice President, Regulatory Affairs
750 Corporate Drive
Mahwah, NJ 07430

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated February 22, 2010, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Mupirocin Cream USP, 2%.

Reference is also made to your amendments dated June 1, 2010; August 16, 2011; and January 19, January 27, April 27, July 18, and July 20, 2012. We also acknowledge receipt of your correspondence dated November 2, 2012, addressing patent issues associated with this ANDA.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Mupirocin Cream USP, 2%, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Bactroban Cream, 2%, of GlaxoSmithKline (GSK).

The RLD upon which you have based your ANDA, GSK's Bactroban Cream, 2%, is subject to a period of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent No. 6,025,389 (the '389 patent) is scheduled to expire on October 20, 2014.

Glenmark Generics Ltd. is not required to submit a certification to the '389 patent because the agency has determined that this

patent was late-listed with respect to this ANDA. See 21 CFR 314.94(a)(12)(vi).

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA 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.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at

http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Gregory P. Geba, M.D., M.P.H.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

01/24/2013

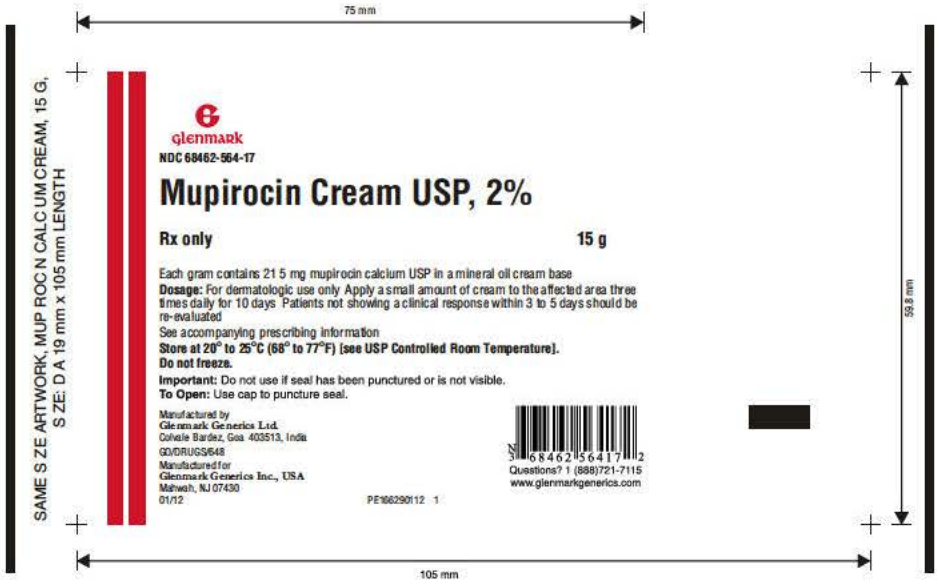
Deputy Director, Office of Generic Drugs, for
Gregory P. Geba, M.D., M.P.H.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

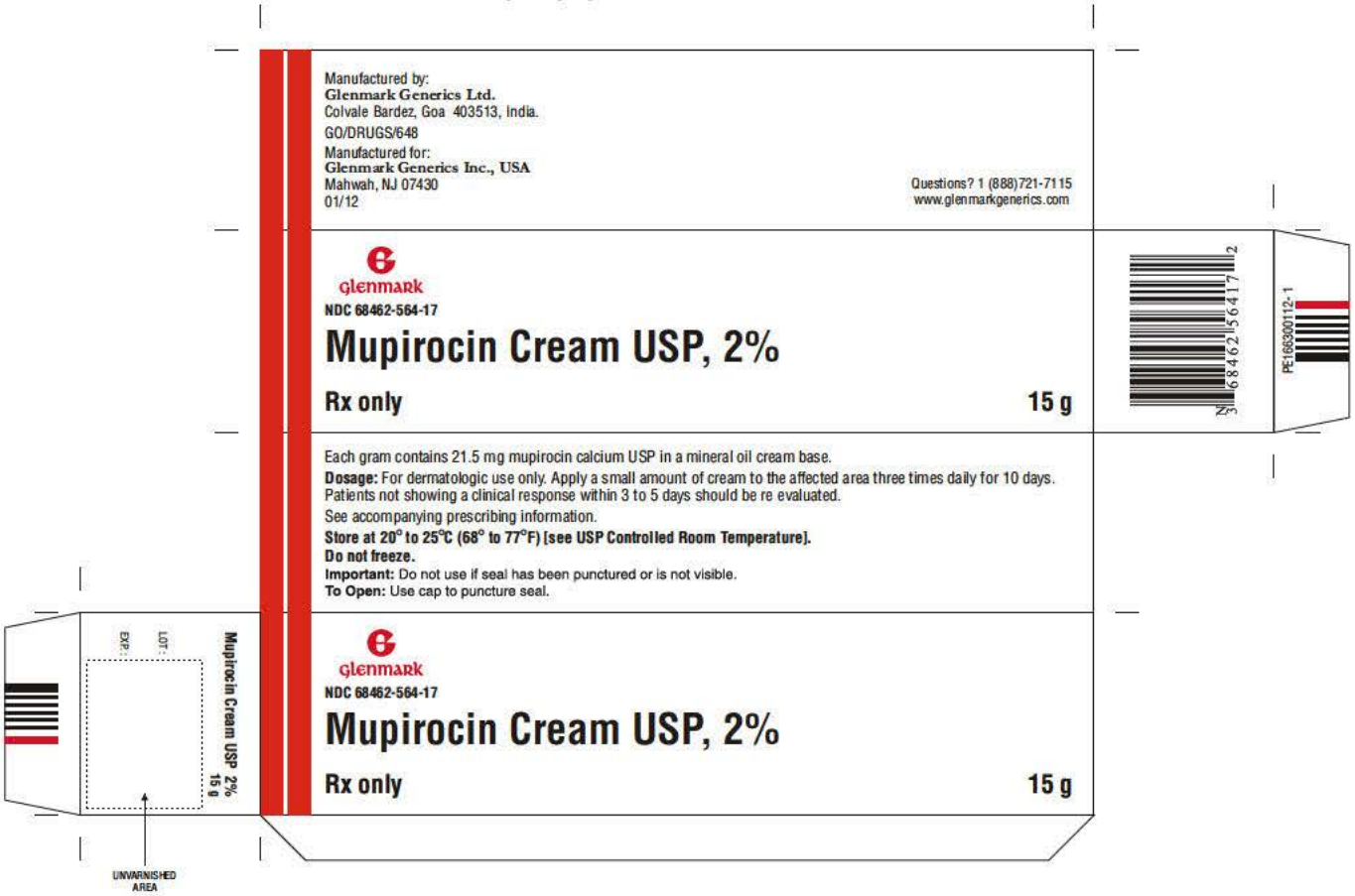
ANDA 201587

LABELING

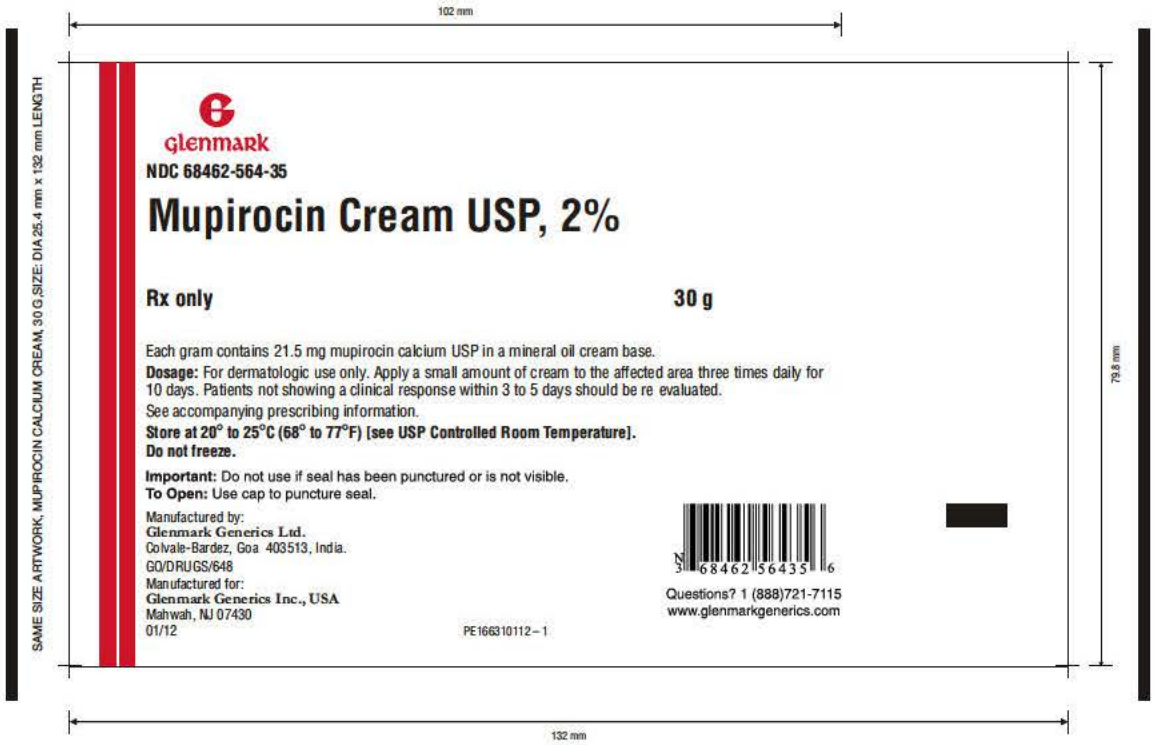


GLENMARK GENERICS LTD.			
PRODUCT NAME: MUPIROCIN CALCIUM CREAM - 2%	DATE:	PANTONE SHADE NO: BLACK (b) (4)	
ITEM CODE: PE16629 VERSION: 0112-1	PKG. DEV.:	Item code, Version, Consistency of Design, overprint area, Pack size, Dimensions & Layout	
LOCATION: GOA	RA	Regulatory Text	
JAR SIZE:	QA:	Entire Text	
PACK SIZE: 15 G TUBE	REMARKS:		
ACTUAL SIZE: 59.8 mm x 105 mm Length			
SPECIFICATION: LDPE TUBE			

SAME SIZE ARTWORK
CARTON SIZE: 111 mm x 24 mm x 27 mm

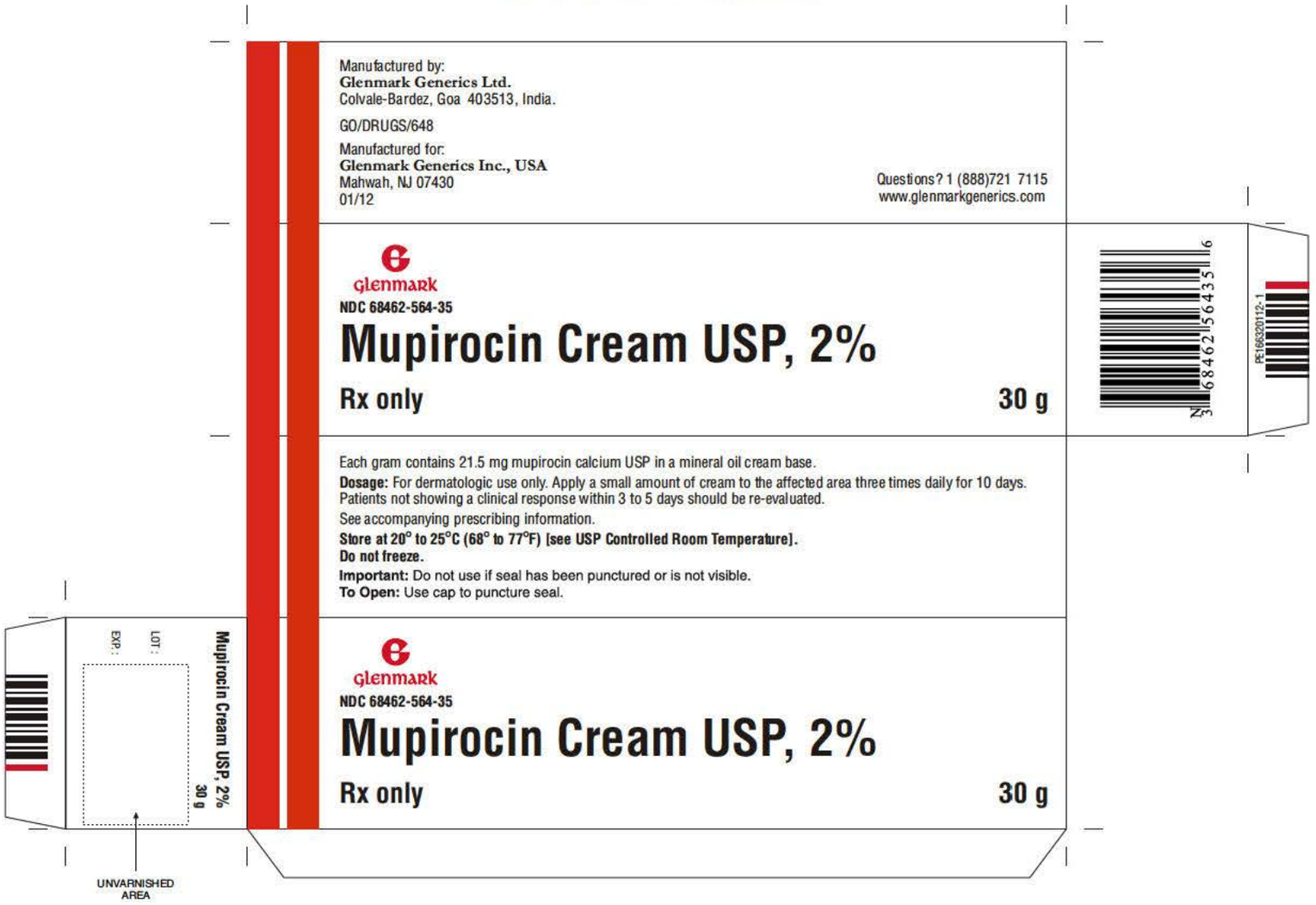


GLENMARK GENERICS LTD.			
PRODUCT NAME: MUPIROCIN CALCIUM CREAM - 2%	DATE:	PANTONE SHADE NO: BLACK (b) (4)	
ITEM CODE: PE16630 VERSION: 0112-1	PKG. DEV.:	Item code, Version, Consistency of Design, overprint area, Pack size, Dimensions & Layout	
PHARMACODE: 192	RA	Regulatory Text	
LOCATION: GOA	QA:	Entire Text	
PACK SIZE: 15 G CRT	REMARKS:		
ACTUAL SIZE: 111 mm x 24 mm x 27 mm			
SPECIFICATION:			



GLENMARK GENERICS LTD.			
PRODUCT NAME: MUPIROCIN CALCIUM CREAM - 2%	DATE:	PANTONE SHADE NO: BLACK (b) (4)	
ITEM CODE: PE16631 VERSION: 0112-1	PKG. DEV.:	Item code, Version, Consistency of Design, overprint area, Pack size, Dimensions & Layout	
LOCATION: GOA	RA	Regulatory Text	
JAR SIZE:	QA:	Entire Text	
PACK SIZE: 30 G TUBE	REMARKS:		
ACTUAL SIZE: 79.8 mm x 132 mm Length			
SPECIFICATION: LDPE TUBE			

SAME SIZE ARTWORK
CARTON SIZE: 135 mm x 30 mm x 35 mm



GLENMARK GENERICS LTD.			
PRODUCT NAME: MUPIROCIN CALCIUM CREAM - 2%	DATE:	PANTONE SHADE NO: BLACK (b) (4)	
ITEM CODE: PE16632 VERSION: 0112-1	PKG. DEV.:	Item code, Version, Consistency of Design, overprint area, Pack size, Dimensions & Layout	
PHARMACODE: 5450	RA	Regulatory Text	
LOCATION: GOA	QA:	Entire Text	
PACK SIZE: 30 G CRT	REMARKS:		
ACTUAL SIZE: 135 mm x 30 mm x 35 mm			
SPECIFICATION:			

Mupirocin Cream USP, 2%

16633

Mupirocin Cream USP, 2%

16633

PRESCRIBING INFORMATION

Mupirocin Cream USP, 2%

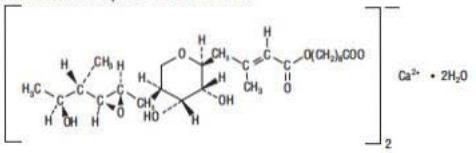
For Dermatologic Use

Rx Only

DESCRIPTION

Mupirocin cream USP, 2% contains the dihydrate crystalline calcium hemi salt of the antibiotic mupirocin. Chemically, it is (α*E*,2*S*,3*R*,4*R*,5*S*) 5 [(2*S*,3*S*,4*S*,5*S*) 2,3 Epoxy 5 hydroxy 4 methylhexyl]tetrahydro 3,4 dihydroxy β methyl 2H pyran 2 crotonic acid, ester with 9 hydroxynonanoic acid, calcium salt (2:1), dihydrate.

The molecular formula of mupirocin calcium USP is $(C_{26}H_{44}O_9)_2Ca{\cdot}2H_2O$, and the molecular weight is 1075.3. The molecular weight of mupirocin free acid is 500.6. The structural formula of mupirocin calcium USP is:



Mupirocin cream USP, 2% is a white cream that contains 2.15% w/w mupirocin calcium USP (equivalent to 2.0% mupirocin free acid) in an oil and water based emulsion. The inactive ingredients are benzyl alcohol, glycerol monostearate, mineral oil, phenoxyethanol, polyoxyl 20 cetostearyl ether, purified water and xanthan gum.

CLINICAL PHARMACOLOGY

Pharmacokinetics: Systemic absorption of mupirocin through intact human skin is minimal. The systemic absorption of mupirocin was studied following application of mupirocin cream three times daily for 5 days to various skin lesions (greater than 10 cm in length or 100 cm^2 in area) in 16 adults (aged 29 to 60 years) and 10 children (aged 3 to 12 years). Some systemic absorption was observed as evidenced by the detection of the metabolite, monic acid, in urine. Data from this study indicated more frequent occurrence of percutaneous absorption in children (90% of patients) compared to adults (44% of patients); however, the observed urinary concentrations in children (0.07 1.3 mcg/mL [1 pediatric patient had no detectable level]) are within the observed range (0.08 10.03 mcg/mL [9 adults had no detectable level]) in the adult population. In general, the degree of percutaneous absorption following multiple dosing appears to be minimal in adults and children. Any mupirocin reaching the systemic circulation is rapidly metabolized, predominantly to inactive monic acid, which is eliminated by renal excretion.

Microbiology: Mupirocin is an antibacterial agent produced by fermentation using the organism *Pseudomonas fluorescens*. It is active against a wide range of gram positive bacteria including methicillin resistant *Staphylococcus aureus* (MRSA). It is also active against certain gram negative bacteria. Mupirocin inhibits bacterial protein synthesis by reversibly and specifically binding to bacterial isoleucyl transfer RNA synthetase. Due to this unique mode of action, mupirocin demonstrates no *in vitro* cross resistance with other classes of antimicrobial agents.

Resistance occurs rarely; however, when mupirocin resistance does occur, it appears to result from the production of a modified isoleucyl tRNA synthetase. High level plasmid mediated resistance (MIC > 1024 mcg/mL) has been reported in some strains of *Staphylococcus aureus* and coagulase negative staphylococci.

Mupirocin is bactericidal at concentrations achieved by topical application. The minimum bactericidal concentration (MBC) against relevant pathogens is generally 8 fold to 30 fold higher than the minimum inhibitory concentration (MIC). In addition, mupirocin is highly protein bound (>97%), and the effect of wound secretions on the MICs of mupirocin has not been determined.

Mupirocin has been shown to be active against most strains of *S. aureus* and *Streptococcus pyogenes*, both *in vitro* and in clinical studies. (See INDICATIONS AND USAGE). The following *in vitro* data are available, BUT THEIR CLINICAL SIGNIFICANCE IS UNKNOWN. Mupirocin is active against most strains of *Staphylococcus epidermidis* and *Staphylococcus saprophyticus*.

INDICATIONS AND USAGE

Mupirocin cream USP, 2 % is indicated for the treatment of secondarily infected traumatic skin lesions (up to 10 cm in length or 100 cm^2 in area) due to susceptible strains of *S. aureus* and *S. pyogenes*.

CONTRAINDICATIONS

Mupirocin cream is contraindicated in patients with known hypersensitivity to any of the constituents of the product.

WARNINGS

Avoid contact with the eyes.

In the event of a sensitization or severe local irritation from mupirocin cream, usage should be discontinued, and appropriate alternative therapy for the infection instituted.

PRECAUTIONS

General: As with other antibacterial products, prolonged use may result in overgrowth of nonsusceptible microorganisms, including fungi. (See DOSAGE AND ADMINISTRATION).

Mupirocin cream is not formulated for use on mucosal surfaces.

Information for Patients:

- Use this medication only as directed by your healthcare provider. It is for external use only. Avoid contact with the eyes.
- The treated area may be covered by gauze dressing if desired.
- Report to your healthcare provider any signs of local adverse reactions. The medication should be stopped and your healthcare provider contacted if irritation, severe itching, or rash occurs.
- If no improvement is seen in 3 to 5 days, contact your healthcare provider.

Drug Interactions: The effect of the concurrent application of topical mupirocin calcium cream and other topical products has not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies in animals to evaluate carcinogenic potential of mupirocin calcium have not been conducted.

Results of the following studies performed with mupirocin calcium or mupirocin sodium *in vitro* and *in vivo* did not indicate a potential for mutagenicity: Rat primary hepatocyte unscheduled DNA synthesis, sediment analysis for DNA strand breaks, *Salmonella* reversion test (Ames), *Escherichia coli* mutation assay, metaphase analysis of human lymphocytes, mouse lymphoma assay, and bone marrow micronuclei assay in mice.

Fertility studies were performed in rats with mupirocin administered subcutaneously at doses up to 49 times a human topical dose of 1 gram/day (approximately 20 mg mupirocin per day) on a mg/m^2 basis and revealed no evidence of impaired fertility from mupirocin sodium.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B. Teratology studies have been performed in rats and rabbits with mupirocin administered subcutaneously at doses up to 78 and 154 times, respectively, a human topical dose of 1 gram/day (approximately 20 mg mupirocin per day) on a mg/m^2 basis and revealed no evidence of harm to the fetus due to mupirocin. 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 during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when mupirocin cream is administered to a nursing woman.

GLENMARK GENERICS LTD.	DATE: 12 01 12	PANTONE SHADE NO: Black	
PRODUCT NAME: Mupirocin Cream USP 2% (Insert Front)	PKG. DEV.:	Item code, Version, Consistancy of Design, overprint area, Pack size, Dimensions & Layout	
ITEM CODE: PE16633 VERSION: 1011 1	RA	Regulatory Text	
LOCATION: Goa	QA:	Entire Text	
JAR SIZE:	REMARKS:		
PACK SIZE:			
ACTUAL SIZE: 160 x 190 mm			
SPECIFICATION: 160 x 22 mm Folding Size			

Pediatric Use: The safety and effectiveness of mupirocin cream have been established in the age groups 3 months to 16 years. Use of mupirocin cream in these age groups is supported by evidence from adequate and well controlled studies of mupirocin cream in adults with additional data from 93 pediatric patients studied as part of the pivotal trials in adults. (See CLINICAL STUDIES).

Geriatric Use: In 2 well controlled studies, 30 patients older than 65 years were treated with mupirocin cream. No overall difference in the efficacy or safety of mupirocin cream was observed in this patient population when compared to that observed in younger patients.

ADVERSE REACTIONS

In 2 randomized, double blind, double dummy trials, 339 patients were treated with topical mupirocin cream plus oral placebo. Adverse events thought to be possibly or probably drug related occurred in 28 (8.3%) patients. The incidence of those events that were reported in at least 1% of patients enrolled in these trials were: Headache (1.7%), rash, and nausea (1.1% each).

Other adverse events thought to be possibly or probably drug related which occurred in less than 1% of patients were: abdominal pain, burning at application site, cellulitis, dermatitis, dizziness, pruritus, secondary wound infection, and ulcerative stomatitis.

In a supportive study in the treatment of secondarily infected eczema, 82 patients were treated with mupirocin cream. The incidence of adverse events thought to be possibly or probably drug related was as follows: nausea (4.9%), headache, and burning at application site (3.6% each), pruritus (2.4%) and 1 report each of abdominal pain, bleeding secondary to eczema, pain secondary to eczema, hives, dry skin, and rash.

OVERDOSAGE

Intravenous infusions of 252 mg, as well as single oral doses of 500 mg of mupirocin, have been well tolerated in healthy adult subjects. There is no information regarding overdose of mupirocin cream.

DOSAGE AND ADMINISTRATION

A small amount of mupirocin cream USP should be applied to the affected area three times daily for 10 days. The area treated may be covered with gauze dressing if desired. Patients not showing a clinical response within 3 to 5 days should be re evaluated.

CLINICAL STUDIES

The efficacy of topical mupirocin cream for the treatment of secondarily infected traumatic skin lesions (e.g., lacerations, sutured wounds, and abrasions not more than 10 cm in length or 100 cm^2 in total area) was compared to that of oral cephalexin in 2 randomized, double blind, double dummy clinical trials. Clinical efficacy rates at follow up in the per protocol populations (adults and pediatric patients included) were 96.1% for mupirocin cream (n 231) and 93.1% for oral cephalexin (n 219). Pathogen eradication rates at follow up in the per protocol populations were 100% for both mupirocin cream and oral cephalexin.

Pediatrics: There were 93 pediatric patients aged 2 weeks to 16 years enrolled per protocol in the secondarily infected skin lesion studies, although only 3 were less than 2 years of age in the population treated with mupirocin cream. Patients were randomized to either 10 days of topical mupirocin cream three times daily or 10 days of oral cephalexin (250 mg four times daily for patients >40 kg or 25 mg/kg/day oral suspension in 4 divided doses for patients ≤40 kg). Clinical efficacy at follow up (7 to 12 days post therapy) in the per protocol populations was 97.7% (43/44) for mupirocin cream and 93.9% (46/49) for cephalexin. Only 1 adverse event (headache) was thought to be possibly or probably related to drug therapy with mupirocin cream in the intent to treat pediatric population of 70 children (1.4%).

HOW SUPPLIED

Mupirocin cream USP, 2% is supplied in 15 gram and 30 gram tubes.

NDC 68462 564 17 (15 gram tube)
NDC 68462 564 35 (30 gram tube)
Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Do not freeze.

Manufactured by:
Glenmark Generics Ltd.
Colvale Bardez, Goa 403 513, India

Manufactured for:
Glenmark
Glenmark Generics Inc., USA
Mahwah, NJ 07430

Questions? 1 (888)721 7115
www.glenmarkgenerics.com

January 2012

PE166331011-1

GLENMARK GENERICS LTD.	DATE: 12 01 12	PANTONE SHADE NO: Black	
PRODUCT NAME: Mupirocin Cream USP 2% (Insert Back)	PKG. DEV.:	Item code, Version, Consistancy of Design, overprint area, Pack size, Dimensions & Layout	
ITEM CODE: PE16633 VERSION: 1011 1	RA	Regulatory Text	
LOCATION: Goa	QA:	Entire Text	
JAR SIZE:	REMARKS:		
PACK SIZE:			
ACTUAL SIZE: 160 x 190 mm			
SPECIFICATION: 160 x 22 mm Folding Size			

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201587

LABELING REVIEWS

APPROVAL SUMMARY #1

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

ANDA Number: 201587

Date of Submission: February 22, 2010 and January 19, 2012

Applicant's Name: Glenmark Generics Inc. USA

Established Name: Mupirocin Cream USP, 2%

REMS required? NO

MedGuides and/or PPIs (505-1(e))	☐ Yes	☐ No
Communication plan (505-1(e))	☐ Yes	☐ No
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes	☐ No
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes	☐ No
Timetable for assessment (505-1(d))	☐ Yes	☐ No

ANDA REMS acceptable?

☐ **Yes** ☐ No ☒ n/a

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): Do you have Final Printed Labels and Labeling? Yes

Container Labels: (15 g) – Satisfactory in final print as of January 19, 2012 electronic submission.

Container Labels: (30g) – Satisfactory in final print as of January 19, 2012 electronic submission.

Carton Labeling: (15 g) – Satisfactory in final print as of January 19, 2012 electronic submission.

Carton Labeling: (30 g) – Satisfactory in final print as of January 19, 2012 electronic submission.

Insert Labeling: Satisfactory in final print as of January 19, 2012 electronic submission.

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Bactroban Cream
- NDA Number: 50-746
- NDA Drug Name: Mupirocin calcium cream, 2%
- NDA Firm: Glaxo Smith Kline
- Established name: Mupirocin cream USP, 2%
- Date of Approval of NDA Insert: NDA 50-746/S-000: Approved December 11, 1997.
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side-by-side comparison
- Basis of Approval for the Carton Labeling: Side-by-side comparison
- Revisions needed post-approval: NO
- Patents/Exclusivities: NONE

FOR THE RECORD:

1. MODEL LABELING:
This review was based on the labeling for the reference listed drug, Bactroban Cream (Mupirocin calcium cream, 2%) [NDA 50-746: Approved December 11, 1997] held by Galderma Laboratories.

2. PATIENTS/EXCLUSIVTIES: NONE

3. INACTIVE INGREDIENTS
There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement. The formulation for the firm's test product is similar to that for the RLD. Cetyl alcohol and stearyl alcohol used in the RLD were replaced with glycerol monosterate.

Mupirocin Cream USP, 2% Glenmark Generics Limited	BACTROBAN CREAM® (mupirocin calcium cream), 2% GlaxoSmithKline	Function
Benzyl alcohol, NF	Benzyl alcohol, NF	(b) (4)
Mineral oil, USP (b) (4)	Mineral oil, NF	
Phenoxyethanol, NF (b) (4)	Phenoxyethanol, NF	
Xanthan gum, NF (b) (4)	Xanthan gum, NF	
Polyoxyl 20 cetostearyl ether, NF (b) (4)	Cetomacrogol 1000	
Glycerol monostearate (b) (4) (b) (4)	---	
Purified water, USP	Purified water, USP	
---	Cetyl alcohol	
---	Stearyl alcohol	

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- USP: Preserve in collapsible tubes or well-closed containers. Store at 25°C excursions permitted between 15° - 30°C.
- RLD: Store at or below 25°C (77°F). Do not freeze.
- ANDA: Store at 20° - 25°C (68 - 77°F) [see USP controlled room temperature] Do not freeze.

5. PACKAGE CONFIGURATION

- RLD: Packaged in 15 g and 30 g tubes.
- ANDA: Packaged in 15 g and 30 g aluminum collapsible tubes with white HDPE caps with piercing point.

6. CONTAINER/CLOSURE: The product is to be packaged in (b) (4) aluminum collapsible tubes in sizes of 15 g and 30 g with white plastic HDPE) caps having a piercing point.

(b) (4)

7. FNISHED DOSAGE FORM

- RLD: Cream
- ANDA: White cream

8. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Glenmark Generics Limited
Plot No. S-7, Colvale Industrial Estate
Colvale, Bardez, Goa 403 513,
India

Date of Submission: February 23, 2010 and January 20, 2012

Primary Reviewer: Beverly Weitzman

Team Leader: John Grace

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BEVERLY WEITZMAN
10/22/2012

JOHN F GRACE
10/22/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201587

CHEMISTRY REVIEWS

ANDA 201587

Mupirocin Calcium Cream USP, 2%

Glenmark Generics Inc. USA

Richard Chang, Ph.D.
OGD/DCI

Chemistry Review #2 addendum 2

Table of Contents

Chemistry Review Data Sheet

1. **ANDA #** 201587

2. **REVIEW #:** 2 addendum 2

3. **REVIEW DATE:** 12-December-2012

4. **REVIEWER:** Richard Chang

5. **PREVIOUS DOCUMENTS:** N/A

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	**Document Date**
Original	22-Feb-2010
Acceptable for filing	23-Feb-2010
Amendment	16-Aug-2011

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Glenmark Generics Ltd.
US Agent:	Glenmark Generics Inc., USA William McIntyre, Ph.D.
Address:	750 Corporate Drive Mahwah, NJ 07430
Telephone:	(201) 684-8017

8. **DRUG PRODUCT NAME/CODE/TYPE:**

   a) Proprietary Name: N/A
   b) Non-Proprietary Name (USAN): Mupirocin Calcium Cream USP, 2%

9. **LEGAL BASIS FOR SUBMISSION:**

The basis for Glenmark's ANDA for Mupirocin Cream USP, 2%, is the approved reference listed drug, Bactroban® (mupirocin calcium) cream, 2%. As provided in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations, current through December 2007, (Section **1.3.5.1** Patent Information)), Bactroban® (mupirocin calcium) cream, 2%. is the subject of NDA # 050746, which was approved on December 11, 1997 and is held by Glaxosmithkline.
According to the information published in the Electronic Orange Book, current through September 2008, there are no unexpired patents and there is no unexpired exclusivity for Bactroban® (mupirocin calcium) cream, 2%.

Patent certification: The firm has provided a Paragraph II certification

10. **PHARMACOL. CATEGORY:**
Indicated for the treatment of secondarily infected traumatic skin lesions due to susceptible strains of S. aureus and S. pyogenes

11. **DOSAGE FORM:** Cream

12. **STRENGTH/POTENCY:** 2%

13. **ROUTE OF ADMINISTRATION:** Topical

14. **Rx/OTC DISPENSED:** _x_ **Rx** ___ **OTC**

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)**

_____SPOTS product – Form Completed

___x__Not a SPOTS product

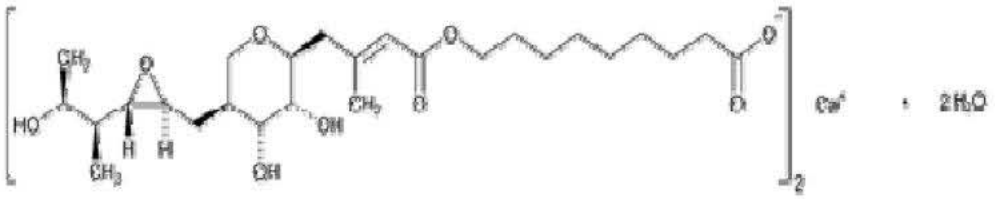
16. **CHEMICAL NAME(s), STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Nonanoic acid, 9-[[3-Methyl-1-oxo-4-[tetrahydro-3,4-dihydroxy-5-[[3-(2-hydroxy-1-methylpropyl) oxiranyl]methyl]-2*H* -pyran-2-yl]-2-butenyl]oxy-, calcium salt (2:1), dihydrate, [2*S* -[2α(*E*),3β,4β,5α[2*R* *,3*R* *(1*R* *,2*R* *)]]]-.

OR

(α*E*,2*S*,3R,4R,5S)-5-[(2*S*,3*S*,4*S*,5*S*)-2,3-Epoxy-5-hydroxy-4-ethylhexyl]tetrahydro-3,4-dihydroxy-β-methyl-2*H* -pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid, calcium salt (2:1), dihydrate.

USAN: Mupirocin Calcium
Chemical formula: $C_{52}H_{86}CaO_{18} \cdot 2H_2O$
Molecular weight: 1075.34
CAS number: [115074-43-6]
Chemical structure:



17. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
(b) (4)	II		(b) (4)	1	adequate	22-October-2012	R. Chang
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. **STATUS:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	22-JUN-2012	A. Inyard
Methods Validation	Not required		
Labeling	Acceptable	10/22/12	B. Wetzman
Bioequivalence	Acceptable-Biometrics Acceptable-Bioequivalence	09/27/2012 10/26/2012	H. Li S. Seung
EA	Categorical exclusion		
Radiopharmaceutical	N/A		

19. **ORDER OF REVIEW**
The application submission(s) covered by this review was taken in the date order of receipt.
__x__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 201587

The Chemistry Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Mupirocin Calcium Cream is a white cream that contains 2.15% w/w mupirocin calcium dihydrate (equivalent to 2.0% mupirocin free acid) in an oil and water-based emulsion. The inactive ingredients are benzyl alcohol, (b) (4) (b) (4), mineral oil, phenoxyethanol, purified water, (b) (4) and xanthan gum. The molecular formula of mupirocin calcium is $(C_{26}H_{43}O_9)_2Ca \cdot 2H_2O$, and the molecular weight is 1075.3. The molecular weight of mupirocin free acid is 500.6.

Mupirocin Calcium Cream is indicated for the treatment of secondarily infected traumatic skin lesions (up to 10 cm in length or 100 cm^2 in area) due to susceptible strains of S. aureus and S. pyogenes.

The drug product is to be stored at 20°-25°C (68° -77°F). Do not freeze.

B. Description of How the Drug Product is Intended to be Used

A small amount of Mupirocin Calcium Cream should be applied to the affected area three times daily for 10 days. The area treated may be covered with gauze dressing if desired. Patients not showing a clinical response within 3 to 5 days should be re-evaluated.

Maximum Daily Dose (MDD) Calculations:

MDD calculation for Mupirocin Calcium Crema, 2% is based on the pack sizes in the market (i.e., 15 gram and 30 gram tubes). (b) (4)

(b) (4)

C. Basis for approvability or Not-approval Recommendation

The ANDA is approvable.

Following this page, 36 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

II. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION

satisfactory
The applicant requests a categorical exclusion from the preparation of an Environmental Assessment as provided under 21 CFR 25.31 (a). The firm also certifies that they are in compliance with the applicable federal, state and local environmental statutes and regulatory requirements. Signed certification is provided.

III. LIST OF DEFICIENCIES TO BE COMMUNICATED (none)

cc: ANDA 201587
ANDA DUP 201587
DIV FILE
Field Copy

Endorsement (Draft and Final with Dates):
HFD-627/R. Chang/December 12, 2012

HFD-627/James Fan/12/13/12

HFD-617/T. Trang/12/17/12

V:\Chemistry Division I\Team 13\FIRMSAM\GLENMARK\LTRS&REV\201587.R02addendum2.doc

TYPE OF LETTER: ANDA is Approvable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD R CHANG
12/17/2012

TRANG Q TRAN
12/17/2012

JAMES M FAN
12/17/2012

ANDRE S RAW
12/18/2012

ANDA 201587

Mupirocin Calcium Cream USP, 2%

Glenmark Generics Inc. USA

Richard Chang, Ph.D.
OGD/DCI

Chemistry Review #2 addendum

Table of Contents

Chemistry Review Data Sheet

1. **ANDA #** 201587

2. **REVIEW #:** 2 addendum

3. **REVIEW DATE:** 22-October-2012

4. **REVIEWER:** Richard Chang

5. **PREVIOUS DOCUMENTS:** N/A

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	**Document Date**
Original	22-Feb-2010
Acceptable for filing	23-Feb-2010
Amendment	16-Aug-2011

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Glenmark Generics Ltd.
US Agent:	Glenmark Generics Inc., USA William McIntyre, Ph.D.
Address:	750 Corporate Drive Mahwah, NJ 07430
Telephone:	(201) 684-8017

8. **DRUG PRODUCT NAME/CODE/TYPE:**

   a) Proprietary Name: N/A
   b) Non-Proprietary Name (USAN): Mupirocin Calcium Cream USP, 2%

9. **LEGAL BASIS FOR SUBMISSION:**

The basis for Glenmark's ANDA for Mupirocin Cream USP, 2%, is the approved reference listed drug, Bactroban® (mupirocin calcium) cream, 2%. As provided in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations, current through December 2007, (Section **1.3.5.1** Patent Information)), Bactroban® (mupirocin calcium) cream, 2%. is the subject of NDA # 050746, which was approved on December 11, 1997 and is held by Glaxosmithkline.
According to the information published in the Electronic Orange Book, current through September 2008, there are no unexpired patents and there is no unexpired exclusivity for Bactroban® (mupirocin calcium) cream, 2%.

Patent certification: The firm has provided a Paragraph II certification

10. **PHARMACOL. CATEGORY:**
Indicated for the treatment of secondarily infected traumatic skin lesions due to susceptible strains of S. aureus and S. pyogenes

11. **DOSAGE FORM:** Cream

12. **STRENGTH/POTENCY:** 2%

13. **ROUTE OF ADMINISTRATION:** Topical

14. **Rx/OTC DISPENSED:** _x_ **Rx** ___ **OTC**

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)**

_____SPOTS product – Form Completed

___x__Not a SPOTS product

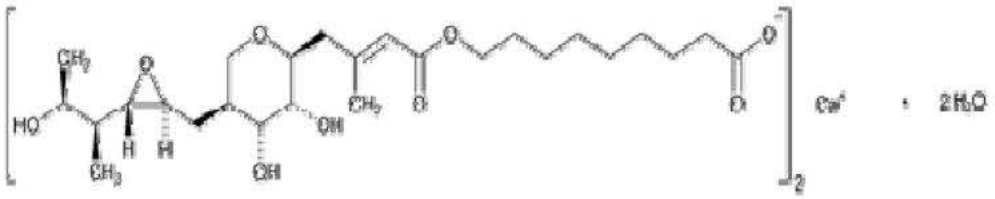
16. **CHEMICAL NAME(s), STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Nonanoic acid, 9-[[3-Methyl-1-oxo-4-[tetrahydro-3,4-dihydroxy-5-[[3-(2-hydroxy-1-methylpropyl) oxiranyl]methyl]-2*H* -pyran-2-yl]-2-butenyl]oxy-, calcium salt (2:1), dihydrate, [2*S* -[2α(*E*),3β,4β,5α[2*R* *,3*R* *(1*R* *,2*R* *)]]]-.

OR

(α*E*,2*S*,3R,4R,5S)-5-[(2*S*,3*S*,4*S*,5*S*)-2,3-Epoxy-5-hydroxy-4-ethylhexyl]tetrahydro-3,4-dihydroxy-β-methyl-2*H* -pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid, calcium salt (2:1), dihydrate.

USAN: Mupirocin Calcium
Chemical formula: $C_{52}H_{86}CaO_{18} \cdot 2H_2O$
Molecular weight: 1075.34
CAS number: [115074-43-6]
Chemical structure:



17. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
(b) (4)	II		(b) (4)	1	adequate	22-October-2012	R. Chang
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. **STATUS:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	22-JUN-2012	A. Inyard
Methods Validation	Not required		
Labeling	Acceptable	10/22/12	B. Wetzman
Bioequivalence	Acceptable-Biometrics Acceptable-Bioequivalence	09/27/2012 10/26/2012	H. Li S. Seung
EA	Categorical exclusion		
Radiopharmaceutical	N/A		

19. **ORDER OF REVIEW**
The application submission(s) covered by this review was taken in the date order of receipt.
__x__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 201587

The Chemistry Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Mupirocin Calcium Cream is a white cream that contains 2.15% w/w mupirocin calcium dihydrate (equivalent to 2.0% mupirocin free acid) in an oil and water-based emulsion. The inactive ingredients are benzyl alcohol, (b) (4) (b) (4), mineral oil, phenoxyethanol, purified water, (b) (4) and xanthan gum. The molecular formula of mupirocin calcium is $(C_{26}H_{43}O_9)_2Ca \cdot 2H_2O$, and the molecular weight is 1075.3. The molecular weight of mupirocin free acid is 500.6.

Mupirocin Calcium Cream is indicated for the treatment of secondarily infected traumatic skin lesions (up to 10 cm in length or 100 cm^2 in area) due to susceptible strains of S. aureus and S. pyogenes.

The drug product is to be stored at 20°-25°C (68° -77°F). Do not freeze.

B. Description of How the Drug Product is Intended to be Used

A small amount of Mupirocin Calcium Cream should be applied to the affected area three times daily for 10 days. The area treated may be covered with gauze dressing if desired. Patients not showing a clinical response within 3 to 5 days should be re-evaluated.

Maximum Daily Dose (MDD) Calculations:

MDD calculation for Mupirocin Calcium Crema, 2% is based on the pack sizes in the market (i.e., 15 gram and 30 gram tubes). (b) (4)

(b) (4)

C. Basis for approvability or Not-approval Recommendation

The ANDA is approvable.

Following this page, 36 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

II. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION

satisfactory
The applicant requests a categorical exclusion from the preparation of an Environmental Assessment as provided under 21 CFR 25.31 (a). The firm also certifies that they are in compliance with the applicable federal, state and local environmental statutes and regulatory requirements. Signed certification is provided.

III. LIST OF DEFICIENCIES TO BE COMMUNICATED (none)

cc: ANDA 201587
ANDA DUP 201587
DIV FILE
Field Copy

Endorsement (Draft and Final with Dates):
HFD-627/R. Chang/October 22, 2012

HFD-627/James Fan/

HFD-617/T. Trang/11/1/12

V:\Chemistry Division I\Team 13\FIRMSAM\GLENMARK\LTRS&REV\201587.R02addendum.doc

TYPE OF LETTER: ANDA is Approvable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD R CHANG
11/04/2012

TRANG Q TRAN
11/05/2012

JAMES M FAN
11/05/2012

ANDRE S RAW
11/07/2012

ANDA 201587

Mupirocin Calcium Cream USP, 2%

Glenmark Generics Inc. USA

Richard Chang, Ph.D.
OGD/DCI

Chemistry Review #2

Table of Contents

Chemistry Review Data Sheet

1. **ANDA #** 201587

2. **REVIEW #:** 2

3. **REVIEW DATE:** 18-August-2011

4. **REVIEWER:** Richard Chang

5. **PREVIOUS DOCUMENTS:** N/A

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	**Document Date**
Original	22-Feb-2010
Acceptable for filing	23-Feb-2010
Amendment	16-Aug-2011

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Glenmark Generics Inc. USA
Address:	750 Corporate Drive Mahwah, NJ 07430
Name:	Glenmark Generics Inc., USA
US Contact:	William McIntyre, Ph.D.
Address:	750 Corporate Drive Mahwah, NJ 07430
Telephone:	(201) 684-8017

8. **DRUG PRODUCT NAME/CODE/TYPE:**

   a) Proprietary Name: N/A
   b) Non-Proprietary Name (USAN): Mupirocin Calcium Cream USP, 2%

9. **LEGAL BASIS FOR SUBMISSION:**

The basis for Glenmark's ANDA for Mupirocin Cream USP, 2%, is the approved reference listed drug, Bactroban® (mupirocin calcium) cream, 2%. As provided in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations, current through December 2007, (Section **1.3.5.1** Patent Information)), Bactroban® (mupirocin calcium) cream, 2%. is the subject of NDA # 050746, which was approved on December 11, 1997 and is held by Glaxosmithkline.
According to the information published in the Electronic Orange Book, current through September 2008, there are no unexpired patents and there is no unexpired exclusivity for Bactroban® (mupirocin calcium) cream, 2%.

Patent certification: The firm has provided a Paragraph II certification

10. **PHARMACOL. CATEGORY:**
Indicated for the treatment of secondarily infected traumatic skin lesions due to susceptible strains of S. aureus and S. pyogenes

11. **DOSAGE FORM:** Cream

12. **STRENGTH/POTENCY:** 2%

13. **ROUTE OF ADMINISTRATION:** Topical

14. **Rx/OTC DISPENSED:** _x_ **Rx** ___ **OTC**

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)**

_____SPOTS product – Form Completed

___x__Not a SPOTS product

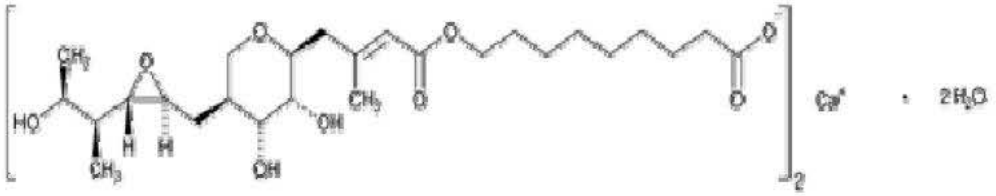
16. **CHEMICAL NAME(s), STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Nonanoic acid, 9-[[3-Methyl-1-oxo-4-[tetrahydro-3,4-dihydroxy-5-[[3-(2-hydroxy-1-methylpropyl) oxiranyl]methyl]-2*H* -pyran-2-yl]-2-butenyl]oxy-, calcium salt (2:1), dihydrate, [2*S* -[2α(*E*),3β,4β,5α[2*R* *,3*R* *(1*R* *,2*R* *)]]]-.

OR

(α*E*,2*S*,3R,4R,5S)-5-[(2*S*,3*S*,4*S*,5*S*)-2,3-Epoxy-5-hydroxy-4-ethylhexyl]tetrahydro-3,4-dihydroxy-β-methyl-2*H* -pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid, calcium salt (2:1), dihydrate.

USAN: Mupirocin Calcium
Chemical formula: $C_{52}H_{86}CaO_{18} \cdot 2H_2O$
Molecular weight: 1075.34
CAS number: [115074-43-6]
Chemical structure:



17. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
(b) (4)	II	(b) (4)		1	adequate	15-April-2011	R. Chang
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. **STATUS:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	acceptable	25-May-2010	A. Inyard
Methods Validation	Not required		
Labeling	Pending		
Bioequivalence	pending		
EA	Categorical exclusion		
Radiopharmaceutical	N/A		

19. **ORDER OF REVIEW**

The application submission(s) covered by this review was taken in the date order of receipt.

__x__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 201587

The Chemistry Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is approvable (CMC)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Mupirocin Calcium Cream is a white cream that contains 2.15% w/w mupirocin calcium dihydrate (equivalent to 2.0% mupirocin free acid) in an oil and water-based emulsion. The inactive ingredients are benzyl alcohol, (b) (4) (b) (4) mineral oil, phenoxyethanol, purified water, (b) (4) and xanthan gum. The molecular formula of mupirocin calcium is $(C_{26}H_{43}O_9)_2Ca \cdot 2H_2O$, and the molecular weight is 1075.3. The molecular weight of mupirocin free acid is 500.6.

Mupirocin Calcium Cream is indicated for the treatment of secondarily infected traumatic skin lesions (up to 10 cm in length or 100 cm^2 in area) due to susceptible strains of S. aureus and S. pyogenes.

The drug product is to be stored at 20°-25°C (68° -77°F). Do not freeze.

B. Description of How the Drug Product is Intended to be Used

A small amount of Mupirocin Calcium Cream should be applied to the affected area three times daily for 10 days. The area treated may be covered with gauze dressing if desired. Patients not showing a clinical response within 3 to 5 days should be re-evaluated.

Maximum Daily Dose (MDD) Calculations:

MDD calculation for Mupirocin Calcium Crema, 2% is based on the pack sizes in the market (i.e., 15 gram and 30 gram tubes). (b) (4)

(b) (4)

C. Basis for approvability or Not-approval Recommendation

The ANDA is approvable (CMC).

Following this page, 36 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

II. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION

satisfactory
The applicant requests a categorical exclusion from the preparation of an Environmental Assessment as provided under 21 CFR 25.31 (a). The firm also certifies that they are in compliance with the applicable federal, state and local environmental statutes and regulatory requirements. Signed certification is provided.

III. LIST OF DEFICIENCIES TO BE COMMUNICATED (none)

cc: ANDA 201587
ANDA DUP 201587
DIV FILE
Field Copy

Endorsement (Draft and Final with Dates):
HFD-627/R. Chang/September 05, 2011

HFD-627/James Fan/9/9/11

HFD-617/T. Trang/9/15/11

V:\Chemistry Division I\Team 13\FIRMSAM\GLENMARK\LTRS&REV\201587.R02.doc

TYPE OF LETTER: Approvable (CMC)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD CHANG
09/15/2011

TRANG Q TRAN
09/15/2011

JAMES M FAN
09/16/2011

ANDA 201587

Mupirocin Calcium Cream USP, 2%

Glenmark Generics Inc. USA

Richard Chang, Ph.D.
OGD/DCI

Chemistry Review #1

Table of Contents

Chemistry Review Data Sheet

1. **ANDA #** 201587

2. **REVIEW #:** 1

3. **REVIEW DATE:** 18-April-2011

4. **REVIEWER:** Richard Chang

5. **PREVIOUS DOCUMENTS:** N/A (review #1)

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	**Document Date**
Original	22-Feb-2010
Acceptable for filing	23-Feb-2010

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Glenmark Generics Inc. USA
Address:	750 Corporate Drive Mahwah, NJ 07430
Name:	Glenmark Generics Inc., USA
US Contact:	William McIntyre, Ph.D.
Address:	750 Corporate Drive Mahwah, NJ 07430
Telephone:	(201) 684-8017

8. **DRUG PRODUCT NAME/CODE/TYPE:**

   a) Proprietary Name: N/A
   b) Non-Proprietary Name (USAN): Mupirocin Calcium Cream USP, 2%

9. **LEGAL BASIS FOR SUBMISSION:**

The basis for Glenmark's ANDA for Mupirocin Cream USP, 2%, is the approved reference listed drug, Bactroban® (mupirocin calcium) cream, 2%. As provided in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations, current through December 2007, (Section **1.3.5.1** Patent Information)), Bactroban® (mupirocin calcium) cream, 2%. is the subject of NDA # 050746, which was approved on December 11, 1997 and is held by Glaxosmithkline.
According to the information published in the Electronic Orange Book, current through September 2008, there are no unexpired patents and there is no unexpired exclusivity for Bactroban® (mupirocin calcium) cream, 2%.

Patent certification: The firm has provided a Paragraph II certification

10. **PHARMACOL. CATEGORY:**
Indicated for the treatment of secondarily infected traumatic skin lesions due to susceptible strains of S. aureus and S. pyogenes

11. **DOSAGE FORM:** Cream

12. **STRENGTH/POTENCY:** 2%

13. **ROUTE OF ADMINISTRATION:** Topical

14. **Rx/OTC DISPENSED:** _x_ **Rx** ___ **OTC**

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)**

_____SPOTS product – Form Completed

___x__Not a SPOTS product

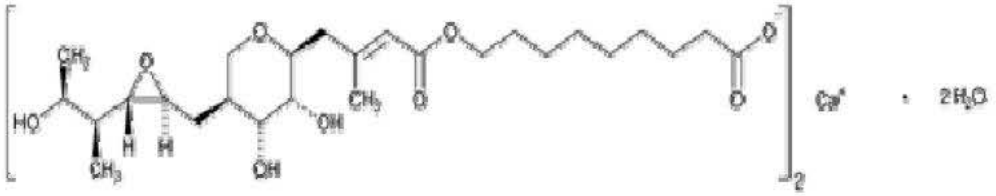
16. **CHEMICAL NAME(s), STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Nonanoic acid, 9-[[3-Methyl-1-oxo-4-[tetrahydro-3,4-dihydroxy-5-[[3-(2-hydroxy-1-methylpropyl) oxiranyl]methyl]-2*H* -pyran-2-yl]-2-butenyl]oxy-, calcium salt (2:1), dihydrate, [2*S* -[2α(*E*),3β,4β,5α[2*R* *,3*R* *(1*R* *,2*R* *)]]]-.

OR

(α*E*,2*S*,3R,4R,5S)-5-[(2*S*,3*S*,4*S*,5*S*)-2,3-Epoxy-5-hydroxy-4-ethylhexyl]tetrahydro-3,4-dihydroxy-β-methyl-2*H* -pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid, calcium salt (2:1), dihydrate.

USAN: Mupirocin Calcium
Chemical formula: $C_{52}H_{86}CaO_{18} \cdot 2H_2O$
Molecular weight: 1075.34
CAS number: [115074-43-6]
Chemical structure:



17. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
(b) (4)	II		(b) (4)	1	adequate	15-April-2011	R. Chang
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. **STATUS:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	acceptable	25-May-2010	A. Inyard
Methods Validation	Not required		
Labeling	Pending		
Bioequivalence	pending		
EA	Categorical exclusion		
Radiopharmaceutical	N/A		

19. **ORDER OF REVIEW**

The application submission(s) covered by this review was taken in the date order of receipt.

__x__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 201587

The Chemistry Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is not approvable at this time

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Mupirocin Calcium Cream is a white cream that contains 2.15% w/w mupirocin calcium dihydrate (equivalent to 2.0% mupirocin free acid) in an oil and water-based emulsion. The inactive ingredients are benzyl alcohol, (b) (4) (b) (4) mineral oil, phenoxyethanol, purified water, (b) (4), and xanthan gum. The molecular formula of mupirocin calcium is $(C_{26}H_{43}O_9)_2Ca \cdot 2H_2O$, and the molecular weight is 1075.3. The molecular weight of mupirocin free acid is 500.6.

Mupirocin Calcium Cream is indicated for the treatment of secondarily infected traumatic skin lesions (up to 10 cm in length or 100 cm^2 in area) due to susceptible strains of S. aureus and S. pyogenes.

The drug product is to be stored at 20°-25°C (68° -77°F). Do not freeze.

B. Description of How the Drug Product is Intended to be Used

A small amount of Mupirocin Calcium Cream should be applied to the affected area three times daily for 10 days. The area treated may be covered with gauze dressing if desired. Patients not showing a clinical response within 3 to 5 days should be re-evaluated.

Maximum Daily Dose (MDD) Calculations:

MDD calculation for Mupirocin Calcium Crema, 2% is based on the pack sizes in the market (i.e., 15 gram and 30 gram tubes). (b) (4)

(b) (4)

C. Basis for approvability or Not-approval Recommendation

The ANDA is non-approvable based on the cited deficiencies (see review for more details).

APPEARS THIS WAY ON ORIGINAL

Following this page, 48 Pages Withheld in Full as (b)(4)

I.

II. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION

satisfactory
The applicant requests a categorical exclusion from the preparation of an Environmental Assessment as provided under 21 CFR 25.31 (a). The firm also certifies that they are in compliance with the applicable federal, state and local environmental statutes and regulatory requirements. Signed certification is provided.

III. LIST OF DEFICIENCIES TO BE COMMUNICATED (see Deficiency letter attached).

Chemistry Comments to be provided to the Applicant.

ANDA: 201587 APPLICANT: Glenmark Generics Inc. USA

DRUG PRODUCT: Mupirocin Cream USP, 2%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)

1.

2.

3.

4.

5.

6.

7.

8.

(b) (4)

9.

10

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Information related to the bioequivalence and labeling is under review. After the reviews are completed, any deficiencies found will be communicated to you under separate covers.

2. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval.

3. Please provide all available long-term drug product stability data.

4. We note that your ANDA was submitted in hard copy paper format for Module 3. We encourage you to submit your future ANDAs (and amendments) using the electronic gateway in order to facilitate the prompt review of your applications.

Sincerely yours,

{See appended electronic signature page}

Paul Schwartz, Ph.D.
Acting Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 201587
ANDA DUP 201587
DIV FILE
Field Copy

Endorsement (Draft and Final with Dates):
HFD-627/R. Chang/May 05, 2011, 06/30/11

HFD-627/James Fan/6/2/11

HFD-617/T. Trang/6/3/11

V:\Chemistry Division I\Team 13\FIRMSAM\GLENMARK\LTRS&REV\201587.R01.doc

TYPE OF LETTER: Not Approvable

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD CHANG
07/05/2011

TRANG Q TRAN
07/06/2011

JAMES M FAN
07/07/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201587

STATISTICAL REVIEWS

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

ANDA/Serial Number:	201587
Drug Name:	Mupirocin Cream USP, 2%
Indication(s):	Treatment of secondarily infected traumatic skin lesion
Reference Listed Drug:	Bactroban® (mupirocin calcium cream), GlaxoSmithKline
Applicant:	Glenmark Generics Inc.
Date(s):	Submitted: 4/27/2012
Biometrics Division:	DB6
Statistical Reviewer:	Huaixiang Li, Ph.D.
Concurring Reviewers:	Stella Grosser, Ph.D.
Medical Division:	Division of Clinical Review (DCR)/OGD
Clinical Team:	Sarah H. Seung, Pharm.D.
Keywords:	Bioequivalence, secondarily infected traumatic skin lesion, success rate

TABLE OF CONTENTS

List of Tables

1 Executive Summary

1.1 Conclusions and Recommendations

The equivalence test passed for primary and secondary endpoints for the FDA's per-protocol (FPP) population. The two active products are statistically significantly better than the placebo for primary and secondary endpoints for the FDA's intent-to-treat (FITT) population except for one secondary endpoint. The active products were better, but not statistically significantly better than placebo for the clinical success rate at visit 3 (end of treatment) for FITT population (see 1.2, below).

1.2 Brief Overview of the Clinical Study

Objectives

Study GLK 605 compared generic Mupirocin Calcium Cream, 2% to Bactroban Cream® (mupirocin calcium cream), 2%, and both active treatments to a vehicle control, in the treatment of secondarily infected traumatic skin lesions.

Design

This was a 17-day, multi-center, double-blind, randomized, vehicle-controlled, parallel-group study in patients 18 months of age or older with a diagnosis of secondarily infected skin lesions (up to 10 cm in length or 100 cm^2 in area) due to susceptible strains of *Staphylococcus aureus* and/or *Streptococcus pyogenes*, to compare the efficacy of generic Mupirocin Calcium Cream, 2% (Test) versus Bactroban Cream® (mupirocin calcium cream), 2% (Reference), and their efficacy over the Vehicle Cream (Placebo). The study consisted of a Screening/Baseline visit (Visit 1, Day 1), an On Treatment visit (Visit 2/Day 4), an End of Treatment visit (Visit 3/Day 10), and a Follow-up visit (Visit 4/Day 17).

Six hundred fifty-six (656) patients were randomly assigned in a 1:1:1 ratio to one of the three study formulations. Patients applied study medication topically three times daily for 10 days.

The primary endpoint was clinical success rate as determined at the follow-up visit (Visit 4).

There were three secondary endpoints:

Clinical success rate at the end of treatment visit (Visit 3)
Bacteriological success rate at the end of treatment visit (Visit 3)
Bacteriological success rate at the follow-up visit (Visit 4)

1.3 Statistical issues and findings

The efficacy analysis was carried out using the FDA Intend-to-Treat (FITT) population. The test and reference products were statistically significantly better than placebo for the clinical success rate at visit 4 (follow-up visit) with rates of 79.65% (test), 80.36% (reference), and 57.76% (placebo). They were better, but not statistically significantly better than placebo at visit 3 (end of treatment). The test and reference products were statistically significantly better than placebo for the bacteriological success rate at visit 4 (follow-up visit) and at visit 3 (end of treatment).

The test and reference products were found to be clinically equivalent for the clinical and bacteriological success rates at visit 4 (follow-up visit) and visit 3 (end of treatment) for the FDA Per-Protocol (FPP) population. The clinical success rates at visit 4 (follow-up visit) were 79.28% (test) and 79.81 (reference).

2 Introduction

2.1 Overview

Mupirocin is an antibacterial agent active against a wide range of gram positive bacteria and has become a recognized topical treatment for impetigo since the approval of Bactroban® Ointment (NDA 050591). In 1997, the FDA approved Bactroban® Cream (NDA 050746) for the topical treatment of secondarily infected traumatic skin lesions (up to 10 cm in length or 100 cm^2 in area) due to susceptible strains of *Staphylococcus aureus* and *Streptococcus pyogenes*. The approved labeling recommends three times daily application to the affected area for 10 days. Patients not showing a clinical response within 3 to 5 days should be re-evaluated. The safety and effectiveness for pediatric use (aged 3 months to 16 years) was demonstrated to be similar to adult patients. Only headache was thought to be possibly or probably related to Bactroban® Cream in children.

Remark

Original submission was received on February 22, 2010.

On April 27, 2012, Glenmark submitted an amendment in response to OGD "Request for Information" letter on 10/17/2011 and a deficiency letter on 3/8/2012.

The amendment on 4/27/2012 was carried out as below.

- Evaluable Subject is a subject who has data collected on either type and/or cause of wound that clearly denotes the secondarily infected wound was not a result of an insect bite. (Note: a subject who does not have data collected for both type and cause of wound is considered non-evaluable).
- Clinical Success/Cure: complete resolution (SIRS scores of 0) of signs and symptoms of infection. No additional antibiotic therapy required after End of Treatment.
- The inclusion criterion for baseline SIRS total score is a total score of at least 8.
- Compliance is generally defined as 75% to 125% of the scheduled applications.

- Visit window for visit 4 is defined as ±4 days.

On July 18 and 20, 2012, Glenmark submitted additional amendment and updated SAS datasets in response to OGD "Request for Information" letter on 7/3/2012.

The amendment on 7/18/2012 provided the information:

- A copy of the original source document and an English translated copy, if the source document is written in a foreign language, for the following 18 patients : Patient (b) (6) (b) (6). For these patients, the cause of the wound has been identified as “scratching”. Information on the original wound, which leads to the “scratching”, is needed to determine the patient’s status for the pre-protocol population.
- Summary datasets reflecting all the changes noted in the sponsor’s April 27, 2012 Clinical Bioequivalence Amendment in electronic (*.xpt) format.

The amendment on 7/20/2012 provided all the XPT files (specifically the formatted data) based on OGD "Request for Information" letter on 7/3/2012.

2.2 Data Sources

The data were submitted electronically. The data files are located in the following directory:

\\cdsesub1\EVSPROD\ANDA201587**0005**\m5\datasets\glk605\tabulations\

3 Statistical Evaluation

3.1 Statistical Methodologies

Binary endpoint

The clinical and bacteriological success rates based on the 100% clearance of all lesions and culture within the treatment area at Visit 4/Day17 and at Visit 3/Day10 in the FITT/FPP populations were used for the statistical analysis.

Efficacy Analysis

Tests for superiority of each active treatment over the placebo were conducted using a two-sided Fisher’s exact test at the 5% level of significance. The efficacy of each active treatment was tested separately by comparing it with the placebo. The active treatment should be better than placebo.

Equivalence Analysis

Based on the usual method used in the Office of Generic Drugs (OGD) for binary outcomes, the 90% confidence interval for the difference in proportions between the test and reference treatments should be contained within -0.20 to 0.20 in order to establish equivalence.

The compound hypothesis to be tested is:

H_0: $p_T - p_R < -0.20$

or $p_T - p_R > 0.20$

versus

H_A : $-0.20 \leq p_T - p_R \leq 0.20$

where

p_T = success rate of test treatment and p_R = success rate of reference treatment.

Let

n_T = sample size of test treatment, n_R = sample size of reference treatment,

and

$$se = (\hat{p}_T(1-\hat{p}_T)/n_T + \hat{p}_R(1-\hat{p}_R)/n_R)^{1/2}$$

where

$\hat{p}_T$ = observed success rates for the test treatment and

$\hat{p}_R$ = observed success rates for the reference treatment.

The 90% confidence interval for the difference in proportions between test and reference was calculated as follows, using Yates' correction:

$$L = (\hat{p}_T - \hat{p}_R) - 1.645\ se - (1/n_T + 1/n_R)/2$$
$$U = (\hat{p}_T - \hat{p}_R) + 1.645\ se + (1/n_T + 1/n_R)/2$$

We reject H_0 if $L \geq -0.20$ and $U \leq 0.20$. Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

3.2 Study Design and Endpoints

Objectives

To evaluate the therapeutic equivalence and safety of the Test Product, Mupirocin Cream USP, 2% (Glenmark Generics Inc.), and the Reference Product, Bactroban® (mupirocin calcium

cream) Gel, 3% (GlaxoSmithKline), in the treatment of secondarily infected traumatic skin lesions.

To demonstrate the superiority of the efficacy of the Test and Reference Products over the vehicle control (Glenmark Generics Inc.) in the treatment of secondarily infected traumatic skin lesions.

Design

The study GLK 605 was a multicenter, double-blind, randomized, vehicle-controlled, parallel-group study. There were a total of four study visits: Baseline visit (Visit 1/Day 1), On treatment visit (Visit 2/Day 4), End of treatment visit (Visit 3/Day 10), and a Follow-up/Early Discontinuation visit (Visit 4/Day 17).

Treatments

Six hundred fifty-six (656) patients satisfying all inclusion/exclusion criteria were randomly assigned in a 1:1:1 ratio to one of the three study formulations. Patients applied study medication topically three times daily for 10 days.

Article	Description
Test (TRT A)	Mupirocin Cream USP, 2% (Glenmark Generics Inc.) Lot Number: Q15748002
Reference (TRT B)	Bactroban ® (mupirocin calcium cream), 2% (GlaxoSmithKline) Lot numbers: C328473
Placebo (TRT C)	PlaceboVehicle (Glenmark Generics Inc.) Lot Number: QP15748001

Outcome Variables

The investigator or sub-investigator assessed clinical signs of the wound at each visit using the Skin Infection Rating Scale (SIRS) for each of the signs: exudate/pus, crusting, erythema/inflammation, tissue warmth, and edema. Symptoms (itching and pain) were scored by the patient.

Skin Infection Rating Scale (per Sponsor)*

Score	Description
0	Absent; no evidence of sign/symptom
1	Mild; sign/symptom present but not intense
2	Moderate; sign/symptom clearly evident and somewhat bothersome to patient
3	Severe; sign/symptom clearly evident, intense and extremely bothersome to patient

* From Sponsor's Protocol GLK 605 version 1.0 Appendix IV.

Bacteriological response was measured at visit 3 (end of treatment) and at visit 4 (follow-up). The response was recorded as 1 = Presumed Eradication, 2 = Super Infection, 3 = Failure, 4 = Relapse, and 5 = Unable to determine.

Endpoints

The primary endpoint was clinical success rate at the follow-up visit (Visit 4)

There were three secondary endpoints:

Clinical success rate at the end of treatment visit (Visit 3)
Bacteriological success rate at the follow-up visit (Visit 4)
Bacteriological success rate at the end of treatment visit (Visit 3)

Clinical success/cure is defined as complete resolution (SIRS scores of 0) of signs and symptoms of infection. No additional antibiotic therapy required after End of Treatment.

Bacteriological success/cure is defined as elimination of *Staphylococcus aureus* and *Streptococcus pyogenes*, or, response was such that no culture material was available and therefore there was evidence of pathogen eradication.

3.3 Patient Disposition

Six hundred and fifty-six (656) patients were enrolled and randomized. The sponsor's MITT and PP populations had 341 and 337 patients respectively. The FDA's ITT (same as MITT) and PP populations had 335 and 331 patients respectively.

The patient disposition for the sponsor's and the FDA's populations are given in Table 1.

Table 1 Patient disposition - Sponsor's MITT and PP, FDA's FITT and FPP Populations*

	Test	Reference	Placebo	Total
Enrolled and Randomized	**220**	**217**	**219**	**656**
Total sponsor's MITT population (MITT)	**113**	**112**	**116**	**341**
Total exclusion from the sponsor's MITT population	107	105	103	315
Reason for exclusion from sponsor's MITT				
Total baseline scores less than 8	61	58	63	182
Cause of wound by scratching of insect bite	9	9	9	27
Cause of wound not available	11	15	12	38
Violation of inclusion/exclusion criteria	26	23	19	68
Total sponsor's PP population (PP)	**111**	**111**	**115**	**337**
Total Exclusion from the sponsor's PP population	109	106	104	319
Reason for exclusion from sponsor's PP				
Excluded from MITT population	107	105	103	315
Out of visit window at visit 4	1	1		2
Protocol violation	1			1
Not compliance			1	1
Total FDA's ITT population (FITT)	**113**	**110**	**112**	**335**
Total Exclusion from the FDA's FITT population	107	107	107	321
Reason for exclusion from FDA's FITT				
Exclusion from sponsor's MITT	107	105	103	315
Cause of wound by scratching and subsequent infection[#1]		2	4	6
Total FDA's PP population (FPP)	**111**	**109**	**111**	**331**
Total Exclusion from the FDA's PP population	109	108	108	325
Reason for exclusion from FDA's FPP				
Exclusion from sponsor's PP	109	106	104	319
Cause of wound by scratching and subsequent infection[#1]		2	4	6

*: Patient may have multiple reasons to be excluded from the MITT, PP, FITT, and FPP populations.

[redacted] (b) (6) had the original wound, which lead to the "scratching" and subsequent infection, based on the information in July 18, 2012 amendment. These patients should be excluded from FITT and FPP populations.

3.4 Demographics and Baseline

The demographic characteristics and baseline scores for the FITT population at baseline are presented below. Gender and race were analyzed using a Chi-square test. Age was analyzed using a general linear model (GLM). There is no statistically significant difference in the three treatments. Demographic and baseline characteristics for the FPP population were similar to that of the FITT population.

Table 2 Demographic characteristics in the FDA's ITT population

	Test N=113	Reference N=110	Placebo N=112	Total N=335	p-value
Gender					
Female	54	56	44	154	0.1974
Male	59	54	68	181	
Race					
Black or African American	10	15	14	39	0.8415
White	44	42	42	128	
Other	59	53	56	168	
Age (years)					
Mean (STD)	13.6 (11.5)	14.6 (14.0)	13.8 (14.3)	14.0 (13.3)	0.8408
Median	10.8	9.7	9.1	9.6	
Range	1.6 – 64.6	1.7 – 80.8	1.6 – 82.1	1.6 - 82.1	
Total baseline score*					
Mean (STD)	9.58 (1.55)	9.65 (1.41)	9.65 (1.23)	9.63 (1.40)	0.9233
Median	9	9	10	9	
Range	8 – 15	8 - 15	8 - 14	8 - 15	

*: The baseline score was analyzed as continuous variable as an additional check.

An analysis for homogeneity of the total scores at baseline visit for the FITT and FPP populations was performed using the chi-square test. There were differences for FITT (P=0.0308) and FPP (P=0.0302) populations. The P-values of chi-square test were 0.0377 and 0.0409 for test versus reference, 0.2642 and 0.2872 for test versus placebo, 0.0804 and 0.0599 for reference versus placebo for FITT and FPP populations.

Frequency table of the baseline score for FITT and FPP populations

Total score	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**Total**
FITT Population	34	24	31	16	1	3	2	2	113
	23	38	22	15	9	1	1	1	110
	21	29	42	13	3	3	1	0	112
FPP Population	32	24	31	16	1	3	2	2	111
	23	38	21	15	9	1	1	1	109
	20	29	42	13	3	3	1	0	111

3.5 Results and Conclusions

3.5.1 Sponsor's Analysis Results

According to the sponsor's reanalysis in the amendment on 4/27/2012, the test group and the reference group were comparable in regard to clinical success (defined as SIRS scores of 0 for signs and symptoms of infection) at the 7 day follow-up visit (Visit 4). In the revised PP population, 79.3% of the test group and 80.2% of the reference group were considered a clinical success. In this amendment, the sponsor's calculated 90% confidence interval for the difference in clinical success rate between the test group and the reference group in the PP population is (-0.1068, 0.0888) at the 7 day follow-up visit (Visit 4). Both the test group and the reference group continued to show superiority over the placebo group in the revised mITT population at the 7 day follow-up visit/Visit 4 (both $p<0.001$).

The sponsor summarized the results, below, in the amendment on 4/27/2012.

Primary Bioequivalence Reanalysis – Clinical Success at the Follow-Up Visit (Visit 4) in the PP Population (per sponsor)

	Test (N=111)	Reference (N=111)	90% CI[1]
Success (n,%)	88(79.3%)	89(80.2%)	(-10.68, 8.88)

[1] Confidence interval calculated using Wald's method with Yates' continuity correction.
[Sponsor's 4/27/12 Clinical Bioequivalence Amendment Table 2.1].

Primary Superiority Reanalysis – Clinical Success at the Follow-Up Visit (Visit 4) in the mITT Population (per sponsor)

	Test (N=113)	Reference (N=112)	Placebo (N=116)	P-values[1]	
				Test vs Placebo	Reference vs Placebo
Success (n,%)	90 (79.6%)	90 (80.4%)	67 (57.8%)	<0.001	<0.001

[1] P-values for treatment comparisons from two-sided Z-test with Yates' continuity correction.
[Sponsor's 4/27/12 Clinical Bioequivalence Amendment Table 2.1].

Secondary Bioequivalence Analyses using the PP Population (per sponsor)

	Test (N=111)	Reference (N=111)	90% CI[1]
Clinical Success at Visit 3 (n, %)	34 (30.6%)	36 (32.4%)	(-12.96, 9.36)
Presumed Eradication at Visit 4 (n, %)	88 (79.3%)	89 (80.2%)	(-10.68, 8.88)
Presumed Eradication at Visit 3 (n, %)	108 (97.3%)	107 (96.4%)	(-3.86, 5.66)

[1] Confidence interval calculated using Wald's method with Yates' continuity correction.
[Sponsor's 4/27/12 Clinical Bioequivalence Amendment Tables 2.2, 2.3 and 2.4].

Secondary Superiority Analyses using the mITT Population (per sponsor)

	Test (N=113)	Reference (N=112)	Placebo (N=116)	P-values[1]	
				Test vs Placebo	Reference vs Placebo
Clinical Success at Visit 3 (n, %)	35 (31.0%)	36 (32.1%)	33 (28.4%)	0.784	0.643
Presumed Eradication at Visit 4 (n, %)	90 (79.6%)	90 (80.4%)	67 (57.8%)	<0.001	<0.001
Presumed Eradication at Visit 3 (n, %)	110 (97.3%)	108 (96.4%)	93 (80.2%)	<0.001	<0.001

[1] P-values for treatment comparisons from two-sided Z-test with Yates' continuity correction.
[Sponsor's 4/27/12 Clinical Bioequivalence Amendment Tables 2.2, 2.3 and 2.4].

3.5.2 Reviewer's Results

The test and reference products were statistically significantly better than placebo for the clinical success rate at visit 4 (follow-up visit; primary endpoint), better than placebo, but not statistically significantly so, at visit 3 (end of treatment) for the FITT population. The test and reference products were statistically significantly better than placebo for the bacteriological success rate at visit 4 (follow-up visit) and at visit 3 (end of treatment) for the FITT population.

Table 3 Efficacy analyses for the success rate at visit 4 (follow-up visit) and visit 3 (end of treatment) per FDA's ITT population

				P-value*	
Endpoint	Test (N=113)	Reference (N=110)	Placebo (N=112)	Test vs. Placebo	Reference vs. Placebo
Clinical success rate at visit 4[@]	79.65% (N=90)	80.00% (N=88)	58.04% (N=65)	<0.0001	<0.0001
Clinical success rate at visit 3	30.97% (N=35)	30.91% (N=34)	28.57% (N=32)	*0.7710*	*0.7695*
Bacteriological success rate at visit 4	79.65% (N=90)	80.00% (N=88)	58.04% (N=65)	<0.0001	<0.0001
Bacteriological success rate at visit 3	97.35% (N=110)	96.36% (N=106)	80.36% (N=90)	<0.0001	<0.0001

*: P-values were derived from the two-sided Fisher's exact test.
@: Primary endpoint.

The test and reference products were found to be clinically equivalent for the clinical and bacteriological success rates at visit 4 (follow-up visit) and visit 3 (end of treatment) for the FPP population.

Table 4 Equivalence analyses for the success rate at visit 4 (follow-up visit) and visit 3 (end of treatment) per FDA's PP population

Endpoint	Test (N=111)	Reference (N=109)	The 90% CI for the Test and Reference (%)	Is the 90% CI within [-20% , 20%]?
Clinical success rate at visit 4[@]	79.28% (N=88)	79.82% (N=87)	-10.39, 9.32	Yes
Clinical success rate at visit 3	30.63% (N=34)	31.19% (N=34)	-11.72, 10.60	Yes
Bacteriological success rate at visit 4	79.28% (N=88)	79.82% (N=87)	-10.39, 9.32	Yes
Bacteriological success rate at visit 3	97.30% (N=108)	96.33% (N=105)	-3.84, 5.77	Yes

@: Primary endpoint.

4 Conclusions

4.1 Comments on the Sponsor's Analyses

There are some small differences between our analyses and the sponsor's analyses caused by the two sources.

There were small differences between the sponsor's and the FDA's Intent-to-treatment and per-protocol populations. Six patients, two in the reference group and four in the placebo group, had the original wound, which lead to the "scratching" and subsequent infection. They were included in the sponsor's MITT and PP populations, but excluded from the FDA's FITT and FPP populations based on the FDA clinical reviewer's comments.

For efficacy analysis, we used the two-sided Fisher's exact test. The sponsor carried out the treatment comparisons using the two-sided Z-test with Yates' continuity correction.

4.2 Conclusions

Efficacy: The test and reference products were statistically significantly better than placebo for the clinical success rate at visit 4 (follow-up visit) (primary endpoint); and better but not statistically significantly better than placebo at visit 3 (end of treatment) for the FDA's intent-to-treat (FITT) population. The test and reference products were statistically significantly better than placebo for the bacteriological success rate at visit 4 (follow-up visit) and at visit 3 (end of treatment) for the FITT population.

Equivalence: The test and reference products were found to be clinically equivalent for the clinical and bacteriological success rates at visit 4 (follow-up visit) and visit 3 (end of treatment) for the FDA's per-protocol (FPP) population.

_____ _____

Huaixiang Li, Ph.D.
Mathematical Statistician, DB6/OB

Stella C. Grosser, Ph.D.
Team Leader, DB6/OB

_____

Stella G. Machado, Ph.D.
Director, DB6/OB
cc:
HFD-600 John R. Peters, Sarah H. Seung, Nitin K Patel

HFD-705 Stella G. Machado, Donald J. Schuirmann, Stella C. Grosser, Huaixiang Li

HFD-700 Lillian Patrician OB

5 References

Joseph L. Fleiss, Bruce Levin, and MyungHee Cho Paik. (1981). Statistical Methods for Rates and Proportions (2nd edition). New York: Wiley-Interscience.

Clopper, C. and Pearson, S. (1934) The use of confidence or fiducially limits illustrated in the case of the binomial. Biometrika 26: 404-413.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HUAIXIANG LI
09/27/2012

STELLA C GROSSER
09/27/2012

STELLA G MACHADO
09/27/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201587

BIOEQUIVALENCE REVIEWS

Second Addendum to Clinical Review of a Bioequivalence Study with a Clinical Endpoint

ANDA:	201587
Drug Product:	Mupirocin Cream USP, 2%
Sponsor:	Glenmark Generics Inc., USA
Reference Listed Drug (RLD):	Bactroban® Cream, 2% (NDA 050746) Glaxo SmithKline
Original Submission Date:	2/22/10
Original Primary Reviewer:	Sarah H. Seung, Pharm.D.

On 2/22/10, Glenmark Generics Inc., USA (Glenmark) submitted an abbreviated new drug application (ANDA) for Mupirocin Cream USP, 2%. In support for the ANDA, Glenmark conducted a double-blind, randomized, multi-center, parallel-group, placebo controlled study (GLK 605) in the treatment of secondarily infected skin lesions to demonstrate that Glenmark's Mupirocin Cream USP, 2% is bioequivalent to the reference listed drug (RLD), Glaxo SmithKline's Bactroban® (mupirocin calcium) Cream, 2%. In this clinical endpoint bioequivalence (BE) study, Glenmark included patients with secondarily infected insect bites in the study population, which is specified to be an exclusion criterion in the *Draft Guidance for Mupirocin Calcium Cream/Topical EQ 2% Base (revised October 2011)*.

On 10/17/2011, the Division of Clinical Review (DCR) issued a "Request for Information" to Glenmark to "provide a description of the target treatment site for each patient in detail." In their 1/27/12 response, Glenmark was unable to provide this information for patients from 10 of the 13 clinical sites (i.e., 465 patients out of 656 enrolled patients with unknown lesion type).

On 3/8/12, DCR issued a deficiency letter to Glenmark. On 4/27/12, Glenmark submitted a response to the 3/8/12 deficiency letter. In the process of reviewing the 4/27/12 amendment, additional information was requested from Glenmark on 7/2/12. On 7/18/12 and 7/20/12, Glenmark submitted the response to the 7/2/12 Information Request. Based on all the information submitted by Glenmark, DCR recommended approval of the test product, from a clinical bioequivalence perspective (DCR review finalized on 10/26/2012).

In the 10/26/2012 DCR review (Section 2.7: Formulation), the RLD formulation was referenced as follows:

Table 1: RLD Formulation*

Ingredient	Function	RLD (%w/w)
Mupirocin calcium (micronized)	Active	2.15**
Mineral oil, USP		
(b) (4)		
Stearyl alcohol, NF		
Cetyl Alcohol, NF		
Benzyl alcohol, NF		
Xanthan gum, NF		
Purified water, USP		

** Equivalent to 2.0% mupirocin free acid.

Although not referenced in the 10/26/2012 DCR review, the amount of mupirocin calcium listed in the above table was also verified and taken from the RLD label[1]:

> "BACTROBAN CREAM is a white cream that contains 2.15% w/w mupirocin calcium (equivalent to 2.0% mupirocin free acid) in an oil and water-based emulsion. "

However, in the 8/12/11 Supplement-17 submission to the RLD (NDA 050746), the amount of the active ingredient (mupirocin calcium) is noted to be:

> Mupirocin Calcium equivalent to (b) (4) % w/w Mupirocin free acid (Label claim of 2.0% w/w Mupirocin free acid (b) (4) Actual amount to be calculated based on the Mupirocin free acid potency value for the individual Mupirocin Calcium lots.

Although the discrepancy in the reported active ingredient amount in the two references changes the quantitative difference between the RLD and the proposed generic formulation, the study results show no apparent effect of the formulation differences on product performance or safety. Therefore, from a clinical bioequivalence standpoint, this application is recommended for approval

{See appended electronic signature page}

Sarah H. Seung, Pharm.D. Date
Clinical Reviewer, Division of Clinical Review
Office of Generic Drugs
{See appended electronic signature page}

John R. Peters, M.D. Date
Director, Division of Clinical Review
Office of Generic Drugs

[1] http://dailymed nlm nih.gov/dailymed/lookup.cfm?setid=9257f9cd-abaf-4bb2-d9ac-4bc8f65ae558

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SARAH H Seung
01/09/2013

JOHN R PETERS
01/10/2013

Addendum to Review of a Bioequivalence Study with Clinical Endpoints

ANDA# 201587
Mupirocin Cream USP, 2%
Glenmark Generics Inc., USA

Submission Date(s) Reviewed:
April 27, 2012
July 18, 2012
July 20, 2012

Sarah H. Seung, Pharm.D.
Clinical Reviewer
Division of Clinical Review
Office Generic Drugs

Table of Contents

Review of a Bioequivalence Study with Clinical Endpoints for ANDA 201587

1 Executive Summary

On 2/22/10, Glenmark Generics Inc., USA (Glenmark) submitted an abbreviated new drug application (ANDA) for Mupirocin Cream USP, 2%. In support for the ANDA, Glenmark conducted a double-blind, randomized, multi-center, parallel-group, placebo controlled study (GLK 605) in the treatment of secondarily infected skin lesions to demonstrate that Glenmark's Mupirocin Cream USP, 2% (Test) is bioequivalent to the reference listed drug (RLD), Glaxo SmithKline's Bactroban® (mupirocin calcium) Cream, 2% (Reference). In this clinical endpoint bioequivalence (BE) study, Glenmark included patients with secondarily infected insect bites in the study population, which is specified to be an exclusion criterion in the *Draft Guidance for Mupirocin Calcium Cream/Topical EQ 2% Base (revised October 2011)*.

On 10/17/2011, the Division of Clinical Review (DCR) issued a "Request for Information" to Glenmark to "provide a description of the target treatment site for each patient in detail." In their 1/27/12 response, Glenmark was unable to provide this information for patients from 10 of the 13 clinical sites (i.e., 465 patients out of 656 enrolled patients with unknown lesion type).

On 3/8/12, DCR issued a deficiency letter to Glenmark with the following deficiencies identified:

1. The *Draft Guidance for Mupirocin Calcium Cream/Topical EQ 2% Base (revised October 2011)* recommends that "secondarily infected animal/human or insect bite" be excluded from clinical endpoint bioequivalence study for Mupirocin Cream USP, 2%. The study report for Study GLK 605 states that "infections resulting from the scratching of an insect bite were considered secondarily infected traumatic skin lesions." Infections resulting from the scratching of an insect bite are superficial and considered secondarily infected insect bite. Given that patients with secondarily infected insect bites cannot be identified from all clinical sites in order to exclude from the analysis populations, this study is not acceptable unless you can provide evidence to justify the inclusion of these patients in the analysis populations. If no such evidence is available, a new clinical endpoint bioequivalence study, which follows the recommendations provided in the *Draft Guidance for Mupirocin Calcium Cream/Topical EQ 2% Base (revised October 2011)*, should be conducted and submitted for agency review.
2. Clinical cure is defined as a Skin Infection Rating Scale (SIRS) score of 0 for all signs and symptoms on a 4-point scale. "Sustained improvement" is not part of the definition. The inclusion of patients with sustained improvement in the clinical cure group is not acceptable as it could reduce the sensitivity of the clinical endpoint study in distinguishing differences between drug products and placebo.
3. The inclusion criterion for baseline SIRS total score is a total sore of at least 8.
4. The exclusion criterion for the use of topical therapeutic agents is within 48 hours (not 24

hours) prior to study entry.
5. Patients with diabetes should be excluded from the study.
6. Compliance is generally defined as 75% to 125% of the scheduled applications.
7. Visit window is defined as ±4 days.

On 4/27/12, Glenmark submitted a response to the 3/8/12 deficiency letter, which is the subject of this review.

In the process of reviewing the 4/27/12 amendment, the following additional information was requested from Glenmark on 7/2/12:

1. Please provide a copy of the original source document and an English translated copy, if the source document is written in a foreign language, for the following 18 patients: Patients (b) (6) (b) (6). For these patients, the cause of the wound has been identified as "scratching". Information on the original wound, which lead to the "scratching", is needed to determine the patient's status for the per-protocol population.
2. Please resubmit your datasets reflecting all the changes noted in your April 27, 2012 Clinical Bioequivalence Amendment in electronic (.xpt) format. Additional information concerning the format of the electronic data can be found on the FDA website for *Individual Product Bioequivalence Recommendations: Draft Guidance on Mupirocin Calcium Cream, (June 2010).*

On 7/18/12 and 7/20/12, Glenmark submitted the response to the 7/2/12 Information Request, which is also the subject of this review.

1.1 Approval Recommendation

The data submitted to ANDA 201587, using the difference in clinical success rate between Test and Reference at the 7 day follow-up visit (Visit 4), are adequate to demonstrate bioequivalence of Glenmark's Mupirocin Cream USP, 2% with the RLD, Glaxo SmithKline's Bactoban® Cream, 2%. Therefore, from a clinical bioequivalence perspective, the test product is recommended for approval.

1.2 Summary of Clinical Findings

1.2.1 Brief Overview of Clinical Program

Glenmark conducted a clinical endpoint study, enrolling 656 patients, to establish the bioequivalence of their proposed Mupirocin Cream USP, 2% to the RLD, Bactoban® Cream, 2%, in the topical treatment of secondarily infected traumatic skin lesions. All patients were randomized in a 1:1:1 ratio to apply either the Glenmark product (Test), Bactoban® Cream (Reference) or the vehicle cream (Placebo) three times daily for 10 days.

1.2.2 Comparative Efficacy

The primary endpoint of this study was clinical success at the 7 day follow-up visit (Visit 4) after completion of a 10-day treatment. Clinical success is defined as complete resolution (SIRS scores of 0 on a 4-point scale) of all signs and symptoms of infection. According to the FDA's analysis, the success rate in the PP population at Visit 4 was 79.28% in the test group and 79.82% in the reference group. The 90% CI of the difference in success rate between the two active products is (-0.1039, 0.0932), which is within the established bioequivalence limits of [-0.20 to +0.20].

1.2.3 Comparative Safety

Previous review (Clinical Endpoint Review finalized on 3/5/12) of the safety data submitted in this ANDA confirmed that the test product did not cause any worse adverse events compared to the reference product in the topical treatment of secondarily infected traumatic skin lesions.

2 Clinical Review

2.1 Introduction and Background

Mupirocin is a topical antibacterial agent active against a wide range of gram positive bacteria and has become a recognized topical treatment for impetigo since the approval of Bactroban® Ointment (NDA 050591). In 1997, the FDA approved Bactroban® Cream (NDA 050746) for the topical treatment of secondarily infected traumatic skin lesions (up to 10 cm in length or 100 cm^2 in area) due to susceptible strains of *Staphylococcus aureus* and *Streptococcus pyogenes*. The approved labeling recommends three times daily application to the affected area for 10 days. Patients not showing a clinical response within 3 to 5 days should be re-evaluated. The safety and effectiveness for pediatric use (aged 3 months to 16 years) was demonstrated to be similar to adult patients. Only headache was thought to be possibly or probably related to Bactroban® Cream in children.

2.1.1 Summary of Drug Information

Drug Established Name	Mupirocin Cream, 2%
Drug Class	Antibacterial agent
Reference Listed Drug	Bactroban® Cream
RLD Firm	Glaxo SmithKline
NDA #	050746
Date of RLD Approval	December 11, 1997
Approved Indication(s)	topical treatment of secondarily infected traumatic skin lesions (up to 10 cm in length or 100 cm^2 in area) due to susceptible strains of *Staphylococcus aureus* (*S. aureus*) and *Streptococcus pyogenes* (*S. pyogenes*)

Recommended Dosing Regimens	Apply three times daily for 10 days, the treated area may be covered with gauze dressing if desired. Patients not showing a clinical response within 3 to 5 days should be re-evaluated.

2.1.2 Regulatory Background

2.1.2.1 INDs, Protocols, or Control Documents submitted by Sponsor

The contract research organization (Symbio, LLC) submitted a protocol (P04-004), dated January 23, 2004, for this drug product. Comments regarding the protocol were forwarded to Symbio, LLC on September 24, 2004.

Reviewer Comments:

The protocol submitted by Symbio, LLC (OGD's P04-004; Symbio LLC protocol number SYM-2003-08) excluded "subjects who have a secondarily infected bite (animal, human or insect) or puncture wound." (exclusion criteria #8). The protocol did not specify a special circumstance (as noted in the exclusion criteria #8 for this ANDA) whereby "infections resulting from the scratching of an insect bite were considered secondarily infected traumatic skin lesions." In addition, OGD's comments to Symbio LLC included a statement that "the type of wound and site of wound should be compared and tabulated for each treatment group" (Comment #9) and that "the preferred definition of clinical cure is a Skin Infection Rating Scale (SIRS) score of 0 (absent) for all evaluated primary clinical sings and symptoms" (Comment #7).

2.1.2.2 INDs, Protocols, or Control Documents submitted by other sponsors

Several INDs, protocols and controls have been submitted by other sponsors for this drug product. Each of these sponsors were given the same advice as that forwarded in the DCR response of 9/24/2004 to Symbio regarding their protocol for this study.

2.1.2.3 Previous ANDA submissions for same product

There is no approved ANDA for this drug product. (b) (4) (b) (4)

2.1.3 Other Relevant Information

The FDA has posted a *Draft Guidance on Mupirocin Calcium Cream/Topical, EQ 2% Base, (Revised October 2011)* on the FDA website:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM217146.pdf. This *Draft Guidance* represents the most recent recommendations of the OGD.

Reviewer's Comments:

With the changes provided in the 4/27/12 Clinical Bioequivalence Amendment, the sponsor's study is consistent with this Draft Guidance.

2.2 Description of Clinical Data and Sources

Protocol Number	GLK 605
Study Title	A multi-center, double-blind, randomized, vehicle-controlled, parallel group study comparing generic Mupirocin Calcium Cream, 2% to Bactroban Cream® (mupirocin calcium cream), 2% and both active treatments to a vehicle control in the treatment of secondarily infected traumatic skin lesions
CRO	Symbio, LLC
Study Period	First Patient Enrolled: July 14, 2008 Last Patient Completed: June 8, 2009

Study Centers, Principal Investigators and Enrollment

The study was performed at 12 sites in North, Central, and South America. See previous Clinical Endpoint Review finalized on 3/5/12 for a complete listing.

2.3 Clinical Review Methods

2.3.1 Overview of Materials Consulted in Review

Original Submission:

February 22, 2010 (Non-eCTD electronic submission)

Study Amendments:

- June 1, 2010 (Clinical Bioequivalence Amendment/Response to Information Request) - number of patients enrolled at each site.
- January 27, 2012 (Clinical Bioequivalence Amendment/Response to Information Request) - incomplete description of target lesion.
- April 27, 2012 (Clinical Bioequivalence Amendment/Response to Information Request) - additional description of target lesion and reanalysis of data.
- July 18, 2012 (Clinical Bioequivalence Amendment/Response to Information Request) - source document to identify cause of lesion and resubmission of updated datasets.
- July 20, 2012 (Clinical Bioequivalence Amendment/Response to Information Request) - resubmission of remaining datasets omitted in July 18, 2012 submission.

FDA Statistical Review:

FDA Statistical Review and Evaluation finalized on September 27, 2012 by Huaixiang Li, Ph.D. The results of the Statistical Review are incorporated into this Clinical Review.

2.3.2 Overview of Methods Used to Evaluate Data Quality and Integrity

Office of Scientific Investigations (OSI) Report:

Found acceptable in previous Clinical Endpoint Review finalized on 3/5/12.

2.3.3 Were Trials Conducted in Accordance with Accepted Ethical Standards

Found acceptable in previous Clinical Endpoint Review finalized on 3/5/12.

2.3.4 Evaluation of Financial Disclosure

Found acceptable in previous Clinical Endpoint Review finalized on 3/5/12.

2.4 Review of a Clinical Endpoint Bioequivalence Study

2.4.1 Brief Statement of Conclusions

Based on the FDA's analyses, this study meets the bioequivalence limits of the difference in clinical success (a SIRS score of 0 for all signs and symptoms on a 4-point scale) between Test and Reference at the 7 day follow-up visit (Visit 4) after completion of a 10-day treatment.

2.4.2 General Approach to Review of the Comparative Efficacy of the Drug

The sponsor's study (Protocol # GLK 605) was reviewed to evaluate the bioequivalence of the test and reference products. The primary endpoint of this study is clinical success at the 7 day follow-up visit (Visit 4) after completion of a 10-day treatment. **The sponsor's proposed primary parameter was evaluated for bioequivalence and secondary parameters were considered as supportive information.**

The sponsor's study amendment dated April 27, 012 was reviewed for changes to the study population and the analyses results.

2.4.3 Detailed Review of Bioequivalence Studies with Clinical Endpoints

2.4.3.1 Protocol Review

Sponsor's protocol #:	GLK 605
Title	A multi-center, double-blind, randomized, vehicle-controlled, parallel-group study comparing generic Mupirocin Calcium Cream, 2% to Bactroban Cream® (mupirocin calcium cream), 2% and both active treatments to a vehicle control in the treatment of secondarily infected traumatic skin lesions
Objectives	The objectives of this study were to demonstrate comparable safety and efficacy of Generic Mupirocin Calcium Cream, 2% and Bactroban Cream® (mupirocin calcium cream), 2% and to show the superior efficacy of the two active creams over that of the Vehicle (placebo) in the treatment of secondarily infected skin lesions.

2.4.3.1.1 Study Design

Overall Study Design and Plan

This was a 17 day, multi-center, double-blind, randomized, vehicle-controlled, parallel-group study in patients 18 months of age or older with a diagnosis of secondarily infected skin lesions (up to 10 cm in length or 100 cm^2 in area) due to susceptible strains of *Staphylococcus aureus* and/or *Streptococcus pyogenes*, to compare the efficacy of generic Mupirocin Calcium Cream, 2% (Test) versus Bactroban Cream® (mupirocin calcium cream), 2% (Reference), and their efficacy over the Vehicle Cream (Placebo). The study consisted of a Screening/Baseline visit (Visit 1, Day 1), an On Treatment visit (Visit 2/Day 3-5), an End of Treatment visit (Visit 3/Day 10-12), and a Follow-up visit (Visit 4/Day 17-21). The study schedule is depicted in Table 1.

Patients satisfying all inclusion/exclusion criteria were randomly assigned in a 1:1:1 ratio to one of the three study formulations. Patients applied study medication topically three times daily for 10 days.

If at any time, the investigator determined that the infection had become systemic, was not responding to treatment or that the study treatment was not sufficient to treat the degree of disease activity present, he or she could remove the patient from the study and prescribe appropriate treatment or refer the patient to another physician. Use of rescue therapy was documented in the CRF.

The sponsor's primary efficacy endpoint was the clinical response (success or failure) as determined at the follow-up visit (Visit 4). The sponsor's secondary efficacy endpoints were bacteriological response at the follow-up visit (Visit 4) and at the end of treatment visit (Visit 3); and clinical response at the end of treatment visit (Visit 3).

Procedures and Observations:

A summary of the study procedures performed at each visit is given in Table 1.

Table 1: Study Schedule

Procedure	Visit 1 Screening/ Baseline (Day 1)	Visit 2 On Treatment (Day 3-5)	Visit 3 End of Treatment (Day 10-12)	Visit 4 Follow-up (Day 17-21)	Unscheduled/ Early Termination Visit
Screening/Informed Consent	X				
Inclusion/Exclusion Criteria	X				
Medical History	X				
Physical Examination (including vital signs)	X				
Urine Pregnancy Test*	X				
Skin Infection Rating	X	X	X	X	X
Clinical Response			X	X	X
Bacteriology Specimen Collection	X		X	X	X
Bacteriological Response			X	X	X
Adverse Event Reporting		X	X	X	X
Concurrent Medication	X	X	X	X	X
Randomization/Drug Dispensing	X				
Patient Instruction/Compliance	X	X	X	X	X
Drug Return, Accountability		X	X		X

* For women of child-bearing potential - to be completed in doctor's office prior to enrollment

Deficiency #7 identified in Clinical Endpoint Review finalized on 3/5/12:

Visit window is defined as ±4 days.

Sponsor Response:

Visit 4 window has been updated to ±4 days. The PP definition has been changed to include the updated Visit 4 window.

Reviewer Comments:

Acceptable.

Study Population:

Inclusion Criteria:

Patients were required to meet all of the following criteria:

1. Patients 18 months of age or older with a definite clinical diagnosis of a secondarily infected traumatic skin lesion (up to 10 cm in length or 100 cm^2 in area) due to susceptible strains of *S. aureus* and/or *S. pyogenes*.

2. Patients with a SIRS total score of at least 4 and white blood cells observed on Wright stain or Gram stain slide prepared from wound exudates.
3. Women of childbearing potential (excluding women who are surgically sterilized or post menopausal for at least 2 years), in addition to having a negative urine pregnancy test, were willing to use an acceptable form of birth control during the study.
4. Patients 18 years of age or older provided IRB approved written informed consent.
5. Patients under the age of 18 had parent or legal guardian provide IRB approved written informed consent. For Patients 12-17 years of age, an assent form for minors was completed.
6. Patients were willing and able to understand and comply with the requirements of the study, apply the medication as instructed, return for the required treatment period visits, comply with therapy prohibitions, and were able to complete the study.
7. Patients were in good health and free from any clinically significant disease, other than secondarily infected traumatic skin lesions, that might have interfered with the study evaluations.

Deficiency #3 identified in Clinical Endpoint Review finalized on 3/5/12:

The inclusion criterion for baseline SIRS total score is a total sore of at least 8.

Sponsor Response:

The sponsor's mITT and PP population analyses have been revised to reflect the change in inclusion criterion from a SIRS total score of at least 4 to a SIRS total score of at least 8.

Reviewer Comments:

Acceptable.

Exclusion Criteria:

Patients were excluded if any of the following were present:

1. Patients who were pregnant, nursing, or planning a pregnancy within the study participation period.
2. Patients with any other confounding skin condition.
3. Patients with clinically significant systemic disease (i.e., immunological deficiencies), unstable medical disorders, life-threatening disease, or current malignancies.
4. Patients with systemic signs or symptoms of infection.
5. Patients who required surgical intervention for treatment of infection.
6. Patients who had a known hypersensitivity to any of the following (in any dosage form): penicillins, cephalosporins, other beta-lactam antimicrobials or mupirocin and/or to any component of the study medications.
7. Patients with a bacterial skin infection that, because of depth or severity, should not have been treated with a topical antibiotic (e.g., cellulitis, abscess, ulcer, furunculosis).
8. Patients who had a secondarily infected bite (animal, human or insect) or puncture wound. Note: Infections resulting from the scratching of an insect bite were considered secondarily infected traumatic skin lesions.

9. Patients who applied any topical therapeutic agent directly to the wound within 24 hours prior to study entry.
10. Patients who had been treated with systemic antibacterial or steroid within 7 days prior to study entry.
11. Patients who consumed excessive amounts of alcohol, abused drugs, or had any condition that would compromise compliance with this protocol.
12. Patients who had been treated with an investigational drug or investigational device within a period of 4 weeks prior to study entry.
13. Patients who had been previously enrolled in this study.

Deficiency #1 identified in Clinical Endpoint Review finalized on 3/5/12:

The Draft Guidance for Mupirocin Calcium Cream/Topical EQ 2% Base (revised October 2011) recommends that "secondarily infected animal/human or insect bite" be excluded from clinical endpoint bioequivalence study for Mupirocin Cream USP, 2%. The study report for Study GLK 605 states that "infections resulting from the scratching of an insect bite were considered secondarily infected traumatic skin lesions." Infections resulting from the scratching of an insect bite are superficial and considered secondarily infected insect bite. Given that patients with secondarily infected insect bites cannot be identified from all clinical sites in order to exclude from the analysis populations, this study is not acceptable unless you can provide evidence to justify the inclusion of these patients in the analysis populations. If no such evidence is available, a new clinical endpoint bioequivalence study, which follows the recommendations provided in the Draft Guidance for Mupirocin Calcium Cream/Topical EQ 2% Base (revised October 2011), should be conducted and submitted for agency review.

Sponsor Response:

Although not a specific requirement of the GLK 605 protocol, most of the investigators recorded the type and cause of the wound as a notation in subjects' medical records. Upon receipt of the 3/8/12 deficiency, copies of this notation taken from the medical records for Sites 01, 02, 03, 04, 05, 06, and 13 (629 total subjects) (b) (4) (b) (4) From Sites 02, 06 and 13, there were 11 subjects whose medical records were retrieved; however no data was available on either type or cause of wound. For Sites 10, 11, and 12, a total of 27 subjects, the type and cause of wound were not captured in other medical documentation; therefore no information pertaining to the type or cause of wound could be collected from these sites. Refer This supplemental data was documented from the study provided source document page 4 (location of wound) and medical notes listing nature and cause of wound. Since data on type or cause of wound was available for the majority of the subjects, the sponsor grouped the data into categories of either evaluable or non-evaluable subjects for the purpose of re-analysis. An evaluable subject is defined by the sponsor as a subject who has data collected on either type and/or cause of wound that clearly denotes the secondarily infected wound was not a result of an insect bite. A non-evaluable subject is defined by the sponsor as a subject who has data collected on either type and/or cause of wound that clearly denotes the secondarily infected wound is a result of an insect bite or scratching of an insect bite, or a subject who does not have data collected for both type and cause of wound. Table 2 summarizes the number of subjects enrolled at each site, the number of evaluable subjects, and the number of non-evaluable subjects with an insect bite or with no data on type or cause of wound.

Table 2: Summary of Data Collected from Sites (per Sponsor)*

Site Number	No. of Subjects Enrolled	No. of Evaluable Subjects[1]	No. of Non-Evaluable Subjects with Insect Bite[2]	No. of Non-Evaluable Subjects with No Data[3]
01	75	75	0	0
02	74	71	0	3
03	107	107	0	0
04	114	92	22	0
05	115	114	1	0
06	51	44	1	6
10	12	0	0	12
11	12	0	0	12
12	3	0	0	3
13	93	86	5	2
Total	**656**	**589**	**29**	**38**

* From Sponsor's 4/27/12 Clinical Bioequivalence Amendment Table 1.1.
[1] Evaluable Subject = a subject who has data collected on either type and/or cause of wound that clearly denotes the secondarily infected wound was not a result of an insect bite. (Note: a subject who does not have data collected for both type and cause of wound is considered non-evaluable)
[2] Non-Evaluable Subject with Insect Bite = a subject who has data collected on either type and/or cause of wound that clearly denotes the secondarily infected wound is a result of an insect bite.
[3] Non-Evaluable Subject with No Data = a subject who does not have data collected for both type and cause of wound

According to the sponsor, of the 656 subjects enrolled, 589 subjects were considered evaluable and 67 subjects were considered non-evaluable. Of those 67 non-evaluable subjects, 29 were reported to have a secondarily infected wound that resulted from an insect bite and 38 subjects did not have any data collected on both the type and cause of wound.

Reviewer Comments:

In the April 27, 2012 amendment, the cause of the wound has been identified as "scratching" for the following patients: Patients (b) (6) (b) (6)*. Information on the original wound, which lead to the "scratching" is needed to determine the patient's status for the per-protocol population. The sponsor was requested to provide a copy of the original source document and an English translated copy, if the source document was written in a foreign language, for these 18 patients. The sponsor submitted the information in the July 18, 2012 amendment. Based on the information in the July 18, 2012 amendment, the following changes to the sponsor's PP population was recommended:*

- *The original wound, which lead to the "scratching" and subsequent infection, for the following 15 patients were not identified in the source documents:* (b) (6) (b) (6) *Therefore, these patients are recommended to be excluded from the FDA's PP and ITT populations.*
- *The original wound, leading to the secondary infection, were identified for the following 3 patients:* (b) (6)

However, Patients (b) (6) had other reasons (negative baseline culture and baseline SIRS score <8, respectively) for exclusion from the PP and ITT populations. Therefore, only Patient (b) (6) can remain included in the FDA's PP and ITT populations.

Deficiency #4 identified in Clinical Endpoint Review finalized on 3/5/12:

The exclusion criterion for the use of topical therapeutic agents is within 48 hours (not 24 hours) prior to study entry.

Sponsor Response:

All subjects' records of concurrent and prior medications were reviewed by the sponsor and there were no subjects found to be reported using topical therapeutic agents within 48 hours prior to study entry. Therefore this exclusion criterion had no impact on the results provided above.

Reviewer Comments:

Acceptable. All patients stopped use of topical therapeutic agents at least two days prior to the baseline visit.

Deficiency #5 identified in Clinical Endpoint Review finalized on 3/5/12:

Patients with diabetes should be excluded from the study.

Sponsor Response:

All subjects' medical history was reviewed by the sponsor and there were no subjects found that had a history of diabetes or reported having diabetes at the time of study entry. Therefore this exclusion criterion had no impact on the results provided above.

Reviewer Comments:

Acceptable. None of the enrolled patients had diabetes.

Criteria for removal from the study:

Acceptable per previous Clinical Endpoint Review finalized on 3/5/12.

Prior and Concomitant Therapy:

Acceptable per previous Clinical Endpoint Review finalized on 3/5/12.

Treatments:

Patients were randomly assigned in a 1:1:1 ratio to one of the three treatment groups:

Test*	Mupirocin Cream USP, 2% three times daily for 10 days Manufacturer: Glenmark Generics Limited Lot Number: Q15748002 Expiry Date: December 2009
Reference*	Bactroban® Cream (mupirocin calcium cream), 2% three times daily for 10 days Manufacturer: GlaxoSmithKline Lot numbers: C328473 Expiry Date: May 2009
Placebo*	Vehicle of test product three times daily for 10 days Manufacturer: Glenmark Generics Limited Lot Number: QP15748001 Expiry Date: December 2009

* Glenmark supplied the investigational treatments. (b) (4) labeled, assembled, and shipped study medications.

Compliance:

Patients were to apply the medication three times daily for 10 days. Compliance was determined from the diary card, in which the patient was instructed to record all applications made or missed. The number of applications missed was totaled by the study coordinator and recorded on the compliance page of the CRF. Compliant patients made at least 20 (66.6%) and no more than 30 (100%) applications of study medication, inclusive of medication applications during participation in the study, and missed no more than six consecutive doses. The used tubes of study medication were collected by the study site at appropriate visits or early termination.

Deficiency #6 identified in Clinical Endpoint Review finalized on 3/5/12:

Compliance is generally defined as 75% to 125% of the scheduled applications.

Sponsor Response:

The compliance rate has been changed by the sponsor to 75% to 125%. The sponsor's PP population definition has been changed to include the changed compliance rate.

Reviewer Comments:

Acceptable.

Randomization:

Acceptable per previous Clinical Endpoint Review finalized on 3/5/12.

Blinding:

Acceptable per previous Clinical Endpoint Review finalized on 3/5/12.

2.4.3.1.2 Endpoints/Variables

Clinical Evaluation

Investigator or sub-investigator assessed clinical signs of the wound at each visit using the SIRS scoring scale (see Table 3 below) for each of the following signs: exudate/pus, crusting, erythema/inflammation, tissue warmth, and edema. Symptoms (itching and pain) were scored by the patient.

Table 3: Skin Infection Rating Scale (per Sponsor)*

Score	Description
0	Absent; no evidence of sign/symptom
1	Mild; sign/symptom present but not intense
2	Moderate; sign/symptom clearly evident and somewhat bothersome to patient
3	Severe; sign/symptom clearly evident, intense and extremely bothersome to patient

* From Sponsor's Protocol GLK 605 version 1.0 Appendix IV.

Reviewer Comments:

Acceptable per previous Clinical Endpoint Review finalized on 3/5/12.

Clinical Response

Clinical Success: complete resolution (SIRS scores of 0) or sustained improvement (SIRS scores of 0 for exudate/pus, crusting, tissue warmth, edema and pain; and 0 or 1 for erythema/inflammation and itching) of signs and symptoms of infection. No additional antibiotic therapy required after End of Treatment.

Clinical Failure: inability to clear or improve the presenting signs/symptoms (SIRS scores of >0 for exudate/pus, crusting, tissue warmth, edema and pain; or SIRS score >1 for erythema/inflammation and itching).

Deficiency #2 identified in Clinical Endpoint Review finalized on 3/5/12:

Clinical cure is defined as a Skin Infection Rating Scale (SIRS) score of 0 for all signs and symptoms on a 4-point scale. "Sustained improvement" is not part of the definition. The inclusion of patients with sustained improvement in the clinical cure group is not acceptable as it could reduce the sensitivity of the clinical endpoint study in distinguishing differences between drug products and placebo.

Sponsor Response:

The sponsor changed the definition of clinical success/cure as follows: complete resolution (SIRS scores of 0) of signs and symptoms of infection. No additional antibiotic therapy required after End of Treatment.

Reviewer Comments:

Acceptable.

Bacteriological Evaluation

As a result of the clinical cure definition change in the 4/27/12 Clinical Bioequivalence Amendment, the definition for Presumed Eradication at Visit 4/Follow-up was revised to the following:

Presumed Eradication at Visit 4/Follow-up: culture was negative or not clinically indicated (i.e. no culturable material present) and SIRS scores indicative of clinical success (SIRS scores of 0 for all signs and symptoms of infection).

All other definitions remained the same.

Reviewer Comments:

Acceptable.

Primary Endpoint:

The sponsor's primary endpoint was the clinical response as determined at the follow-up visit (Visit 4). Clinical response was defined by the sponsor as one of the following: clinical success or clinical failure.

Reviewer's Comments:

Acceptable. Per the Draft Guidance for Mupirocin Calcium Cream/Topical EQ 2% Base (revised October 2011), the FDA recommended primary endpoint of this study is the proportion of patients in the PP population with clinical success at the follow-up visit (7 days after the end of treatment).

Secondary Endpoints:

Secondary efficacy evaluations included comparing the proportions of:

1. Presumed Eradication at Visit 4 (Follow-up)
2. Clinical Success at Visit 3 (End of Treatment)
3. Presumed Eradication at Visit 3 (End of Treatment)

Reviewer's Comments:

Acceptable. The sponsor's secondary endpoints are consistent with the Draft Guidance for Mupirocin Calcium Cream/Topical EQ 2% Base (revised October 2011) and considered supportive information.

2.4.3.1.3 Statistical analysis plan

The statistical analysis plan is provided in Appendix 16.1.9 of the sponsor's study report.

Patient Populations:

The sponsor identified three patient populations: Intent-to-Treat (ITT), Modified Intent-to-Treat (mITT), and Per-Protocol (PP) Populations. The sponsor's efficacy analyses were performed on

the mITT and PP populations. The mITT population was the primary population for analysis of superiority of the active products over the Placebo. The PP population was the primary population for the therapeutic equivalence comparison between the two active products. Safety analyses were performed on the ITT population. The three patient populations were defined as follows:

Intent-to-Treat (ITT) Population

- enrolled into the study
- received at least one application of study medication

Reviewer's Comments:

The sponsor's definition for the ITT population is acceptable.

Modified Intent-to-Treat (mITT) Population

- enrolled into the study
- met all inclusion/exclusion criteria including a positive baseline culture
- received at least one application of study medication
- had at least one post-screening visit

Reviewer's Comments:

The sponsor's definition for the mITT population is acceptable.

Per-Protocol (PP) Population

The sponsor's PP population has been changed in the 4/27/12 Clinical Bioequivalence Amendment to include a compliance rate of 75% to 125% and update the Visit 4 window to ± 4 days. The following is the revised PP definition:

1. enrolled into the study and met inclusion/exclusion criteria including a positive baseline culture,
2. had not taken any concomitant medications prohibited by the protocol or had any other significant protocol violations,
3. was compliant with applications of study medication (75% to 125%) and did not miss more than 6 consecutive doses of study drug treatment during the treatment period,
4. did not miss more than 2 consecutive required visits, AND
5. returned for Visit 4 within visit window (±4 days) with data on the primary efficacy variables for bacteriologic and clinical evaluations unless discontinued from the study early due to insufficient therapeutic response after at least 3 days of applications (with a compliance rate of at least 75% and not more than 125%).

Reviewer's Comments:

The sponsor's revised definition for the PP population is acceptable.

Primary Bioequivalence and Superiority Analyses:

The primary efficacy analyses were the comparisons between Test and Reference for the proportion of patients with Clinical Success at the follow-up visit (Visit 4).

According to the sponsor, Wald's 90% confidence interval was constructed for the difference between Test and Reference in the proportion of patients with Clinical Success. Yates' continuity correction was incorporated into the calculation. If the confidence interval was contained within the interval –0.20 to +0.20, then Test was considered therapeutically equivalent (bioequivalent) to Reference in the treatment of secondarily infected wounds.

Continuity-corrected Z-tests were conducted by the sponsor for the difference between each active product's Clinical Success proportion and that of Placebo (Test vs. Placebo, and Reference vs. Placebo). If the product's Clinical Success proportion exceeded that of Placebo, and the difference was statistically significant ($p<0.05$), then the active product was considered superior to Placebo in the treatment of secondary wound infections.

Reviewer's Comments:

To establish bioequivalence, the 90% confidence intervals of the test-reference difference in the proportion of patients with clinical success (SIRS score of 0 for all signs and symptoms) at the follow-up visit (7 days after completion of 10 days of treatment) must be contained within [-0.20, +0.20] for dichotomous variables (success/failure), using the PP population. In addition, as a parameter for determining adequate study sensitivity, Test and Reference should both be statistically superior to Placebo ($p<0.05$, two sided) with regard to the proportion of patients with clinical success at the follow-up visit using the mITT population and LOCF.

Secondary Endpoint Bioequivalence and Superiority Analyses

According to the sponsor, the same tests/methods as for the primary analyses were conducted for the secondary endpoints.

Missing values or Dropouts:

According to the sponsor, a patient who terminated the study prematurely due to insufficient therapeutic response after at least 3 days of study medication application was carried forward as a treatment failure in both the PP and mITT populations if the patient met all other criteria for inclusion.

For the analysis of superiority, a last-observation-carried-forward (LOCF) approach was used for missing superiority results in the mITT population by the sponsor. In the PP population, the LOCF approach was used only for patients who discontinued due to treatment failure for their subsequent visits after discontinuation.

2.4.3.2 Study Conduct

Patient Disposition:

As a result of the changes made to the mITT and PP populations in the 4/27/12 Clinical Bioequivalence Amendment, Table 4 summarizes total enrollment and eligibility for analysis of all subjects enrolled into the study with the sponsor's revised mITT and PP populations.

Six hundred fifty six (656) subjects were enrolled into the study and randomized to one of the three treatment groups. Of these enrolled subjects, 655 (99.8%) were confirmed to receive treatment and included in the intent-to-treat (ITT) analyses: 220 subjects received Test, 217 subjects received Reference, and 219 subjects received Placebo; no change from the original submission.

The following have changed as a result of the modification to the sponsor's population definitions to address deficiencies:

Modified Intent-to-Treat analysis:

- 315 (48.0%) subjects were excluded from the sponsor's revised mITT analysis compared to 118 (18.0%) from the sponsor's original mITT analysis.
- 341 (52.0%) subjects were included in the sponsor's revised mITT analyses compared to 538 (82.0%) from the sponsor's original mITT analysis.

Per-Protocol analysis:

- 319 (48.6%) subjects were excluded from the sponsor's revised PP analysis compared to 146 (22.3%) from the sponsor's original PP analysis.
- 337 (51.4%) subjects were included in the sponsor's revised PP analysis compared to 510 (77.7%) from the sponsor's original PP analysis.

Table 4: Patient Enrollment (by Sponsor)[1]

	Number (%) of Patients			
	Test	**Reference**	**Placebo**	**Overall**
Number Enrolled	220	217	219	656
Patients Excluded from the Intent-to-Treat Analysis	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
Patients Included in the Intent-to-Treat Analysis	220 (100%)	216 (99.5%)	219 (100%)	655 (99.8%)
Patients Excluded from the Modified Intent-to-Treat Analysis	107 (48.6%)	105 (48.4%)	103 (47.0%)	315 (48.0%)
Patients Included in the Modified Intent-to-Treat Analysis	113 (51.4%)	112 (51.6%)	116 (53.0%)	341 (52.0%)
Patients Excluded from the Per-Protocol Analysis	109 (49.5%)	106 (48.8%)	104 (47.5%)	319 (48.6%)
Patients Included in the Per-Protocol Analysis	111 (50.5%)	111 (51.2%)	115 (52.5%)	337 (51.4%)

[1] From Sponsor's 4/27/12 Clinical Bioequivalence Amendment Table 1.2.

Reviewer's Comments:

Based on the information in the July 18, 2012 amendment, the following changes to the sponsor's PP and ITT populations were recommended to the FDA statistician:

- *The original wound, which lead to the "scratching" and subsequent infection, for the following 15 patients were not identified in the source documents: [redacted], [redacted] Therefore, these patients are recommended to be excluded from the FDA's PP and ITT populations.*
- *The original wound, leading to the secondary infection, were identified for the following 3 patients: [redacted] However, Patients [redacted] had other reasons (negative baseline culture and baseline SIRS score <8, respectively) for exclusion from the PP and ITT populations. Therefore, only Patient [redacted] can remain included in the FDA's PP and ITT populations.*

Table 5 provides the FDA's summary of patient disposition.

Table 5: Patient Disposition (per FDA Statistician)

	Test	Reference	Placebo	Total
Enrolled and Randomized	**220**	**217**	**219**	**656**
Total Sponsor's mITT Population	**113**	**112**	**116**	**341**
Exclusion from Sponsor's mITT Population	107	105	103	315
Total baseline scores less than 8	61	58	63	182
Cause of wound by scratching insect bite	9	9	9	27
Cause of wound not available	11	15	12	38
Violation of inlusion/exclusion criteria	26	23	19	68
Total Sponsor's PP Population	**111**	**111**	**115**	**337**
Exclusion from Sponsor's PP Population	109	106	104	319
Excluded from mITT population	107	105	103	315
Out of visit window at visit 4	1	1	0	2
Protocol violation	1	0	0	1
Non compliance	0	0	1	1
FDA's ITT (FITT) Population	**113**	**112**	**112**	**335**
Exclusion from FPP population	107	107	107	321
Excluded from sponsor's mITT	107	105	103	315
Cause of wound by scratching and subsequent infection	0	2	4	6
FDA's PP (FPP) Population	**111**	**109**	**111**	**331**
Exclusion from FPP population	109	108	108	325
Excluded from sponsor's PP	109	106	104	319
Cause of wound by scratching and subsequent infection	0	2	4	6

Retention of Reserve Samples:

Acceptable per previous Clinical Endpoint Review finalized on 3/5/12.

Baseline Characteristics:

Baseline characteristics for the ITT population is provided in the Clinical Endpoint Review finalized on 3/5/12. Revised baseline characteristics for the mITT and PP populations were not provided by the sponsor.

2.4.3.3 Results

Primary Endpoint

As a result of the clinical cure definition change and changes to the PP and mITT population definitions in the 4/27/12 Clinical Bioequivalence Amendment, the primary endpoint was reanalyzed by the sponsor. According to the sponsor's reanalysis, the test group and the reference group were comparable in regard to clinical success (defined as SIRS scores of 0 for signs and symptoms of infection) at the 7 day follow-up visit (Visit 4) in the revised PP population:79.3% for the test group and 80.2% for the reference group were considered a clinical success. The sponsor's recalculated 90% confidence interval of the difference in clinical success rate between the test group and the reference group in the PP population is (-0.1068, 0.0888) at the 7 day follow-up visit (Visit 4). Both the test group and the reference group continued to show superiority over the placebo group in the revised mITT population at the 7 day follow-up visit (Visit 4) (both $p<0.001$).

Table 6: **Primary Bioequivalence Reanalysis – Clinical Success at the Follow-Up Visit (Visit 4) in the PP Population (per sponsor)***

	Test (N=111)	Reference (N=111)	90% CI[1]
Success (n, %)	88 (79.3%)	89 (80.2%)	(-10.68, 8.88)

* From Sponsor's 4/27/12 Clinical Bioequivalence Amendment Table 2.1.
[1] Confidence interval calculated using Wald's method with Yates' continuity correction.

Table 7: **Primary Superiority Reanalysis – Clinical Success at the Follow-Up Visit (Visit 4) in the mITT Population (per sponsor)***

	Test (N=113)	Reference (N=112)	Placebo (N=116)	P-values[1]	
				Test vs Placebo	Reference vs Placebo
Success (n, %)	90 (79.6%)	90 (80.4%)	67 (57.8%)	<0.001	<0.001

* From Sponsor's 4/27/12 Clinical Bioequivalence Amendment Table 2.1.
[1] P-values for treatment comparisons from two-sided Z-test with Yates' continuity correction.

Reviewer's Comments:

Table 8 summarizes the FDA's BE analysis results for the clinical success rate at the follow-up visit (Visit 4). Based on the FDA analysis on the difference in clinical success rate between Test and Reference, the BE test passed in the FPP population.

Table 8: Bioequivalence Analysis for the Success Rate at Visit 4 (Follow-up Visit) in the FDA's Per-Protocol Population (per FDA statistician)

Test (N=111)	Reference (N=109)	90% CI (%) for the Test and Reference	Is the 90% CI within [-20, 20%]?
79.28% (88)	79.81% (87)	-10.39, 9.31	Yes

Table 9 summarizes the FDA's superiority analysis results for the clinical success rate. Based on the FDA analysis, each active treatment group was statistically significantly better than placebo for the difference in clinical success rate between Test and Reference in the FITT population.

Table 9: Analysis of Success Rate at Visit 4 (Follow-up Visit) in the FDA's ITT Population (per FDA statistician)

	Test (N=113)	Reference (N=110)	Placebo (N=112)	p-values[2]	
				Test vs. Placebo	Reference vs. Placebo
LS Mean ± Std	79.65% (90)	80.00% (88)	58.04% (65)	<0.0001	<0.001

Secondary Endpoints

The results of the sponsor's secondary endpoints reanalyses are presented in Table 10 and Table 11.

Table 10: Secondary Bioequivalence Analyses using the PP Population (per sponsor)*

	Test (N=111)	Reference (N=111)	90% CI[1]
Clinical Success at Visit 3 (n, %)	34 (30.6%)	36 (32.4%)	(-12.96, 9.36)
Presumed Eradication at Visit 4 (n, %)	88 (79.3%)	89 (80.2%)	(-10.68, 8.88)
Presumed Eradication at Visit 3 (n, %)	108 (97.3%)	107 (96.4%)	(-3.86, 5.66)

* From Sponsor's 4/27/12 Clinical Bioequivalence Amendment Tables 2.2, 2.3 and 2.4.
[1] Confidence interval calculated using Wald's method with Yates' continuity correction.

Table 11: Secondary Superiority Analyses using the mITT Population (per sponsor)*

	Test (N=113)	Reference (N=112)	Placebo (N=116)	P-values[1]	
				Test vs Placebo	Reference vs Placebo
Clinical Success at Visit 3 (n, %)	35 (31.0%)	36 (32.1%)	33 (28.4%)	0.784	0.643
Presumed Eradication at Visit 4 (n, %)	90 (79.6%)	90 (80.4%)	67 (57.8%)	<0.001	<0.001
Presumed Eradication at Visit 3 (n, %)	110 (97.3%)	108 (96.4%)	93 (80.2%)	<0.001	<0.001

* From Sponsor's 4/27/12 Clinical Bioequivalence Amendment Tables 2.2, 2.3 and 2.4.

[1] P-values for treatment comparisons from two-sided Z-test with Yates' continuity correction.

Reviewer's Comments:

According to the sponsor's reanalyses, all of the secondary endpoints are within the BE limits of [-0.20, +0.20]. Both the test and reference groups were statistically superior to the placebo groups ($p<0.05$) for all the secondary endpoints except for clinical success at end of treatment ($p=0.784$ for Test vs Placebo and $p=0.643$ for Reference vs Placebo). Both the test and reference groups were better than placebo for clinical success at end of treatment, but not statistically significantly better.

Table 8 summarizes the FDA's BE analysis results for the secondary analyes. Based on the FDA analysis, the BE test passed for all the secondary endpoints in the FPP population.

Table 12: Bioequivalence Analyses for the Secondary Endpoints in the FDA's Per-Protocol Population (per FDA statistician)

Endpoint	Test (N=111)	Reference (N=109)	90% CI (%) for the Test and Reference	Is the 90% CI within [-20, 20%]?
Clinical Success at Visit 3	30.63% (34)	31.19% (34)	-11.72, 10.60	Yes
Bacteriological Success at Visit 4	79.28% (88)	79.82% (87)	-10.39, 9.32	Yes
Bacteriological Success at Visit 3	97.30% (108)	96.33% (105)	-3.84, 5.77	Yes

Table 9 summarizes the FDA's superiority analyses results for the secondary endpoints. Based on the FDA analyses, each active treatment group was better but not statistically significantly better than placebo for the difference in clinical success rate at the end of treatment visit and statistically significantly better than placebo for the difference in bacteriological success at Visit 3 and Visit 4 in the FITT population.

Table 13: Analysis of Success Rate at Visit 4 (Follow-up Visit) in the FDA's ITT Population (per FDA statistician)

Endpoint	Test (N=113)	Reference (N=110)	Placebo (N=112)	p-values[2]	
				Test vs. Placebo	Reference vs. Placebo
Clinical Success at Visit 3	30.97% (35)	30.91% (34)	28.57% (32)	0.7710	0.7695
Bacteriological Success at Visit 4	79.65% (90)	80.00% (88)	58.04% (65)	<0.0001	<0.0001
Bacteriological Success at Visit 3	97.35% (110)	96.36% (106)	80.36% (90)	<0.0001	<0.0001

2.4.4 Bioequivalence Conclusion

The FDA's statistical analysis shows the 90% CI of the difference in success rate between the two active products is (-0.1039, 0.0932), which is within the established bioequivalence limits of [-0.20 to +0.20]. The success rate of both products were demonstrated by the FDA's analysis to be statistically superior to placebo, demonstrating that the study is sufficiently sensitive to discriminate differences between products.

2.5 Comparative Review of Safety

Previous review (Clinical Endpoint Review finalized on 3/5/12) of the safety data submitted in this ANDA confirmed that the test product did not cause any worse adverse events compared to the reference product in the topical treatment of secondarily infected traumatic skin lesions.

2.6 Relevant Findings From Other Consultant Reviews

2.6.1 Review of the DSI Report

Found acceptable in previous Clinical Endpoint Review finalized on 3/5/12.

2.6.2 Review of the FDA Statistical Report

The FDA statistical analyses support the bioequivalence of the Test and the Reference products. The FDA's statistical analysis shows that the 90% CI of the difference in success rate between the two active products was (-0.1039, 0.0932), which is within the established bioequivalence limits of [-0.20 to +0.20]. The success rate of both products were demonstrated by the FDA's analysis to be statistically superior to placebo. For details of the FDA statistical analyses, please see Section 2.4.3.3 ("Results") of this review.

2.7 Formulation

Table 14: RLD Formulation*

Ingredient	Function	RLD (%w/w)
Mupirocin calcium (micronized)	Active	2.15**
Mineral oil, USP	(b) (4)	
(b) (4)		
Stearyl alcohol, NF		
Cetyl Alcohol, NF		
Benzyl alcohol, NF		
Xanthan gum, NF		
Purified water, USP		

(b) (4)

** Equivalent to 2.0% mupirocin free acid.

Table 15: Test Formulation (per sponsor)

Ingredient	Function	Test (%w/w)
Mupirocin calcium*	Active	(b) (4)
Benzyl alcohol, NF	(b) (4)	
Mineral oil, USP		
Phenoxyethanol		
Xanthan gum, NF		
Polyoxyl 20 cetostearyl ether		
Glycerol monostearate (b) (4)		
(b) (4)		
Purified water, USP		

(b) (4)

Reviewer's Comments:

These qualitative and quantitative differences are acceptable at the levels listed from a regulatory perspective, as determined by the filing review from the Regulatory Support Branch, and the study results show no apparent effect of the formulation differences on product performance or safety.

2.8 Conclusion and Recommendation

2.8.1 Conclusion

The clinical endpoint data presented in this ANDA 201587 demonstrate that Glenmark's Mupirocin Cream USP, 2%, is bioequivalent to the reference listed drug, Bactoban® Cream. The FDA's statistical analysis shows that the 90% CI of the difference in success rate between the two active products at the 7 day follow-up visit (Visit 4) after completion of a 10-day treatment was (-0.1039, 0.0932), which is within the established bioequivalence limits of [-0.20 to +0.20]. The test and reference products also demonstrate superiority over the placebo arm, demonstrating that the study is sensitive enough to detect a difference between products.

2.8.2 Recommendations

This application is recommended for approval from a clinical bioequivalence standpoint.

OFFICE OF GENERIC DRUGS CLINICAL REVIEW

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 201587 APPLICANT: Glenmark Generics Inc., USA

DRUG PRODUCT: Mupirocin Cream USP, 2%

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

The data submitted to ANDA 201587, using the primary endpoint of the difference in clinical success rate between Test and Reference at the 7 day follow-up visit (Visit 4) after completion of a 10-day treatment are adequate to demonstrate bioequivalence of Glenmark's Mupirocin Cream USP, 2%, with the reference listed drug, Bactoban® Cream.

Please note that the bioequivalence 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 bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

John R. Peters, M.D.
Director, Division of Clinical Review
Office of Generic Drugs
Center for Drug Evaluation and Research

Barbara M. Davit, PhD, JD
Director, Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SARAH H Seung
10/15/2012

JOHN R PETERS
10/15/2012

BARBARA M DAVIT
10/26/2012

Review of a Bioequivalence Study with Clinical Endpoints

ANDA# 201587 Mupirocin Cream USP, 2% Glenmark Generics Inc., USA

Submission Date(s) Reviewed:
February 22, 2010
June 1, 2010
January 27, 2012

Sarah H. Seung, Pharm.D.
Clinical Reviewer
Office Generic Drugs

Table of Contents

Review of a Bioequivalence Study with Clinical Endpoints for ANDA 201587

1 Executive Summary

The sponsor conducted a double-blind, randomized, multi-center, parallel-group, placebo controlled study in the treatment of secondarily infected skin lesions to demonstrate that Glenmark Generics Inc., USA (Glenmark's) Mupirocin Cream USP, 2% (Test) is bioequivalent to the reference listed drug (RLD), Glaxo SmithKline's Bactoban® (mupirocin calcium) Cream, 2% (Reference). Based on the Sponsor's analyses, a total of 656 patients were eligible for randomization, of which 655 patients qualified for the sponsor's Intent-to-Treat (ITT) population, 538 patients for the sponsor's Modified Intent-to-Treat (mITT) and 510 patients for the sponsor's per protocol (PP) population.

The sponsor defined clinical success as complete resolution (Skin Infection Rating Scale (SIRS) scores of 0 on a 4-point scale) OR sustained improvement (SIRS scores of 0 for exudate/pus, crusting, tissue warmth, edema and pain; and 0 or 1 for erythema/inflammation and itching) of signs and symptoms of infection. According to the sponsor's analysis, the clinical success rate in the PP population at the 7 day follow-up visit (Visit 4) after completion of a 10-day treatment was 90.3% in the test group and 91.2% in the reference group.

The FDA recommended definition for clinical success is a SIRS score of 0 for all signs and symptoms on a 4-point scale. "Sustained improvement" is not included in the FDA definition. The sponsor's statistical analysis conclude that the 90% Confidence Interval (CI) of the difference in clinical success rate (complete resolution or sustained improvement) between Test and Reference, in the PP population, at Visit 4 is (-0.0661, 0.0482), within the bioequivalence limits of [-0.20 to +0.20]. Both Test and Reference are shown in the sponsor's analysis to be statistically superior to the vehicle cream (Placebo) ($p<0.001$) at Visit 4 in the mITT population, demonstrating that the study is sufficiently sensitive to discriminate differences between products.

However, in addition to the use of a more liberal definition of clinical cure, the sponsor included patients with secondarily infected insect bites ("infections resulting from the scratching of an insect bite") in the study population. This is specifically recommended as an **exclusion criterion** in the *Draft Guidance for Mupirocin Calcium Cream/Topical EQ 2% Base (revised October 2011)*. (b) (4)

(b) (4)

On 10/17/2011 the Division of Clinical Review (DCR) contacted the sponsor with the following request:

> "In order to confirm the appropriate diagnosis and adequately compare treatment groups at baseline, the OGD requests that you review source documents and provide a description of the target treatment site for each patient in detail, including the nature of the wound at baseline (e.g., laceration, abrasion, sutured, insect bite, etc..), dimensions of the wound, site or location on the body (e.g., left arm, nose etc..) and any other available description of the target lesion at baseline."

Glenmark was unable to provide this information for patients from 10 of the 13 clinical sites (i.e., 465 patients out of 656 enrolled patients with unknown lesion type). Therefore, given that patients with secondarily infected insect bites cannot be identified and excluded from the analysis, this study is not acceptable.

1.1 Approval Recommendation

According to the sponsor's analysis, the data submitted to ANDA 201587, using the difference in clinical success rate between Test and Reference at the 7 day follow-up visit (Visit 4), demonstrate bioequivalence of Glenmark's Mupirocin Cream USP, 2% with the RLD, Glaxo SmithKline's Bactoban® Cream, 2%. However, we are unable to confirm that the sponsor conducted the study using a sufficient number of patients meeting the acceptable inclusion and exclusion criteria, since the sponsor was unable to provide the requested additional information. Therefore, from a bioequivalence perspective, this application is not recommended for approval.

1.2 Summary of Clinical Findings

1.2.1 Brief Overview of Clinical Program

Glenmark conducted a clinical endpoint study, enrolling 656 patients, to establish the bioequivalence of their proposed Mupirocin Cream USP, 2% to the RLD, Bactoban® Cream, 2%, in the topical treatment of secondarily infected traumatic skin lesions. All patients were randomized in a 1:1:1 ratio to apply either the Glenmark product (Test), Bactoban® Cream (Reference) or the vehicle cream (Placebo) three times daily for 10 days. It is noted that the sponsor included patients with secondarily infected insect bites in the study population. This has been specifically recommended as an exclusion criterion in the *Draft Guidance for Mupirocin Calcium Cream/Topical EQ 2% Base (revised October 2011).*

Reviewer Comments:

Although the Draft Guidance for Mupirocin Calcium Cream/Topical EQ 2% Base (revised October 2011) was posted after this study, the contract research organization (Symbio, LLC) requested recommendation on a protocol design (OGD's P04-004; Symbio LLC's protocol number SYM-2003-08) for a clinical endpoint study using a generic mupirocin cream, 2% and Bactrobn Cream, 2% "in the treatment of secondarily infected wounds" on January 23, 2004 (prior to this study initiation). Protocol SYM-2003-08 excluded "subjects who have a secondarily infected bite (animal, human or insect) or puncture wound." (exclusion criteria #8). Protocol SYM-2003-08 did not specify a special circumstance (as noted in the exclusion criteria #8 for this ANDA) whereby "infections resulting from the scratching of an insect bite were considered secondarily infected traumatic skin lesions." In addition, OGD provided specific instructions to Symbio, LLC (letter dated September 24, 2004) that "the type of wound and site of wound should be compared and tabulated for each treatment group" (Comment #9) so that any patients with inappropriate diagnosis can be excluded from analysis.

It should also be noted that in OGD's response letter, Symbio, LLC was provided with FDA's recommended definition for clinical success as a SIRS score of 0 (absent) for all signs and symptoms.

1.2.2 Comparative Efficacy

The primary endpoint of this study evaluated by the sponsor was clinical success at the 7 day follow-up visit (Visit 4) after completion of a 10-day treatment. The sponsor defined clinical success as complete resolution (SIRS scores of 0 on a 4-point scale) or sustained improvement (SIRS scores of 0 for exudate/pus, crusting, tissue warmth, edema and pain; and 0 or 1 for erythema/inflammation and itching) of signs and symptoms of infection. The FDA recommended definition of clinical success is only a SIRS score of 0 for all signs and symptoms on a 4-point scale. According to the sponsor's analysis, the success rate in the PP population at Visit 4 was 90.3% in the test group and 91.2% in the reference group. The 90% CI of the difference in success rate between the two active products is (-0.0661, 0.0482), which is within the established bioequivalence limits of [-0.20 to +0.20].

Reviewer Comments:

The use of a more liberal definition of clinical cure, in addition to the inclusion of patients with secondarily infected insect bites (which often spontaneously resolves with no antimicrobial treatment), would tend to overstate the clinical cure for both the test product and the RLD in comparison to the placebo. Thus, potentially suggesting superiority to placebo where there was none and reducing the sensitivity of the clinical endpoint study to distinguish differences between the drug products.

1.2.3 Comparative Safety

The safety data submitted in this ANDA confirm that the test product did not cause any worse adverse events compared to the reference product in the topical treatment of secondarily infected traumatic skin lesions. A total of 655 patients received medication. Of these, 220 received the test product, 216 received the reference product and 219 received the placebo.

A total of 60 patients (22 in the test, 15 in the reference, and 23 in the vehicle group) experienced one or more treatment-emergent adverse events and 2 patients discontinued the study due to an adverse event. All of the AEs were mild or moderate in severity.

According to the sponsor's analysis, there was no statistically significant difference between the test and reference products in the proportion of subjects reporting any AEs and in the proportion of subjects reporting AEs definitely or probably or possibly related to study medication (all $p>0.05$).

No SAEs or deaths were reported.

2 Clinical Review

2.1 Introduction and Background

Mupirocin is an antibacterial agent active against a wide range of gram positive bacteria and has become a recognized topical treatment for impetigo since the approval of Bactroban® Ointment (NDA 050591). In 1997, the FDA approved Bactroban® Cream (NDA 050746) for the topical treatment of secondarily infected traumatic skin lesions (up to 10 cm in length or 100 cm^2 in area) due to susceptible strains of *Staphylococcus aureus* and *Streptococcus pyogenes*. The approved labeling recommends three times daily application to the affected area for 10 days. Patients not showing a clinical response within 3 to 5 days should be re-evaluated. The safety and effectiveness for pediatric use (aged 3 months to 16 years) was demonstrated to be similar to adult patients. Only headache was thought to be possibly or probably related to Bactroban® Cream in children.

2.1.1 Summary of Drug Information

Drug Established Name	Mupirocin Cream, 2%
Drug Class	Antibacterial agent
Reference Listed Drug	Bactroban® Cream
RLD Firm	Glaxo SmithKline
NDA #	050746
Date of RLD Approval	December 11, 1997

Approved Indication(s)	topical treatment of secondarily infected traumatic skin lesions (up to 10 cm in length or 100 cm^2 in area) due to susceptible strains of *Staphylococcus aureus* (*S. aureus*) and *Streptococcus pyogenes* (*S. pyogenes*)
Recommended Dosing Regimens	Apply three times daily for 10 days, the treated area may be covered with gauze dressing if desired. Patients not showing a clinical response within 3 to 5 days should be re-evaluated.

2.1.2 Regulatory Background

2.1.2.1 INDs, Protocols, or Control Documents submitted by Sponsor

The contract research organization (Symbio, LLC) submitted a protocol (P04-004), dated January 23, 2004, for this drug product. Comments regarding the protocol were forwarded to Symbio, LLC on September 24, 2004.

Reviewer Comments:

The protocol submitted by Symbio, LLC (OGD's P04-004; Symbio LLC protocol number SYM-2003-08) excluded "subjects who have a secondarily infected bite (animal, human or insect) or puncture wound." (exclusion criteria #8). The protocol did not specify a special circumstance (as noted in the exclusion criteria #8 for this ANDA) whereby "infections resulting from the scratching of an insect bite were considered secondarily infected traumatic skin lesions." In addition, OGD's comments to Symbio LLC included a statement that "the type of wound and site of wound should be compared and tabulated for each treatment group" (Comment #9) and that "the preferred definition of clinical cure is a Skin Infection Rating Scale (SIRS) score of 0 (absent) for all evaluated primary clinical sings and symptoms" (Comment #7).

2.1.2.2 INDs, Protocols, or Control Documents submitted by other sponsors

Several INDs, protocols and controls have been submitted by other sponsors for this drug product. Each of these sponsors were given the same advice as that forwarded in the DCR response of 9/24/2004 to Symbio regarding their protocol for this study.

2.1.2.3 Previous ANDA submissions for same product

There is no approved ANDA for this drug product. There is another ANDA under review for this drug product.

2.1.3 Other Relevant Information

The FDA has posted a *Draft Guidance on Mupirocin Calcium Cream/Topical, EQ 2% Base, (Revised October 2011*) on the FDA website:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guid

ances/UCM217146.pdf. This *Draft Guidance* represents the most recent recommendations of the OGD.

Reviewer's Comments:

Although the CRO for the sponsor did contact the Agency regarding recommendations for the protocol design to compare bioequivalence of a generic mupirocin cream, 2% to the RLD and the Agency's comments were forwarded to the CRO, the study conducted for this ANDA did not follow the submitted protocol or the recommendations provided to the CRO. Details of Glenmark's protocol, such as inclusion/exclusion criteria and definition of clinical cure, are not consistent with our recommendations or the current Draft Guidance.

2.2 Description of Clinical Data and Sources

Protocol Number	GLK 605
Study Title	A multi-center, double-blind, randomized, vehicle-controlled, parallel group study comparing generic Mupirocin Calcium Cream, 2% to Bactroban Cream® (mupirocin calcium cream), 2% and both active treatments to a vehicle control in the treatment of secondarily infected traumatic skin lesions
CRO	Symbio, LLC
Study Period	First Patient Enrolled: July 14, 2008 Last Patient Completed: June 8, 2009

Study Centers, Principal Investigators and Enrollment

The study was performed by the following investigators at 12 sites. Dr. Ortiz replaced Dr. Aguilar as principal investigator at Site No. 6 during the conduct of the study.

Table 1: Study Centers

Site Number	Principal investigator and Location	Number Enrolled
01	Manuel Briones, M.D. Guayaquil, Ecuador	75
02	Zila Espinosa, M.D. Clínica Metrópolis II Panama City, Panama	74
03	Nelly Paz, M.D. Centro Orquídea Blanca San Pedro Sula, Honduras	107
04	Daisy Blanco, M.D. Instituto Dermatológico Santo Domingo, Republica Dominicana	114
05	Josefina Fernandex, M.D. Departamento de Enfermedades Infecciosas, Hospital Infantil Santo Domingo, Rep. Dominicana	115
06	Arnoldo Aguilar, M.D. and Carlos Ortiz, M.D. San Salvador, El Salvador	51

Site Number	Principal investigator and Location	Number Enrolled
07	Kimball Silverton, D.O. DO, Silverton Skin Institute Grand Blanc, MI 48439	0
08	Charles Griff, M.D. Visions Clinical Research West Palm Beach, FL 33406	0
09	Did not enroll patients	0
10	Alex White, M.D. Avivoclin Clinical Services Port Orange, FL 32127	12
11	Lawrence C. Parish, M.D. Paddington Testing Co. Philadelphia, PA 19103	12
12	Patricia Chang, M.D. Paseo Plaza Clinic Center Cludad de Guatemala, Guatemala	3
13	Ynca Nina Vasquez, M.D. Instituto Dermatololo'gico Unidad Sur Santa Domingo, Republica Dominicana	93

2.3 Clinical Review Methods

2.3.1 Overview of Materials Consulted in Review

Original Submission:

February 22, 2010 (Non-eCTD electronic submission)

Study Amendments:

- June 1, 2010 (Clinical Bioequivalence/Response to Information Request) - number of patients enrolled at each site.
- January 27, 2012 (Clinical Bioequivalence/Response to Information Request) - description of target lesion.

Reviewer's Comments:

On 10/17/2011 the DCR contacted the sponsor to provide a description of the target treatment site for each patient in detail, including the nature, dimensions, site or location of the wound, and any other available description of the target lesion at baseline.

In the 1/27/2012 amendment, Glenmark states that "the exact nature or dimension was not captured as an essential part of the source documentation nor the CRF." It is noted in the amendment response that "Symbio (Clinical Research Organization) was able to collect the description of wound for all subjects from two sites…These 2 investigators routinely made notation in the subject's medical records of the nature of the wound, which was not the case at all sites." Thus, the sponsor was unable to describe the nature of the wound for patients from 10 of the 13 clinical sites (i.e., 465 patients out of 656 enrolled patients had unknown lesion type). Given that all patients with secondarily

infected insect bites cannot be identified (in order to exclude from analysis), the sponsor's response is inadequate.

2.3.2 Overview of Methods Used to Evaluate Data Quality and Integrity

Office of Scientific Investigations (OSI) Report:

An OSI inspection was requested on July 29, 2010. Sites 04 (PI:Daisy Blanco, MD), 05 (PI:Josefina Fernandez, MD) and 13 (PI:Ynca Nina Vasquez, MD) were inspected. The inspection (EIR review dated July 12, 2011) revealed that all three sites had objectionable findings for which Form FDA-483 was issued. All three sites have been classified as Voluntary Action Indicated. For details of the observations, please see Section 2.6.1 ("Review of the DSI Report ") of this review.

2.3.3 Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor stated:

> The protocol, informed consent form, and any advertisements employed to recruit patients were approved by an Institutional Review Board (IRB) whose operations were in compliance with Section 56 of Title 21 of the Code of Federal Regulations (CFR), prior to enrollment of any study patients. Any changes to the protocol as well as a change of investigator, which were approved by the sponsor, were also approved by the site's IRB and documentation of this approval provided to the sponsor or designee…. This study was conducted in compliance with U.S. Food and Drug Administration (FDA) regulations (21 CFR Parts 50, 54, 56, and 312), the ethical principles of the Declaration of Helsinki, all applicable International Conference on Harmonization (ICH) guidelines, and all local laws and regulations concerning clinical studies. Prior to initiation of the study, each Principal Investigator signed Form FDA 1572, agreeing to conduct the trial in compliance with the protocol and according to Good Clinical Practice (GCP).

Reviewer's Comments:

The sponsor's study appears to be in compliance with accepted ethical standards.

2.3.4 Evaluation of Financial Disclosure

Each Principal Investigator and Sub-Investigator certified that, in compliance with 21 Code of Federal Regulations (CFR) Part 54, no financial arrangements have been made where the study outcome could affect compensation, that each have no proprietary interest in the tested product, that each do not have a significant equity interest in the sponsor or any subsidiary worldwide of the covered study, and that each have not received significant payments, grants, and/or equipment from the sponsor of this study. The sponsor did not use Form FDA 3454.

2.4 Review of a Clinical Endpoint Bioequivalence Study

2.4.1 Brief Statement of Conclusions

Based on the sponsor's analysis, the study meets the bioequivalence limits of the difference in clinical success (a SIRS score of 0 for all signs and symptoms on a 4-point scale) between Test and Reference at the 7 day follow-up visit (Visit 4) after completion of a 10-day treatment. However, we are unable to confirm that the sponsor conducted the study using a sufficient number of patients meeting the acceptable inclusion and exclusion criteria, since the sponsor was unable to provide the requested additional information.

2.4.2 General Approach to Review of the Comparative Efficacy of the Drug

The sponsor's study (Protocol # GLK 605) was reviewed to evaluate the bioequivalence of the test and reference products. The primary endpoint of this study is clinical success at the 7 day follow-up visit (Visit 4) after completion of a 10-day treatment. The sponsor's proposed primary parameter was evaluated for bioequivalence and secondary parameters were considered as supportive information.

2.4.3 Detailed Review of Bioequivalence Studies with Clinical Endpoints

2.4.3.1 Protocol Review

Sponsor's protocol #:	GLK 605
Title	A multi-center, double-blind, randomized, vehicle-controlled, parallel-group study comparing generic Mupirocin Calcium Cream, 2% to Bactroban Cream® (mupirocin calcium cream), 2% and both active treatments to a vehicle control in the treatment of secondarily infected traumatic skin lesions
Objectives	The objectives of this study were to demonstrate comparable safety and efficacy of Generic Mupirocin Calcium Cream, 2% and Bactroban Cream® (mupirocin calcium cream), 2% and to show the superior efficacy of the two active creams over that of the Vehicle (placebo) in the treatment of secondarily infected skin lesions.

2.4.3.1.1 Study Design

Overall Study Design and Plan

This was a 17 day, multi-center, double-blind, randomized, vehicle-controlled, parallel-group study in patients 18 months of age or older with a diagnosis of secondarily infected skin lesions (up to 10 cm in length or 100 cm^2 in area) due to susceptible strains of *Staphylococcus aureus* and/or *Streptococcus pyogenes*, to compare the efficacy of

generic Mupirocin Calcium Cream, 2% (Test) versus Bactroban Cream® (mupirocin calcium cream), 2% (Reference), and their efficacy over the Vehicle Cream (Placebo). The study consisted of a Screening/Baseline visit (Visit 1, Day 1), an On Treatment visit (Visit 2/Day 3-5), an End of Treatment visit (Visit 3/Day 10-12), and a Follow-up visit (Visit 4/Day 17-21). The study schedule is depicted in Table 2.

Patients satisfying all inclusion/exclusion criteria were randomly assigned in a 1:1:1 ratio to one of the three study formulations. Patients applied study medication topically three times daily for 10 days.

If at any time, the investigator determined that the infection had become systemic, was not responding to treatment or that the study treatment was not sufficient to treat the degree of disease activity present, he or she could remove the patient from the study and prescribe appropriate treatment or refer the patient to another physician. Use of rescue therapy was documented in the CRF.

The sponsor's primary efficacy endpoint was the clinical response as determined at the follow-up visit (Visit 4). The sponsor's secondary efficacy endpoints were bacteriological response (defined by one of the following: presumed eradication, super infection, failure, relapse, or unable to determine) at the follow-up visit (Visit 4) and at the end of treatment visit (Visit 3); and clinical response at the end of treatment visit (Visit 3). Clinical response was defined by the sponsor as one of the following: clinical success or clinical failure. The sponsor defined clinical success as complete resolution (SIRS scores of 0 on a 4-point scale) or sustained improvement (SIRS scores of 0 for exudate/pus, crusting, tissue warmth, edema and pain; and 0 or 1 for erythema/inflammation and itching) of signs and symptoms of infection.

Reviewer Comments:

The sponsor's overall study design, primary endpoint and secondary endpoints are consistent with the Draft Guidance for Mupirocin Calcium Cream/Topical EQ 2% Base (revised October 2011). However, the sponsor's definition for clinical success is not consistent with this Draft Guidance. The Draft Guidance defines clinical success as a SIRS score of 0 for all signs and symptoms on a 4-point scale. "Sustained improvement" is not included in the Draft Guidance definition.

Procedures and Observations:

A summary of the study procedures performed at each visit is given in Table 2.

Table 2: Study Schedule

Procedure	Visit 1 Screening/ Baseline (Day 1)	Visit 2 On Treatment (Day 3-5)	Visit 3 End of Treatment (Day 10-12)	Visit 4 Follow-up (Day 17-21)	Unscheduled /Early Termination Visit
Screening/Informed Consent	X				
Inclusion/Exclusion Criteria	X				

Procedure	Visit 1 Screening/ Baseline (Day 1)	Visit 2 On Treatment (Day 3-5)	Visit 3 End of Treatment (Day 10-12)	Visit 4 Follow-up (Day 17-21)	Unscheduled /Early Termination Visit
Medical History	X				
Physical Examination (including vital signs)	X				
Urine Pregnancy Test*	X				
Skin Infection Rating	X	X	X	X	X
Clinical Response			X	X	X
Bacteriology Specimen Collection	X		X	X	X
Bacteriological Response			X	X	X
Adverse Event Reporting		X	X	X	X
Concurrent Medication	X	X	X	X	X
Randomization/Drug Dispensing	X				
Patient Instruction/Compliance	X	X	X	X	X
Drug Return, Accountability		X	X		X

* For women of child-bearing potential - to be completed in doctor's office prior to enrollment

Study Population:

Inclusion Criteria:

Patients were required to meet all of the following criteria:

1. Patients 18 months of age or older with a definite clinical diagnosis of a secondarily infected traumatic skin lesion (up to 10 cm in length or 100 cm^2 in area) due to susceptible strains of *S. aureus* and/or *S. pyogenes*.
2. Patients with a SIRS total score of at least 4 and white blood cells observed on Wright stain or Gram stain slide prepared from wound exudates.
3. Women of childbearing potential (excluding women who are surgically sterilized or post menopausal for at least 2 years), in addition to having a negative urine pregnancy test, were willing to use an acceptable form of birth control during the study.
4. Patients 18 years of age or older provided IRB approved written informed consent.
5. Patients under the age of 18 had parent or legal guardian provide IRB approved written informed consent. For Patients 12-17 years of age, an assent form for minors was completed.
6. Patients were willing and able to understand and comply with the requirements of the study, apply the medication as instructed, return for the required treatment period visits, comply with therapy prohibitions, and were able to complete the study.

7. Patients were in good health and free from any clinically significant disease, other than secondarily infected traumatic skin lesions, that might have interfered with the study evaluations.

Reviewer Comments:

The FDA generally recommends enrolling patients with a SIRS total sore of at least 8. The protocol (OGD P04-004; Sponsor protocol #SYM-2003-08) submitted by the CRO (Symbio, LLC) had a SIRS score of at least 8 for inclusion.

Exclusion Criteria:

Patients were excluded if any of the following were present:

1. Patients who were pregnant, nursing, or planning a pregnancy within the study participation period.
2. Patients with any other confounding skin condition.
3. Patients with clinically significant systemic disease (i.e., immunological deficiencies), unstable medical disorders, life-threatening disease, or current malignancies.
4. Patients with systemic signs or symptoms of infection.
5. Patients who required surgical intervention for treatment of infection.
6. Patients who had a known hypersensitivity to any of the following (in any dosage form): penicillins, cephalosporins, other beta-lactam antimicrobials or mupirocin and/or to any component of the study medications.
7. Patients with a bacterial skin infection that, because of depth or severity, should not have been treated with a topical antibiotic (e.g., cellulitis, abscess, ulcer, furunculosis).
8. Patients who had a secondarily infected bite (animal, human or insect) or puncture wound. Note: Infections resulting from the scratching of an insect bite were considered secondarily infected traumatic skin lesions.
9. Patients who applied any topical therapeutic agent directly to the wound within 24 hours prior to study entry.
10. Patients who had been treated with systemic antibacterial or steroid within 7 days prior to study entry.
11. Patients who consumed excessive amounts of alcohol, abused drugs, or had any condition that would compromise compliance with this protocol.
12. Patients who had been treated with an investigational drug or investigational device within a period of 4 weeks prior to study entry.
13. Patients who had been previously enrolled in this study.

Reviewer Comments:

- *The FDA recommended exclusion for topical therapeutic agents is use within 48 hours prior to baseline. All patients stopped use of topical therapeutic agents at least two days prior to the baseline visit.*

- *The FDA generally recommends excluding patients with diabetes. Even though the sponsor did not specify to exclude patients with diabetes, none of the enrolled patients had diabetes.*
- *Infections resulting from scratching an insect bite is not acceptable. The* Draft Guidance for Mupirocin Calcium Cream/Topical EQ 2% Base (revised October 2011) and the recommendations forwarded to this protocol *define secondarily infected traumatic skin lesion as "a laceration, sutured wound or abrasion." The protocol ((OGD P04-004; Sponsor protocol #SYM-2003-08) submitted by the CRO did not have this exception to the exclusion criteria. In a Memorandum to the sponsor, dated and finalized on October 17, 2011, Glenmark was requested to "provide a description of the target treatment site for each patient in detail, including the nature of the wound at baseline (e.g., laceration, abrasion, sutured, insect bite, etc.), dimensions of the wound, site or location on the body (e.g., left arm, nose etc.) and any other available description of the target lesion at baseline." In Glenmark's January 27, 2012 response, Glenmark stated that "the exact nature or dimension was not captured as an essential part of the source documentation nor the CRF." However, description of the wound was collected from 2 clinical sites where the "investigators routinely made notation in the subject's medical records of the nature of the wound." These 2 sites enrolled 190 patients.*

Criteria for removal from the study:

Patients were free to leave the trial at any time for any reason without prejudice to future care by the physician or at the institution. The investigator and sponsor also had the right to withdraw patients from the study in the event of insufficient therapeutic response, intercurrent illness, AEs, protocol violation, baseline culture negative for causative organisms, use of concomitant therapy which would interfere with the results of the study, or other reasons. The reasons for withdrawal were clearly documented in the CRF. If a patient decided to withdraw, all efforts were made to complete and report the end of study evaluations as thoroughly as possible.

In the event that a patient discontinued from the study at any time due to an AE, the reason for discontinuation, the nature of the event and its clinical course were fully documented. For such a patient, the investigator strived to follow the patient until the AE resolved, became clinically insignificant, was stabilized, or the patient was lost to follow-up.

Reviewer Comments:

No patients became pregnant during this study.

Prior and Concomitant Therapy:

The following were prohibited during this study:

1. Any topical therapeutic agent applied directly to the wound.
2. The use of any anti-infective to the treated area other than study medication.

3. Systemic corticosteroids (intranasal or inhaled corticosteroids were acceptable if kept constant throughout the study) or immunosuppressive agents.
4. Topical corticosteroids applied to the treated areas.
5. Systemic antibacterials or corticosteroids.

Medications necessary for the health and well being of the patient were permitted. Patients were allowed the use of analgesics, such as aspirin, acetaminophen, or ibuprofen, and the use of medications for the treatment of seasonal diseases (colds, flu, etc.). Anti-infective therapy (other than the study medication) was not allowed throughout the study.

Reviewer Comments:

The sponsor's list of prohibited concomitant medications is acceptable.

Treatments:

Patients were randomly assigned in a 1:1:1 ratio to one of the three treatment groups:

Test*	Mupirocin Cream USP, 2% Manufacturer: Glenmark Generics Limited Lot Number: Q15748002 Expiry Date: December 2009
Reference*	Bactroban® Cream (mupirocin calcium cream), 2% Manufacturer: GlaxoSmithKline Lot numbers: C328473 Expiry Date: May 2009
Placebo*	Vehicle of test product Manufacturer: Glenmark Generics Limited Lot Number: QP15748001 Expiry Date: December 2009

* Glenmark supplied the investigational treatments. (b) (4) labeled, assembled, and shipped study medications.

The following instructions were given to each patient:

- You have been given one (1) tube of cream for use in the study. Store tube at or below 25°C (77°F). Do not freeze.
- It is important that you bring your medications with you at each visit in order to determine if you are using the cream properly.
- The cream should be applied three times (3X) daily for 10 days. Apply the cream at the same time each day. Please note: The cream is for external use only. Avoid contact with eyes.
- As demonstrated during your visit, clean the wound with warm water using only nonantibacterial soap, pat dry and apply a thin layer of study medication to the entire wound using a sterile gauze sponge. Rub in gently and completely.
- Continue to apply the cream three times each day for 10 days (no more than 30 applications).

- If instructed by your doctor, you may cover the treated area with gauze dressing.
- Do not shower, bathe, wash, or swim for at least two (2) hours after applying the cream.
- Do not apply any antibacterial products or any other treatments (other creams, lotions, gels, ointments, etc.) to affected areas for the entire time you are participating in the study without your doctor's permission.
- Please bring the study medication with you to each return study visit. All used and unused tubes must be returned to your doctor's office.
- If you see a doctor for another medical problem while you are participating in this study, please have him/her call your physician.

The first dose of study medication was applied under the supervision of a member of the site staff not responsible for clinical or bacteriological assessments (e.g. the third-party dispenser) to ensure understanding of the study medication application procedure. Patients were given diary cards to record medication doses. The treatment period was 10 days. Treatment continued for the entire treatment period. All study medication was required to be returned to the study site.

Compliance:

Patients were to apply the medication three times daily for 10 days. Compliance was determined from the diary card, in which the patient was instructed to record all applications made or missed. The number of applications missed was totaled by the study coordinator and recorded on the compliance page of the CRF. Compliant patients made at least 20 (66.6%) and no more than 30 (100%) applications of study medication, inclusive of medication applications during participation in the study, and missed no more than six consecutive doses. The used tubes of study medication were collected by the study site at appropriate visits or early termination.

Reviewer Comments:

OGD generally recommends compliance to be 75% to 125%. However, in OGD's September 24, 2004 response to the CRO, OGD included a statement that "less than 20 (66.6%) or more than 30 applications should be considered as non-compliant with study treatment and should be excluded from the per protocol population" (Comment #6).

Randomization:

The randomization scheme was generated so that Test, Reference, and Placebo were assigned in a 1:1:1 ratio. (b) (4) prepared the randomization schedule. The patient numbers were assigned sequentially in the order in which patients were enrolled at each center.

In order to ensure that information which could potentially bias handling of data was not disclosed, only 6 copies of the randomization schedule with drug assignments were generated. These 6 copies remained stored and filed in a filing cabinet in (b) (4) (b) (4). The 6 copies remain filed at (b) (4) until

Glenmark approves their destruction. The original approved randomization schedule was sent to (b) (4) documentation department and filed under the specified project binder.

Reviewer Comments:

(b) (4) *labeled, assembled, and shipped study medication, and prepared the randomization schedule for this study. No issue with maintaining a sealed/blinded randomization code at the clinical sites was observed during the OSI inspections.*

Blinding:

This was a double-blind study. The investigators, staff at the study sites, study monitors, and data analysis/management personnel were blinded to the patient assignment.

Study medication tubes were labeled and packaged so that neither the patient nor the investigator could identify the treatment. In order to nullify any remaining differences in product packaging, the investigator/sub-investigator performing the study evaluations was not involved with the dispensing or return of the study medication. Periodically and at the study conclusion, the integrity of the dispensing and blinding was checked by the study monitor.

Patients were assigned treatments in sequential order, in blocks of 3, according to a computer-generated randomization schedule. The study medication was provided to the investigators in blocks of 3 patient kits by (b) (4) Each kit was labeled with a 2-part, double-blind label which clearly disclosed the protocol number, patient number, content statement, storage statement, caution statement, and sponsor's name and address. The tear off kit label, which also contained the compound name, strength, and lot number in the blinded panel, was attached to the Study Medication Dispensing Log at the time of dispensing. Each kit contained two 30-gram tubes, each of which was labeled with a single panel label that clearly disclosed the protocol number, patient number, directions for use, storage statement, caution statement, and sponsor's name and address. In the event of an emergency, the patient-specific treatment could be identified by removing the overlay of the two-part label, which was attached to the Study Medication Dispensing Log after dispensing; however, every effort was made to maintain the blind. The Sponsor was to be notified in the event the blind was broken.

Reviewer Comments:

The blinding is acceptable.

2.4.3.1.2 Endpoints/Variables

Diagnosis

The investigator or sub-investigator examined the patient to establish the clinical diagnosis of secondarily infected traumatic skin lesions. The location of the wound (target) was recorded on the anatomical diagram in the patient's source documentation. A wound was defined in the protocol as a laceration or sutured wound 10 cm or less in length with surrounding erythema $\leq$ 2 cm from edge of lesion OR an abrasion no more

than 100 cm^2 in total area with surrounding erythema no more than 2 cm from abrasion edge.

Reviewer Comments:

As previously stated, the sponsor stated that in the January 27, 2012 amendment that "the exact nature or dimension was not captured as an essential part of the source documentation nor the CRF." Although descriptions of the wound was collected from 2 clinical sites, the clinical diagnosis of secondarily infected traumatic skin lesions could not be verified for all the enrolled patients. Of the 190 patients enrolled at these 2 clinical sites, 19 were noted to have lesions due to scratching, scratching an insect bite or scratching a lesion.

Clinical Evaluation

Investigator or sub-investigator assessed clinical signs of the wound at each visit using the SIRS scoring scale (see Table 3 below) for each of the following signs: exudate/pus, crusting, erythema/inflammation, tissue warmth, and edema. Symptoms (itching and pain) were scored by the patient.

Table 3: Skin Infection Rating Scale (per Sponsor)*

Score	Description
0	Absent; no evidence of sign/symptom
1	Mild; sign/symptom present but not intense
2	Moderate; sign/symptom clearly evident and somewhat bothersome to patient
3	Severe; sign/symptom clearly evident, intense and extremely bothersome to patient

* From Sponsor's Protocol GLK 605 version 1.0 Appendix IV.

Clinical Response was derived at both End of Treatment (Visit 3) and Follow-up (Visit 4) visits using the following definitions:

Clinical Success: complete resolution (SIRS scores of 0) or sustained improvement (SIRS scores of 0 for exudate/pus, crusting, tissue warmth, edema and pain; and 0 or 1 for erythema/inflammation and itching) of signs and symptoms of infection. No additional antibiotic therapy required after End of Treatment.

Clinical Failure: inability to clear or improve the presenting signs/symptoms (SIRS scores of >0 for exudate/pus, crusting, tissue warmth, edema and pain; or SIRS score >1 for erythema/inflammation and itching).

Reviewer Comments:

- *The sponsor's Skin Infection Rating Scale for all six signs and symptoms is consistent with the Draft Guidance for Mupirocin Calcium Cream/Topical EQ 2% Base (revised October 2011).*

- *The FDA recommended definition for clinical success is a SIRS score of 0 for all signs and symptoms as per the Draft Guidance for Mupirocin Calcium Cream/Topical EQ 2% Base (revised October 2011). This recommended definition was provided to the CRO in OGD's letter dated September 24, 2004 for P04-004 (Comment #7). The inclusion of patients with sustained improvement in the clinical success group is not acceptable as it could reduce the sensitivity of the clinical endpoint study in distinguishing differences between drug and placebo.*

Bacteriological Evaluation

Bacteriology Specimen Collection: A wound exudate sample for culture and sensitivity testing was taken with a swab and sent to a designated laboratory for culture. A positive culture (*S. aureus* or *S. pyogenes*) was required for study inclusion although patients were enrolled providing there were white blood cells observed on Wright stain or Gram stain slide prepared from wound exudates. Patients with negative baseline cultures were to be discontinued as soon as possible after negative results were received by the clinical site.

Bacteriological Response was determined by the investigator at both End of Treatment (Visit 3) and Follow-up (Visit 4) visits using the following definitions:

Presumed Eradication at End of Treatment (Visit 3): culture was not clinically indicated (negative culture or no culturable material present).

Presumed Eradication at Follow-up (Visit 4): culture was negative or not clinically indicated (i.e. no culturable material present and SIRS scores indicative of clinical success [SIRS scores of 0 for exudate/pus, crusting, tissue warmth, edema and pain; and 0 or 1 for erythema/inflammation and itching]).

Super Infection: pre-therapy pathogen was eliminated but a different pathogen was isolated.

Failure: non-eradication of initial pathogen.

Relapse: initial pathogen eliminated at End of Treatment but re-emerges at Follow-up.

Unable to determine: bacteriological evaluation could not be made.

Primary Endpoint:

The sponsor's primary endpoint was the clinical response as determined at the follow-up visit (Visit 4). Clinical response was defined by the sponsor as one of the following: clinical success or clinical failure. The sponsor defined clinical success as complete resolution (SIRS scores of 0 on a 4-point scale) or sustained improvement (SIRS scores of 0 for exudate/pus, crusting, tissue warmth, edema and pain; and 0 or 1 for erythema/inflammation and itching) of signs and symptoms of infection.

Reviewer's Comments:

Per the Draft Guidance for Mupirocin Calcium Cream/Topical EQ 2% Base (revised October 2011), the FDA recommended primary endpoint of this study is the proportion of patients in the PP population with clinical success at the follow-up visit (7 days after the end of treatment). The sponsor's primary endpoint is acceptable; however, the sponsor's definition of clinical success is not acceptable. As previously mentioned, the FDA recommended definition for clinical success is a SIRS score of 0 for all signs and symptoms on the 4-point scale.

Secondary Endpoints:

Secondary efficacy evaluations included comparing the proportions of:

1. Presumed Eradication at Visit 4 (Follow-up)
2. Clinical Success at Visit 3 (End of Treatment)
3. Presumed Eradication at Visit 3 (End of Treatment)

Reviewer's Comments:

The sponsor's secondary endpoints are consistent with the Draft Guidance for Mupirocin Calcium Cream/Topical EQ 2% Base (revised October 2011).

2.4.3.1.3 Statistical analysis plan

This study was conducted under the same protocol across all study sites. No formal statistical analyses were performed to detect treatment-by-site differences.

For each continuous variable, the summary included the mean, standard deviation (SD), and range. For each categorical variable, the summary included frequencies and percentages.

The statistical analysis plan is provided in Appendix 16.1.9 of the sponsor's study report.

Patient Populations:

The sponsor identified three patient populations: Intent-to-Treat (ITT), Modified Intent-to-Treat (mITT), and Per-Protocol (PP) Populations. The sponsor's efficacy analyses were performed on the mITT and PP populations. The mITT population was the primary population for analysis of superiority of the active products over the Placebo. The PP population was the primary population for the therapeutic equivalence comparison between the two active products. Safety analyses were performed on the ITT population. The three patient populations were defined as follows:

Intent-to-Treat (ITT) Population

- was enrolled into the study
- received at least one application of study medication

Reviewer's Comments:

The sponsor's definition for the ITT population is acceptable.

Modified Intent-to-Treat (mITT) Population

- was enrolled into the study
- met all inclusion/exclusion criteria including a positive baseline culture
- received at least one application of study medication
- had at least one post-screening visit

Reviewer's Comments:

The sponsor's definition for the mITT population is acceptable.

Per-Protocol (PP) Population

- was enrolled into the study and met inclusion/exclusion criteria including a positive baseline culture
- had not taken any concomitant medications prohibited by the protocol or had any other significant protocol violations
- was compliant with applications of study medication (66.6% to 100%) and did not miss more than 6 consecutive doses of study drug treatment during the treatment period
- did not miss more than 2 consecutive required visits
- returned for Visit 4 within visit window with data on the primary efficacy variables for bacteriologic and clinical evaluations unless discontinued from the study early due to insufficient therapeutic response after at least 3 days of applications (with a compliance rate of at least 66.6% and not more than 100%)

Reviewer's Comments:

See previous comment regarding compliance.

Protocol Violations

The sponsor defined a “study protocol violation” as any patient or investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy. Potential study protocol violations included:

- violation of inclusion/exclusion criteria
- negative baseline culture
- for patients who were considered treatment failures, failure to apply the study medication for at least 3 days with a compliance rate of 66.6% to 100%
- failure to return for Visit 4 (Follow-up) within the visit window unless discontinued early as a treatment failure
- no primary efficacy outcome data available for Visit 4 (Follow-up) unless discontinued early as a treatment failure

- the compliance rate of study treatment applications was not within the range of 66.6% to 100%
- missed more than 6 consecutive doses of study drug treatment during the treatment period
- missed more than 2 consecutive required visits
- used prohibited medications
- premature unblinding of the study medication

Demographic and Baseline Characteristics Analysis

According to the sponsor, baseline variables (e.g., sex, age, ethnic origin) were evaluated, adjusting for center, to identify differences between treatment groups, which were not eliminated by randomization. Any significant baseline differences were reviewed for their potential impact on the efficacy findings.

Continuous demographic variables at baseline were examined by analysis of variance (ANOVA) when normal error and homogeneous variance assumptions were satisfied, or by the nonparametric rank-based ANOVA when they were not, to compare treatment group differences.

Categorical variables such as gender, race, etc., were examined by Cochran-Mantel-Haenszel (CMH) test, stratified by center.

Primary Endpoint Bioequivalence and Efficacy Analyses:

The primary efficacy analyses were the comparisons between Test and Reference for the proportion of patients with Clinical Success at the follow-up visit (Visit 4).

According to the sponsor, Wald's 90% confidence interval was constructed for the difference between Test and Reference in the proportion of patients with Clinical Success. Yates' continuity correction was incorporated into the calculation. If the confidence interval was contained within the interval –0.20 to +0.20, then Test was considered therapeutically equivalent (bioequivalent) to Reference in the treatment of secondarily infected wounds. The analyses were conducted on both the PP and mITT populations. The analyses in the PP population were considered primary and those in the mITT population as supportive.

Continuity-corrected Z-tests were conducted by the sponsor for the difference between each active product's Clinical Success proportion and that of Placebo (Test vs. Placebo, and Reference vs. Placebo). If the product's Clinical Success proportion exceeded that of Placebo, and the difference was statistically significant ($p<0.05$), then the active product was considered superior to Placebo in the treatment of secondary wound infections. The analyses were conducted on both the PP and mITT populations. The analyses in the mITT population were considered primary and those in the PP population as supportive.

Reviewer's Comments:

To establish bioequivalence, the 90% confidence intervals of the test-reference difference in the proportion of patients with clinical success (SIRS score of 0 for all signs and symptoms) at the follow-up visit (7 days after completion of 10 days of treatment) must be contained within [-0.20, +0.20] for dichotomous variables (success/failure), using the PP population. In addition, as a parameter for determining adequate study sensitivity, Test and Reference should both be statistically superior to Placebo ($p<0.05$, two sided) with regard to the proportion of patients with clinical success at the follow-up visit using the mITT population and LOCF.

Secondary Endpoint Bioequivalence and Efficacy Analyses:

According to the sponsor, the same tests/methods as for the primary analyses were conducted on both the PP and mITT populations for the secondary endpoints.

Safety Analysis

Adverse events were monitored throughout the study. The sponsor tabulated the frequency of patients reporting AEs by treatment group, body system, preferred term, severity, and relationship to study medication. The frequency counts reflect the number of patients reporting one or more AEs that map to the body system and preferred term. At each level of summarization (body system or preferred term), patients reporting more than one event were counted only once (under the greatest severity and the strongest relation in the tabulations of AEs by severity and by relationship to study medication). The differences between the active treatment groups in overall AE assessment were compared using the Pearson's Chi-Square test or Fisher's exact test if more appropriate. The sponsor's safety analyses were conducted on the ITT population only.

Missing values or Dropouts:

According to the sponsor, a patient who terminated the study prematurely due to insufficient therapeutic response after at least 3 days of study medication application (with a compliance rate of at least 66.6% and not more than 100%) was carried forward as a treatment failure in both the PP and mITT populations if the patient met all other criteria for inclusion. Patients who terminated early for some other reason were excluded from the PP population and were included in the mITT population if they met all other criteria for inclusion.

Reasons for premature termination were compared between treatments by the sponsor and, if there were sufficient numbers of patients in each category, the frequency of reasons was compared using Pearson's Chi-square test or Fisher's exact test if more appropriate.

For the analysis of efficacy, a last-observation-carried-forward (LOCF) approach was used for missing efficacy results in the mITT population by the sponsor. In the PP population, the LOCF approach was used only for patients who discontinued due to treatment failure for their subsequent visits after discontinuation. For demographic and

baseline characteristics, each variable was analyzed using all available data. Patients with missing data were excluded only from analyses for which data were not available.

Changes to the Planned Analyses

The original protocol, dated April 21, 2008, was approved by the IRB on May 5, 2008. There was one administrative clarification amendment to the protocol. The amendment, dated April 29, 2008, was implemented prior to initiation of any study sites and included changes made to remove the need for the investigator to determine clinical and bacteriological response which required considering responses from previous visits. This was done to avoid confusion when determining the response. The revised options for clinical response were changed to: 1) clinical success or 2) clinical failure. The revised options for bacteriological response were changed to: 1) presumed eradication, 2) super infection, 3) failure, 4) relapse or 5) unable to determine. The amended protocol was approved by the IRB on June 25, 2008.

There were no additional changes to the conduct of the study or planned analyses.

2.4.3.2 Study Conduct

Patient Disposition:

A total of 656 patients were enrolled into the study and randomized to one of the three treatment groups. Of these enrolled patients, 655 (99.8%) were confirmed to receive treatment and included in the sponsor's analyses. Two hundred twenty (220) patients received Test, 216 patients received Reference and 219 patients received Placebo. One hundred eighteen (118) patients were excluded from the sponsor's mITT population; the remaining 538 patients were included in the sponsor's mITT population. One hundred forty-six (146) patients were excluded from the sponsor's PP population; the remaining 510 patients were included in the sponsor's PP population. Table 4 summarizes the total enrollment and eligibility for analysis of all patients enrolled into the study.

Table 4: Patient Enrollment (by Sponsor)[1]

	Number (%) of Patients			
	Test	**Reference**	**Placebo**	**Overall**
Number Enrolled	220	217	219	656
Patients Excluded from the Intent-to-Treat Analysis	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
Patients Included in the Intent-to-Treat Analysis	220 (100%)	216 (99.5%)	219 (100%)	655 (99.8%)
Patients Excluded from the Modified Intent-to-Treat Analysis	39 (17.7%)	36 (16.6%)	43 (19.6%)	118 (18.0%)
Patients Included in the Modified Intent-to-Treat Analysis	181 (82.3%)	181 (83.4%)	176 (80.4%)	538 (82.0%)
Patients Excluded from the Per-Protocol Analysis	45 (20.5%)	47 (21.7%)	54 (24.7%)	146 (22.3%)
Patients Included in the Per-Protocol Analysis	175 (79.5%)	170 (78.3%)	165 (75.3%)	510 (77.7%)

[1] From Sponsor's Clinical Study Report v1.0 GLK605 Table 11.1.

The disposition of patients is summarized in Table 5. As Table 5 indicates, 158 patients discontinued from the study. The most common reasons for discontinuation were the baseline culture was negative (89 patients) and insufficient therapeutic response after at least 3 or more days of application (52 patients). Two patients in the placebo group discontinued the study due to an AE.

Table 5: Patient Discontinuation by Reason (by Sponsor)[1]

	Number (%) of Patients			
	Test	**Reference**	**Placebo**	**Overall**
Number Enrolled	220	217	219	656
Number Completed Study	179 (81.4%)	177 (81.6%)	142 (64.8%)	498 (75.9%)
Total Discontinued	41 (18.6%)	40 (18.4%)	77 (35.2%)	158 (24.1%)
Reason Discontinued				
The patient withdraws his or her consent for any reason	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Insufficient therapeutic response - after at least 3 or more days of applications	9 (4.1%)	8 (3.7%)	35 (16.0%)	52 (7.9%)
The patient's drug code is unblinded	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
The baseline culture is negative	28 (12.7%)	27 (12.4%)	34 (15.5%)	89 (13.6%)
An adverse event occurs	0 (0.0%)	0 (0.0%)	2 (0.9%)	2 (0.3%)
Protocol Violation	3 (1.4%)	4 (1.8%)	5 (2.3%)	12 (1.8%)
A concomitant therapy is reported or required	1 (0.5%)	1 (0.5%)	1 (0.5%)	3 (0.5%)
The patient misses more than 2 consecutive visits	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
The patient becomes pregnant	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[1] From Sponsor's Clinical Study Report v1.0 GLK605 Table 10.1.

Reviewer's Comments:

- *The sponsor's visit window for the follow-up visit (Visit 4) is +4 days. The FDA generally recommends a visit window of ±4 days. The following patients were within -4 days of Visit 4: Patient* (b) (6) (b) (6) *However, Patient* (b) (6) *has a baseline SIRS total score of 5 and would continued to be excluded form the FDA PP population. Patient* (b) (6) *has no other reason to be excluded from the FDA PP population.*
- *All patients who discontinued early due to insufficient therapeutic response are included in the sponsor's PP population as clinical failure. Patient* (b) (6) (b) (6)*, was excluded from the sponsor's PP population since the patient applied the study medication 33 times (110%) and the sponsor's compliance definition is 66.6% to 100%.*

Retention of Reserve Samples:

Each investigational site where study medication was dispensed to at least one patient was required to randomly select one block (3 consecutively numbered patient kits) of study medication to be maintained as retain samples. The investigator maintained one randomly selected block of study medication for each shipment of study medication received. In accordance with 21 CFR 320.38 and 320.63 and Guidance, "Handling and Retention of BA and BE Testing Samples", a sufficient number of samples of the test product, reference product and Placebo were collectively selected by the study centers for use as retain samples. To ensure that the retention samples were representative of the study medication dispensed to the patients, each study center was asked to randomly select at least one block (3 consecutive patients) of undispensed study medication from each shipment to maintain as retain samples. As per the 21 CFR 320.38(e): "Each reserve sample shall be stored under conditions consistent with the product labeling and in an area segregated from the area where testing is conducted and with access limited to authorized personnel. Each reserve sample shall be retained for a period of at least five (5) years following the date on which the application or supplemental application is approved or if such application or supplemental application is not approved, at least five (5) years following the date of completion of the bioavailability study in which the sample from which the reserve samples was obtained was used." The investigator will store the retain sample study medication until such time as notification is received from the sponsor that the samples are no longer required. All used, partially used, and any unused study medication not designated as retain samples were returned to the Sponsor, or designee, at the conclusion of the study.

Baseline Characteristics:

Demographic Information

Demographic data recorded at baseline are summarized in Table 11.2 of the sponsor's study report for the PP population, Table 11.3 for the mITT population, and Table 11.4 (and Table 6 below) for the ITT population, and listed by patient in Appendix 16.2.2 of the sponsor's study report. According to the sponsor's analysis, the ITT treatment groups were comparable for all demographic characteristics (all $p>0.05$), as were the mITT and PP treatment groups (all $p>0.05$).

Baseline Characteristics

Baseline characteristics for the mITT and PP populations are summarized in Table 7.

Table 6: Demographic Characteristics at Baseline in the ITT Population (per sponsor)*

Demographic	Category	Test (N=220)	Reference (N=216)	Placebo (N=219)	Overall (N=655)	p value
Gender (n,%)	Female	100 (45%)	99 (46%)	98 (45%)	297 (45%)	0.975[1]
	Male	120 (55%)	117 (54%)	121 (55%)	358 (55%)	
Ethnicity (n,%)	Hispanic or Latino	212 (96%)	209 (97%)	211 (96%)	632 (96%)	NA[1]
	Not Hispanic or Latino	8 (4%)	7 (3%)	8 (4%)	23 (4%)	
Race[3] (n,%)	White	66 (30%)	60 (28%)	64 (29%)	190 (29%)	0.674[1]
	Black/African American	23 (10%)	34 (16%)	36 (16%)	93 (14%)	
	Asian	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	American Indian / Alaskan Native	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	Native Hawaiian / Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	Other	131 (60%)	122 (56%)	119 (54%)	372 (57%)	
Age (years)	N	220	216	219	655	0.456[2]
	Mean ± SD	15.0 ± 14.9	14.0 ± 13.9	14.1 ± 14.1	14.4 ± 14.3	
	Min, Max	1.6, 81.6	1.6, 80.8	1.4, 82.1	1.4, 82.1	

* From Sponsor's Clinical Study Report v1.0 GLK605 Table 11.4.
[1] P-values for treatment comparisons from Cochran-Mantel-Haenszel test for general association, adjusted for site.
[2] P-values for treatment comparisons from nonparametric rank-based analysis of variance.
[3] For the variable race, the p-value was calculated after combining the following categories: Black or African American, Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander and Other.

Table 7: Baseline SIRS Total Score and Culture in the mITT and PP Populations (per sponsor)*

	Category	Test	Reference	Placebo
mITT Population (N)		181	181	176
Total SIRS	Mean ± SD	8.77 ± 2.10	8.69 ± 2.02	8.63 ± 1.88
	Median	9.00	9.00	9.00
	Min, Max	4, 15	5, 16	4, 14
Culture Results	*S. aureus*	162 (89.5%)	175 (96.7%)	160 (90.9%)
	S. pyogenes	69 (38.1%)	75 (41.4%)	85 (48.3%)
PP Population (N)		175	170	165
Total SIRS	Mean ± SD	8.78 ± 2.12	8.71 ± 1.98	8.67 ± 1.89
	Median	9.00	9.00	9.00
	Min, Max	4, 15	5, 16	4, 14
Culture Results	*S. aureus*	157 (89.7%)	164 (96.5%)	150 (90.9%)
	S. pyogenes	67 (38.3%)	69 (40.6%)	81 (49.1%)

* From Sponsor's Clinical Study Report v1.0 GLK605 Table 11.23 - 11.26

Reviewer's Comments:

Analysis results to determine significant differences between the three treatment arms in baseline SIRS total score and culture results were not provided by the sponsor.

2.4.3.3 Results

Primary Endpoint

According to the sponsor's analysis, the test group and the reference group were comparable in regard to clinical success (defined as complete resolution or sustained improvement of signs and symptoms of infection) at the 7 day follow-up visit (Visit 4) in the PP population; 90.3% for the test group and 91.2% for the reference group were considered a clinical success. The test group and the reference group were also comparable in regard to Clinical Success in the mITT population; 90.6% for the test group and 90.1% for the reference group were considered a Clinical Success, compared to 70.5% for the placebo group. The sponsor's calculated 90% confidence interval of the difference in clinical success rate between the test group and the reference group in the PP population is (-0.0661, 0.0482) at the 7 day follow-up visit (Visit 4). Both the test group and the reference group showed superiority over the placebo group in the mITT population at the 7 day follow-up visit (Visit 4) (both $p<0.001$).

Table 8: **Primary Bioequivalence Analysis – Clinical Success at the Follow-Up Visit (Visit 4) in the PP Population (per sponsor)***

	Test (N=175)	Reference (N=170)	90% CI[1]
Success (n, %)	158 (90.3%)	155 (91.2%)	(-6.61, 4.82)

* From Sponsor's Clinical Study Report v1.0 GLK605 Table 11.5.
[1] Confidence interval calculated using Wald's method with Yates' continuity correction.

Table 9: **Primary Superiority Analysis – Clinical Success at the Follow-Up Visit (Visit 4) in the mITT Population (per sponsor)***

	Test (N=181)	Reference (N=181)	Placebo (N=176)	P-values[1]	
				Test vs Placebo	Reference vs Placebo
Success (n, %)	164 (90.6%)	163 (90.1%)	124 (70.5%)	<0.001	<0.001

* From Sponsor's Clinical Study Report v1.0 GLK605 Table 11.5.
[1] P-values for treatment comparisons from two-sided Z-test with Yates' continuity correction.

Reviewer's Comments:

Based on the sponsor's definition of clinical success as a complete resolution (SIRS scores of 0) or sustained improvement (SIRS scores of 0 for exudate/pus, crusting, tissue warmth, edema and pain; and 0 or 1 for erythema/inflammation and itching) of signs and symptoms of infection with no additional antibiotic therapy required after End of Treatment, the following patients (in Table 10 and Table 11) in the sponsor's mITT and

PP populations with a score >0 have been reported by the sponsor as clinical success. The FDA recommended definition for clinical success is a SIRS score of 0 for all signs and symptoms.

Table 10: Proportion of Patients in the Sponsor's mITT population with SIRS Total Score > 0 defined as Clinical Success (per Reviewer)

Total SIRS	Test (N=181)	Reference (N=181)	Placebo (N=176)	Total (N=538)
1	19	19	19	58
2	0	1	0	1
Total	19	20	19	59

Table 11: Proportion of Patients in the Sponsor's PP population with SIRS Total Score > 0 defined as Clinical Success (per Reviewer)

Total SIRS	Test (N=175)	Reference (N=170)	Placebo (N=165)	Total (N=510)
1	18	18	19	55
2	0	1	0	1
Total	18	19	19	56

Secondary Endpoints

The results of the sponsor's secondary endpoints analyses are presented in Table 12 and Table 13.

Table 12: **Secondary Bioequivalence Analyses using the PP Population (per sponsor)***

	Test (N=175)	Reference (N=170)	90% CI[1]
Clinical Success at Visit 3 (n, %)	109 (62.3%)	111 (65.3%)	(-12.10, 6.08)
Presumed Eradication at Visit 4 (n, %)	157 (89.7%)	155 (91.2%)	(-7.24, 4.32)
Presumed Eradication at Visit 3 (n, %)	170 (97.1%)	166 (97.6%)	(-3.90, 2.89)

* From Sponsor's Clinical Study Report v1.0 GLK605 Table 11.6, 11.7 and 11.8.
[1] Confidence interval calculated using Wald's method with Yates' continuity correction.

Table 13: **Secondary Superiority Analyses using the mITT Population (per sponsor)***

	Test (N=181)	Reference (N=181)	Placebo (N=176)	P-values[1]	
				Test vs Placebo	Reference vs Placebo
Clinical Success at Visit 3 (n, %)	114 (63.0%)	116 (64.1%)	92 (52.3%)	0.052	0.031
Presumed Eradication at Visit 4 (n, %)	163 (90.2%)	163 (90.1%)	124 (70.5%)	<0.001	<0.001
Presumed Eradication at Visit 3 (n, %)	176 (97.2%)	177 (97.8%)	141 (80.1%)	<0.001	<0.001

* From Sponsor's Clinical Study Report v1.0 GLK605 Table 11.6, 11.7 and 11.8.
[1] P-values for treatment comparisons from two-sided Z-test with Yates' continuity correction.

Reviewer's Comments:

According to the sponsor's analyses, all of the secondary endpoints are within the BE limits of [-0.20, +0.20] and both the test and reference groups were statistically superior to the placebo groups (p<0.05) except for clinical success at end of treatment (p=0.052).

2.4.4 Bioequivalence Conclusion

The sponsor's statistical analysis shows that the 90% Confidence Interval (CI) of the difference in clinical success rate between the test and reference products, in the PP population, at the 7 day follow-up visit (Visit 4) after completion of a 10-day treatment is (-0.0661, 0.0482), within the bioequivalence limits of [-0.20 to +0.20]. Both the test and reference products was demonstrated by the sponsor's analysis to be statistically superior to vehicle (Placebo) (p<0.0001) at Visit 4 in the mITT population, demonstrating that the study is sufficiently sensitive to discriminate differences between products. However, the study was conducted using an inappropriate patient population (inclusion of patients with "infections resulting from the scratching of an insect bite"). Furthermore, the sponsor is unable to identify all the patients with secondarily infected insect bites in order to excluded them from analysis. An FDA statistical consultation has not been requested because the patients with incorrect diagnosis cannot be identified for exclusion.

2.5 Comparative Review of Safety

2.5.1 Brief Statement of Conclusions

Of the 655 subjects who took the study medication, 60 experienced one or more treatment-emergent AEs during the study. All of the AEs were mild or moderate in severity. The only AEs that were considered possibly, probably, or definitely related to the study medications were application site pruritus, worsening of ingrowing toenail, pain on right toe, hypersensitivity and wound complication. No SAEs or deaths were reported. Two patients in the placebo group discontinued due to an AE.

2.5.2 Description of Adverse Events

The number of patients reporting one or more treatment-emergent AEs is summarized in Table 14 by the reported strongest relationship to study medication. The percent of patients reporting any AEs regardless of relationship to study medication was 10.0% in the test group, 6.9% in the reference group, and 10.5% in the placebo group. The percent of patients with AEs definitely or probably or possibly related to study medication was 0.9% in the test group, 0.5% in the reference group, and 0.9% in the placebo group.

The only AEs that were considered possibly, probably, or definitely related to the study medications were application site pruritus and worsening of ingrowing toenail in the test group, pain on right toe in the reference group, and hypersensitivity and wound complication in the placebo group, which occurred in only one patient each.

No AE occurred in more than 2.7% of patients in any of the treatment groups. All AEs were mild or moderate in severity.

Two patients in the placebo group (Patients (b) (6)) discontinued due to AEs (varicella zoster and allergic reaction [not within treatment area], respectively).

As indicated in Table 14, there was no statistically significant difference between the test and reference products in the proportion of patients reporting any AEs and in the proportion of patients reporting AEs definitely or probably or possibly related to study medication (all $p>0.05$).

Table 14: Number of Patients Reporting Adverse Event(s) (per sponsor)*

	Test (N=220)	Reference (N=216)	Placebo (N=219)	p-value (Test vs. Reference)[1]
Patients with Adverse Event(s) Regardless of Relationship to Study Medication	22 (10.0%)	15 (6.9%)	23 (10.5%)	0.252
Patients with Adverse Event(s) Possibly, Probably or Definitely Related to Study Medication	2 (0.9%)	1 (0.5%)	2 (0.9%)	1.000

* From Sponsor's Clinical Study Report v1.0 GLK605 Table 12.1

[1] P-values for treatment comparisons between the two active treatment groups from Pearson's chi-square test or Fisher's exact test if appropriate.

There were no deaths, other SAEs, or other AEs considered significant or unexpected as defined in the protocol.

Reviewer's Comment:

The adverse events reported in this study do not suggest a different AE profile for this generic product compared to the RLD.

2.6 Relevant Findings From Other Consultant Reviews

2.6.1 Review of the OSI Report

An OSI inspection was requested on July 29, 2010. Sites 04 (PI:Daisy Blanco, MD), 05 (PI:Josefina Fernandez, MD) and 13 (PI:Ynca Nina Vasquez, MD) were inspected. The inspection (EIR review dated July 12, 2011) revealed that all three sites inspected had objectionable findings for which Form FDA-483 was issued. All three sites have been classified as Voluntary Action Indicated. The following are the objectionable findings at the three sites:

1. Failure to perform the bacteriological evaluation as required in the study protocol. Specifically, baseline cultures for 5 patients (b) (6) at Site 04, 3 patients (b) (6) at Site 05, and 6 patients (Patient (b) (6) at Site 13 were not conducted.

Reviewer's Comment:

The sponsor has already appropriately excluded all of the above patients from the MITT and PP populations.

2. Failure to adhere to the inclusion/exclusion criteria as required in the study protocol. Specifically, patient (b) (6) was enrolled in and completed the study (b) (6)

Reviewer's Comment:

The above finding would not have a significant impact on the overall study outcome. Therefore, no change to the study populations would be needed.

3. Failure to adhere to the study protocol in complying with the total number of study drug applications. Specifically, many patients (e.g. Patient (b) (6) (b) (6) applied the study medication more than 30 times (>100%).

Reviewer's Comment:

The sponsor has already appropriately excluded patients with dosing noncompliance from the PP population.

2.6.2 Review of the FDA Statistical Report

An FDA statistical consultation has not been requested because the sponsor conducted the study using an inappropriate patient population and the patients with incorrect diagnosis cannot be identified for exclusion.

2.7 Formulation

Table 15: RLD Formulation*

Ingredient	Function	RLD (%w/w)
Mupirocin calcium (micronized)	Active	2.15**
Mineral oil, USP	(b) (4)	
(b) (4)		
Stearyl alcohol, NF		
Cetyl Alcohol, NF		
Benzyl alcohol, NF		
Xanthan gum, NF		
Purified water, USP		

(b) (4)

** Equivalent to 2.0% mupirocin free acid.

Table 16: Test Formulation (per sponsor)

Ingredient	Function	Test (%w/w)
Mupirocin calcium*	Active	(b) (4)
Benzyl alcohol, NF	(b) (4)	
Mineral oil, USP		
Phenoxyethanol		
Xanthan gum, NF		
Polyoxyl 20 cetostearyl ether		
Glycerol monostearate (b) (4) (b) (4)		
Purified water, USP		

(b) (4)

Reviewer's Comments:

These qualitative and quantitative differences are acceptable at the levels listed from a regulatory perspective, as determined by the filing review from the Regulatory Support Branch, and the study results show no apparent effect of the formulation differences on product performance or safety.

2.8 Conclusion and Recommendation

2.8.1 Conclusion

The sponsor's data presented in this ANDA 201587 appear to demonstrate that Glenmark's Mupirocin Cream USP, 2%, is bioequivalent to the reference listed drug, Bactoban® (mupirocin calcium) Cream, 2%. The sponsor's statistical analysis shows that the 90% CI of the difference in clinical success (complete resolution or sustained improvement) rate between the test and reference products, in the PP population, at Visit 4 is (-0.0661, 0.0482), within the bioequivalence limits of [-0.20 to +0.20]. The test and reference products also demonstrate superiority over the placebo arm in the sponsor's analysis. However, we are unable to confirm that the sponsor conducted the study using a sufficient number of patients meeting the acceptable inclusion and exclusion criteria since the sponsor was unable to provide the requested additional information.

2.8.2 Recommendations

This application is not recommended for approval from a clinical bioequivalence standpoint.

_____ _____

Sarah H. Seung, Pharm.D.
Clinical Reviewer, Division of Clinical Review
Office of Generic Drugs

_____ _____

John R. Peters, M.D.
Director, Division of Clinical Review
Office of Generic Drugs

_____ _____

Barbara M. Davit, PhD, JD
Acting Director, Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 201587 APPLICANT: Glenmark Generics Inc., USA

DRUG PRODUCT: Mupirocin Cream USP, 2%

The Division of Clinical Review has completed its review of the clinical endpoint bioequivalence study, and the following deficiencies have been identified:

1. The *Draft Guidance for Mupirocin Calcium Cream/Topical EQ 2% Base (revised October 2011)* recommends that "secondarily infected animal/human or insect bite" be excluded from clinical endpoint bioequivalence study for Mupirocin Cream USP, 2%. The study report for Study GLK 605 states that "infections resulting from the scratching of an insect bite were considered secondarily infected traumatic skin lesions." Infections resulting from the scratching of an insect bite are superficial and considered secondarily infected insect bite. Given that patients with secondarily infected insect bites cannot be identified from all clinical sites in order to exclude from the analysis populations, this study is not acceptable unless you can provide evidence to justify the inclusion of these patients in the analysis populations. If no such evidence is available, a new clinical endpoint bioequivalence study, which follows the recommendations provided in the *Draft Guidance for Mupirocin Calcium Cream/Topical EQ 2% Base (revised October 2011)*, should be conducted and submitted for agency review.

2. Clinical cure is defined as a Skin Infection Rating Scale (SIRS) score of 0 for all signs and symptoms on a 4-point scale. "Sustained improvement" is not part of the definition. The inclusion of patients with sustained improvement in the clinical cure group is not acceptable as it could reduce the sensitivity of the clinical endpoint study in distinguishing differences between drug products and placebo.

3. The inclusion criterion for baseline SIRS total score is a total sore of at least 8.

4. The exclusion criterion for the use of topical therapeutic agents is within 48 hours (not 24 hours) prior to study entry.

5. Patients with diabetes should be excluded from the study.

6. Compliance is generally defined as 75% to 125% of the scheduled applications.

7. Visit window is defined as ±4 days.

Sincerely yours,

Barbara M. Davit, PhD, JD
Acting Director, Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SARAH H Seung
03/02/2012

JOHN R PETERS
03/02/2012

BARBARA M DAVIT
03/05/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201587

OTHER REVIEWS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 22, 2013

FROM: Cecelia Parise, R.Ph., Regulatory Policy Advisor to the Director
Office of Generic Drugs

THROUGH: Gregory P. Geba, M.D., M.P.H., Director
Office of Generic Drugs

John Farley, M.D., M.P.H., Director
Division of Anti-Infective Products

SUBJECT: Bactroban Cream (Mupirocin Calcium)
Docket No. 2004-P-0433 (Legacy Docket No. 2004P-0290)

TO: ANDA 0201587 - Mupirocin Calcium Topical Cream
Glenmark Generics Inc., USA

Hogan & Hartson LLP submitted a Citizen Petition, FDA Docket No.2004-P-0433 (formerly 2004P-0290) on behalf of GlaxoSmithKline (collectively, GSK) regarding Bactroban Cream® (mupirocin calcium) on July 7, 2004. GSK also submitted supplements as follows:

December 23, 2004 (Supplement 1)
March 21, 2005 (Supplement 2)
May 5, 2005, (Supplement 3)
October 26, 2006 (Supplement 4)
February 28, 2007 (Supplement 5)

Summary

GSK, manufacturer of Bactroban Cream® (mupirocin calcium), submitted its Citizen Petition on July 7, 2004 asking that the Commissioner:

- refrain from approving any abbreviated new drug application (ANDA) for a topical mupirocin calcium product containing the amorphous form of the active ingredient if Bactroban Cream® (mupirocin calcium) is the reference listed drug (RLD); or in the alternative

- take the following actions before approving any ANDA for a topical mupirocin calcium product containing the amorphous form of the active ingredient:

    - prescribe a standard of identity for mupirocin calcium that takes into account the different polymorphic forms of the active ingredient;
    - require the submission of a suitability petition for a change in dosage form, to the extent that the amorphous form of mupirocin calcium cannot be maintained in a cream base; and
    - determine whether the inactive ingredients of such a product raise issues of safety or effectiveness that require additional *in vitro* or *in vivo* studies, and whether such studies must be submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA).[1]

GSK also submitted five supplements in addition to the above Citizen Petition, discussed in detail below.

Discussion

Glenmark Generics Inc. USA (Glenmark) filed its ANDA for mupirocin cream referencing Bactroban Cream. Prior to approving Glenmark's ANDA, FDA considered whether Glenmark's ANDA implicated any of the issues raised in GSK's citizen petition and supplements. Upon review of the petition and Glenmark's ANDA, FDA has determined, as detailed below, that the issues raised in the citizen petition are not implicated by the ANDA, and thus need not be resolved by the agency prior to approval of this ANDA.

I. The polymorphic form of Glenmark's mupirocin calcium is a crystalline form of the dihydrate calcium salt, as is GSK's Bactroban.

FDA has concluded that the petition and its supplements raise issues that relate to approval of an ANDA for mupirocin cream that contains an amorphous polymorphic form of the active ingredient mupirocin calcium. These issues do not apply to Glenmark's ANDA for mupirocin cream because Glenmark does not use an amorphous form of mupirocin calcium. Rather, it contains a crystalline form of the dihydrate calcium salt (2:1) of mupirocin. Bactroban Cream also contains a crystalline form of the dihydrate calcium salt (2:1) of mupirocin.

To the extent that GSK asserts that an ANDA for mupirocin cream should meet existing USP standards for such a product,[2] FDA notes that the agency has concluded that Glenmark's mupirocin cream meets the USP drug substance monograph for mupirocin calcium and the drug

[1] Citizen Petition, FDA Docket No. 2004-P-0290, at 2 (July 7, 2004).
[2] See, e.g., id., at 6-7.

product monograph for mupirocin cream.[3] Glenmark's product also meets the USP General Chapter <1151> definition for creams: "Creams—Creams are semisolid emulsion dosage forms. They often contain more than 20% water and volatiles and typically contain less than 50% hydrocarbons, waxes, or polyols as the vehicle for the API. Creams generally are intended for external application to the skin or to the mucous membranes. Creams have a relatively soft, spreadable consistency and can be formulated as either a water-in-oil emulsion (e.g., *Cold Cream* or *Fatty Cream* as in the *European Pharmacopoeia*) or as an oil-in-water emulsion (e.g., *Betamethasone Valerate Cream*). Creams generally are described as either nonwashable or washable, reflecting the fact that an emulsion with an aqueous external continuous phase is more easily removed than one with a nonaqueous external phase (water-in-oil emulsion). Where the term 'cream' is used without qualification, a water-washable product is generally inferred."[4] Both Glenmark's proposed mupirocin cream product and Bactroban Cream are an oil-in-water emulsion.

II. Suitability Petition

No Suitability Petition is needed because Glenmark's product is the same dosage form as Bactroban: a cream.

III. Formulation

In reviewing Glenmark's ANDA, FDA has determined that the formulations are similar, and that the relevant data submitted in the ANDA show no apparent effect of the formulation differences on the ANDA product's performance or safety.[5]

The following table compares the excipients for the RLD (per the package insert) and the ANDA test formulations, and clarifies that the cetyl alcohol and stearyl alcohol used in the RLD were replaced with glycerol monosterate in the test product.[6]

[3] See ANDA 0201587 Review Quality-03 (General Review), Page 28 (Dec. 18, 2012). The USP monograph for mupirocin cream requires that the product contain a quantity of mupirocin calcium equivalent to not less than 90.0% and not greater than 120% of the labeled amount of mupirocin. It also provides that such a product may contain one or more suitable buffers, dispersants, and preservatives. See USP35–NF30, Page 3964 (2012).
[4] See USP35-NF 30, Supp. 2, General Chapter <1151> Pharmaceutical Dosage Forms, Page 769 (Dec. 2012).
[5] Addendum to Review of a Bioequivalence Study with Clinical Endpoints, Page 26 (Oct. 26, 2012), ANDA 0201587 Mupirocin Cream USP, 2%, Glenmark Generics Inc., USA; Chemistry Review, Page 21 (July 7, 2011), ANDA 0201587 Mupirocin Cream USP, 2%, Glenmark Generics Inc., US.
[6] Chemistry Review, Page 21 (July 7, 2011), ANDA 0201587 Mupirocin Cream USP, 2%, Glenmark Generics Inc., US.

BACTROBAN CREAM® (mupirocin calcium cream), 2% GlaxoSmithKline	Mupirocin Cream USP, 2% Glenmark Generics Limited	Function
Benzyl alcohol, NF	Benzyl alcohol, NF	(b) (4)
Mineral oil, NF	Mineral oil, USP (b) (4) (b) (4)	
Phenoxyethanol, NF	Phenoxyethanol, NF (b) (4)	
Xanthan gum, NF	Xanthan gum, NF (b) (4)	
Cetomacrogol 1000	Polyoxyl 20 cetostearyl ether, NF (b) (4) (b) (4)	
---	Glycerol monostearate (b) (4) (b) (4)	
Purified water, USP	Purified water, USP	
Cetyl alcohol	---	
Stearyl alcohol	---	

IV. Miscellaneous Issues Raised in the Petition Supplements

- Supplements 1 and 2 ask the Agency to consider comments that GSK submitted to the agency regarding the draft guidance for industry *ANDAs: Pharmaceutical Solid Polymorphism* (Dec. 2004).[7]

Since the petition was submitted, the guidance for industry *ANDAs: Pharmaceutical Solid Polymorphism* (July 2007) was finalized. Comments submitted to the guidance docket prior to finalization were reviewed by the agency.

[7] Supplement to Citizen Petition No. 2004-P-0290 (Dec. 23, 2004); Supplement to Citizen Petition No. 2004-P-0290 (Mar. 21, 2005).

- Supplement 3 provides the Agency with the USP's Pharmacopeial Forum (PF) editions in which USP proposed monographs for the active ingredient mupirocin calcium and the drug product mupirocin cream.[8]

Since the petition was submitted, the USP monographs have been finalized and are now official. As indicated above, Glenmark's drug substance mupirocin calcium and drug product mupirocin cream meet the respective USP monographs.

- Supplement 4 requests that "before approving any ANDA for a topical mupirocin calcium product containing the amorphous form of the active ingredient," the Agency (1) refrain from "implementing the recently announced revisions to the topical dosage form definitions in [FDA's] Dosage Form Monograph, or any additional or alternative revisions, unless and until such revisions have gone through a valid notice-and-comment rulemaking procedure, as would be required for any substantive rule;"[9] and (2) an amended request to require a suitability petition "to the extent that the formulation does not conform to the definition of a cream as it existed prior to the agency's recent revisions to the Data Standards Manual's Dosage Form Monograph."[10] Supplement 5 expands upon GSK's arguments related to the Dosage Form Monograph.[11]

As described above, the Glemark product does not contain an amorphous form of the active ingredient, but rather, like the RLD, contains a crystalline form of mupirocin calcium. Thus, the issues raised and requested actions in Supplements 4 and 5, which concern a generic product containing an amorphous form of the active ingredient, are not implicated in the approval of Glenmark's ANDA. To the extent that GSK asserts in these supplements that FDA should require compliance with the dosage form description developed by USP, FDA notes that FDA has concluded that Glenmark's product meets the USP General Chapter <1151> definition for "creams."[12]

[8] Supplement to Citizen Petition No. 2004-P-0290, at 1 (May 5, 2005).
[9] Supplement to Citizen Petition No. 2004-P-0290, at 2 (Oct. 26, 2006) (emphasis in original).
[10] Id., at 3.
[11] Supplement to Citizen Petition No. 2004-P-0290 (Feb. 28, 2007).
[12] USP 35-NF 30, Supp. 2, General Chapter <1151> Pharmaceutical Dosage Forms (Dec. 2012).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA L DOWNS
01/22/2013

CECELIA M PARISE
01/22/2013

ROBERT L WEST on behalf of GREGORY P GEBA
01/23/2013
Deputy Director, Office of Generic Drugs, for
Gregory P. Geba, M.D., M.P.H.

JOHN J FARLEY
01/23/2013

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 18, 2013

FROM: CAPT Martin H. Shimer
Branch Chief, Regulatory Support Branch
Office of Generic Drugs
Center for Drug Evaluation and Research

THROUGH: Gregory M. Geba, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

SUBJECT: Late Listed Patent for NDA 50746, Bactroban Cream, 2%

TO: The ANDA files for: ANDA 201587, Glenmark Generics Inc. USA

I. Background

Bactroban (Mupiricin calcium 2%) Cream is the subject of NDA 50746, which was approved by the Agency on December 11, 1997 for the treatment of secondarily infected traumatic skin lesions (up to 10 cm in length or 100 cm^2 in area) due to susceptible strains of Staphylococcus aureus and Streptococcus pyogenes. The approval letter for this NDA indicates that at the time of approval, the product was subject to the exception provisions of Section 125(d)(2) of Title 1 of the Food and Drug Administration Modernization Act of 1997 (Public Law No. 105-115) (FDAMA).

Until 1997, FDA approved applications for drug products containing antibiotics like mupiricin calcium, the active ingredient in Bactroban Cream, under section 507 of the Federal Food Drug and Cosmetic Act (FFDCA). That provision was repealed by section 125 of FDAMA, and all full applications previously approved under section 507 were deemed to have been submitted and filed under section 505(b) of the FFDCA, and approved for safety and effectiveness under section 505(c). Section 125(d)(2) of FDAMA expressly exempted these "old antibiotics" approved under section 507 from specified Hatch-Waxman provisions, including those relating to patent listing, patent certification, and exclusivity. *See* Pub. L. No. 105-115, Title I, § 125(d)(2)(A).

Thus, because Bactroban (mupiricin cacium 2%) cream was an NDA product that was subject to the exception provisions of FDAMA, the sponsor of this NDA was not eligible to submit patents for listing in "Approved Drug Products with Therapeutic

Equivalence Evaluations" also known as the Orange Book at the time of its initial approval. An "old antibiotic" is generally identified in the Orange Book as an NDA marketed under a 50,000 series number.

On October 8, 2008, the QI Program Supplemental Funding Act of 2008 (Public Law 110-379) (QI Act) was signed into law, and among other things, added paragraph (v) to Section 505 of the FFDCA, which provides that certain patent listings and other requirements and benefits that apply to 505 drugs also apply to old antibiotics. The first subsection of section 505(v) describes the availability of three-year Hatch-Waxman exclusivity for applications containing old antibiotic drugs approved where such application was submitted after enactment of the QI Act (section 505(v)(1)). The second subsection addresses applications for drug products containing antibiotic drugs submitted after the date of enactment of the QI Act containing antibiotic drugs that were submitted in other applications before the date of enactment of FDAMA but that had never been approved as of the date of enactment of the QI Act. It provides that such antibiotics may elect to be eligible for three- and five-year Hatch Waxman exclusivities, or patent term extensions (section 505(v)(2)). The third subsection expressly limits the eligibility of old antibiotics to the three- and five-year exclusivities and patent term extension described in section 505(v)(1) and 505(v)(2) and further limits the availability of three-year exclusivity for old antibiotics to conditions of use that were never approved before the date of enactment of the QI Act (section 505(v)(3)). The fourth subsection addresses the general applicability of the Hatch-Waxman Amendments to drug products containing old antibiotic drugs. It states that, subject to certain limitations, "notwithstanding section 125, or any other provision, of the Food and Drug Administration Modernization Act of 1997, or any other provision of law…the provisions of the Drug Price Competition and Patent Term Restoration Act of 1984 shall apply to [drug products containing old antibiotic drugs]" (section 505(v)(4)).

Section 4(b) of the QI Act describes specific transition rules provided for patent listing, patent publication, patent certification deadlines, and 180-day exclusivity related certain old antibiotic drugs. Section 4(b) of the Q1 Act provides for the submission of the patent information by certain sponsors of NDAs, the publication of such patent information by FDA, and the certification to such patents by applicants of pending abbreviated new drug applications (ANDAs) in order to be deemed "a first applicant" (as defined in section 505(j)(5)(B)(iv) of the FD&C Act), not later than 60, 90, and 120 days after enactment of the Q1 Act, respectively. Subsection 4(b)(1) in particular provides that "[w]ith respect to a patent issued on or before the date of the enactment of this Act, any patent information required to be filed with the Secretary of Health and Human Services under subsection (b)(1) or (c)(2) of section 505 of the Federal Food, Drug, and Cosmetic Act … to be listed on a drug to which subsection (v)(1) of such section 505 (as added by this section) applies shall be filed with the Secretary not later than 60 days after the date of the enactment of this Act.

In a draft guidance entitled "Submission of Patent Information for Certain Old Antibiotics," issued in November of 2008, the Agency provided NDA holders with information regarding the timely submission of patents under the transition rules of the

QI Act.[1] The QI Act was signed into law on October 8, 2008, therefore sixty days from this date means that the required patent information for previously issued patents needed to be submitted on or before December 5, 2008 to be considered timely listed.[2]

Listing of patent number 6,025,389

GlaxoSmithKline, LLC (GSK) submitted FDA patent listing form 3542 on May 6, 2011, requesting the listing of patent number 6,025,389 ('389 patent) for Bactroban (mupiricin calcium 2%) Cream. GSK's FDA form 3542 identifies the date of approval of the NDA or supplement for this product as December 11, 1997 -- the original approval date for NDA 50746 -- and the issue date of the patent as February 15, 2000. The form indicates that the '389 patent will expire on October 20, 2014 and that it is a use patent for which the proposed use code is "for the treatment of secondarily infected traumatic skin lesions, up to 10 cm in length or 100 cm^2 in area, due to susceptible strains of *S. aureus* or *S. Pyogenes*." Because (1) GSK's Bactoban (mupiricin calcium 2%) Cream NDA was subject to the revised patent listing provisions of the QI Act, (2) the '389 patent was issued in February 2000, and (3) GlaxoSmithKline did not submit the '389 patent for listing until May of 2011, FDA has concluded that this patent was late-listed with respect to ANDA applicants whose applications were pending before May 6, 2011. Accordingly, any ANDA pending on May 2011 is not required to contain a certification to the '389 patent as described in section 505(j)(2)(vii) of the FFDCA.

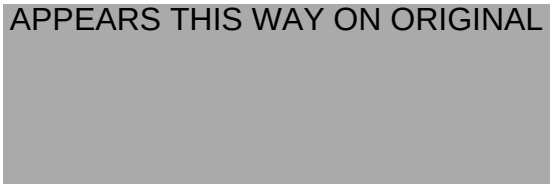
Glenmark Generics Inc. USA is the holder of ANDA 201587, which was submitted to FDA on February 23, 2010. FDA completed the initial filing review of this ANDA and issued an Acknowledgement Letter to Glenmark Generics Inc. USA on May 18, 2010, informing Glenmark that the company's application was received for filing on February 23, 2010. As such, Glenmark's application was received before the '389 patent was listed and was pending on May 11. 2011. Accordingly, the '389 patent is considered late listed as to Glenmark's application.

Conclusion:

Because GlaxoSmithKline LLC did not timely submit its patent information for the '389 patent in accordance with the transition rules of the QI Act (i.e. did not submit the patent on or before December 5, 2008), that patent is considered late listed as to ANDAs pending before its submission. Glenmark Generics Inc. USA's pending ANDA 201587 was pending before the '389 patent was submitted on May 6, 2011, and, thus that patent is considered late listed for that ANDA. Accordingly, Glenmark will not be required to submit a patent certification to the '389 patent for ANDA 201587 as a condition of approval.

---

[1] Draft guidance for industry on *Submission of Patent Information for Certain Old Antibiotics* (Nov. 2008).
[2] Id. at 3.


APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARTIN H Shimer
01/18/2013

ROBERT L WEST on behalf of GREGORY P GEBA
01/18/2013
Deputy Director, Office of Generic Drugs, for Gregory P. Geba, M.D., M.P.H.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 12, 2011

TO: Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs (OGD)

FROM: Jangik Lee, Pharm.D., Ph.D.
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

THROUGH: Martin K. Yau, Ph.D.
Acting Team Leader - Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIRs Covering ANDA 201-587 Mupirocin Cream USP, 2% sponsored by Glenmark Generics Inc. USA

At the request of OGD, DBGC conducted 3 study site inspections of the following clinical endpoint bioequivalence (BE) study:

Study Number: GLK-605
Study Title: "A multi-center, double-blind, randomized, vehicle-controlled, parallel group study comparing generic Mupirocin Calcium Cream, 2% to Bactroban Cream(mupirocin calcium cream), 2% and both active treatments to a vehicle control in the treatment of secondarily infected traumatic skin lesions"

DESCRIPTION OF STUDY

This multi-center clinical study enrolled 656 subjects, 18 months of age or older. The subjects were randomized in a 1:1:1 ratio to Mupirocin Calcium Cream, 2%; GlaxoSmithKline's Bactroban Cream (mupirocin calcium cream), 2%; or the Placebo vehicle group respectively.

The secondarily infected traumatic skin lesions for each subject were recorded as wounds. The wound sizes were assessed using

Skin Infection Rating Scale (SIRS) score. The primary endpoint was the clinical response at follow up visit 4 and was defined as clinical success if SIRS score was 0 or clinical failure if SIRS score was >0. A subject was considered clinically cured if no additional antimicrobial therapy was required after end of treatment (Visit 3). Secondary endpoint included the number of subjects with clinical cure at the end of treatment (Visit 3) and number of subjects showing bacteriological cure at end of treatment (Visit 4). BE was determined using both primary and secondary efficacy variables. Out of 13 clinical sites involved in the study, the inspection of the following 3 new clinical sites were requested:

Clinical Site #04: (N=81)
Instituto Dermatologio
Calle Federico Velasquez
Esq. Albert Thomas Ensanche Maria Aux.
Santo Domingo 1234, Dominican Republic

FEI#: 3008583385
Clinical Investigator: Daisy M. Blanco, M.D.

Clinical Site #05: (N=98)
Departmento de Enfermedades Infecciosas
Hospital Infantil Dr. Robert Reid Cabral
Av. Abraham Lincoln #2
Santo Domingo, Dominican Republic

FEI#: 3008583397
Clinical Investigator: Josefina A. Fernandez, M.D.

Clinical Site #13: (N=72)
Instituto Dermatolo'gico Unidad Sur
Calle Padre Ayala #140
San Cristobal
Santo Domingo, Dominican Republic

FEI#: 3008583411
Clinical Investigator: Ynca Nina Vasquez, M.D.

REVIEW OF ESTABLISHMENT INSPECTION REPORTS (EIRs)

Ms. Rebecca Davis, the Office of Regulatory Affairs (ORA) inspector in San Francisco District Office performed all three clinical study site inspections and sent the EIRs to DBGC. The major findings in the inspections are summarized below:

Clinical Site #04

The inspection of this site was conducted from February 21 to 25, 2011. The ORA inspector issued an FDA Form-483 on the following issues:

1. **Failure to adhere to the inclusion/exclusion criteria as required in the study protocol**

   [redacted], the subject was enrolled in and completed the clinical study. In their written response to the FDA Form-483 (see Attachment 1), the Sponsor and the Clinical Investigator admitted the protocol non-adherence and assured to avoid any future occurrence. The inclusion of the subject will not likely affect BE determination.

2. **Failure to perform the bacteriological evaluation as required in the study protocol**

   Baseline laboratory cultures as required in the protocol were not conducted for 5 subjects [redacted]. In their written response to the FDA Form-483 (see Attachment 1), the Sponsor and the Clinical Investigator explained that, although the culture samples for the subjects listed above were taken and sent to LabConnect, the central laboratory, the samples were not delivered within the proper time frame for process. The Investigator felt that it was not in the subjects' best interest to be terminated prior to the completion of the study since the patients had positive gram stains and showed significant improvement. Since the bacteriological status of such patients is not known at baseline, DBGC recommends that such subjects should be excluded from BE determination.

3. **Failure to adhere to the study protocol in complying the total number of study drug applications**

   On numerous occasions, many study subjects (e.g., Subjects [redacted] applied the study medication more than 30 times as required in the protocol. The Sponsor and the Clinical Investigator explained the difficulty in controlling patient behavior while at home but assured to avoid future occurrence (see Attachment 1). Since the number of study medication application may affect the overall clinical response, DBGC recommends that the subjects applied

the study drug exceedingly should be excluded from BE determination.

Clinical Site #05

The inspection of this site was conducted from February 28 to March 4, 2011. The inspector issued an FDA Form-483 on the following issue:

1. **Failure to perform the bacteriological evaluation as required in the study protocol**

   Baseline bacteriological evaluations as required in the protocol were not conducted for 3 subjects (b) (6) (b) (6) in 4 visits per each subject. In their written response to the FDA Form-483 (see Attachment 2), the Sponsor and the Clinical Investigator responded that Subjects (b) (6) (b) (6) were discontinued from the study prematurely due to the cancellation of the baseline culture. Subject (b) (6) laboratory reports indicating baseline cultures had been cancelled were received after the subject had completed the study. Since the bacteriological status of such patients is not known at baseline, DBGC recommends that such subjects should be included from BE determination.

Clinical Site #13

The inspection of this site was conducted from February 14 to 18, 2011. The inspector issued an FDA Form-483 on the following issue:

1. **Failure to perform the bacteriological evaluation as required in the study protocol**

   Baseline bacteriological evaluations were not conducted for 6 subjects (b) (6), and the subjects were allowed continued participation in the clinical study until completion. In their written response to the FDA Form-483 (see Attachment 3), the Sponsor and the Clinical Investigator explained that, although the culture samples were taken and sent to the central laboratory, the samples were not delivered within the proper time frame for process due to logistic issues with the courier companies, and laboratory reports indicating baseline cultures had been cancelled were received after the subjects had completed the study. Since the bacteriological status of such patients are not known at

baseline, DBGC recommends that such subjects should be excluded from BE determination.

CONCLUSION

Following the evaluation of the inspectional findings from the 3 study sites, DBGC recommends the followings:

1. All 3 clinical study sites failed to perform the bacteriological evaluation as required in the study protocol for some subjects. The number of subjects affected by this failure appears to be small compared with the total number of subjects enrolled in each study site. However, since the bacteriological status of such patients is not known at baseline, DBGC recommends such subjects be excluded from BE determination.

2. Site #4 also failed to adhere to the study protocol in that the total number of study drug applications was more than 30 times that required in the protocol. DBGC recommends the subjects applied the study drug exceedingly be excluded from BE determination.

3. The remaining clinical BE data from the 3 sites inspected are acceptable for the review of Study GLK-605.

After you have reviewed this transmittal memorandum, please append it to the original ANDA submission.

FINAL CLASSIFICATIONS

VAI - Instituto Dermatologio (Site #4)
VAI - Departmento de Enfermedades Infecciosas (Site #5)
VAI - Instituto Dermatolo'gico Unidad Sur (Site #13)

cc:
OSI Ball
DBGC Salewski/Haidar/Lee/Dejernett/CF
OGD Patel/Hixon
SAN-DO Rebecca T.Davis/Joan T Briones
Draft: JIL 7/12/2011
Edit: MKY 7/12, 7/13, 7/14/2011
OSI: 6104; O:\BIOEQUIV\EIRCOVER\EIR Cover Memo-ANDA 201-587 Mupirocin FACS 1200596.doc
FACTS: 1200596

EMAIL: CDER OSI PM TRACK

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANG IK LEE
07/14/2011

MARTIN K YAU
07/14/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201587

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

BIOEQUIVALENCY INFORMATION REQUEST

ANDA 201587

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Glenmark Generics Inc., USA

TEL: 201-684-8017

ATTN: William R. McIntyre, Ph.D.
Executive Vice President, RA

FAX: 201-831-0080

PROJECT MANAGER: (240) 276-8887
(240) 276-8966 (fax)

FROM: Nitin K. Patel

Dear Sir:

This facsimile is a request for information from the Division of Clinical Review, regarding your ANDA 201587 for Mupirocin Cream USP, 2%.

The information request is presented on the attached __1__ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

Your cover letter should clearly indicate that the response is a "Clinical Bioequivalence Amendment". We also request that you include a copy of this communication with your response.

Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

MEMORANDUM

ANDA 201587

To: **Glenmark Generics Inc., USA**

Drug: **Mupirocin Cream USP, 2%**

From: **Sarah H. Seung, PharmD**
Clinical Reviewer, Division of Clinical Review
Office of Generic Drugs

John R. Peters, MD
Director, Division of Clinical Review
Office of Generic Drugs

Date: **June 29, 2012**

Re: **Request for Information**

Reference is made to your April 27, 2012 Clinical Bioequivalence Amendment. In order to complete the review of a bioequivalence study with clinical endpoints for ANDA 201587 (GLK 605), please provide the following information:

1. Please provide a copy of the original source document and an English translated copy, if the source document is written in a foreign language, for the following 18 patients: Patients (b) (6) (b) (6). For these patients, the cause of the wound has been identified as "scratching". Information on the original wound, which lead to the "scratching", is needed to determine the patient's status for the per-protocol population.
2. Please resubmit your datasets reflecting all the changes noted in your April 27, 2012 Clinical Bioequivalence Amendment in electronic (.xpt) format. Additional information concerning the format of the electronic data can be found on the FDA website for *Individual Product Bioequivalence Recommendations: Draft Guidance on Mupirocin Calcium Cream, (June 2010).*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NITIN K PATEL
07/02/2012

SARAH H Seung
07/02/2012

JOHN R PETERS
07/02/2012

BIOEQUIVALENCY AMENDMENT

ANDA 201587

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Glenmark Generics Inc., USA

TEL: 201-684-8017

ATTN: William R. McIntyre, Ph.D.
Executive Vice President, RA

FAX: 201-831-0080

FROM: Nitin K. Patel

PROJECT MANAGER: (240) 276-8887
(240) 276-8966 (fax)

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on February 22, 2010, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mupirocin Cream USP, 2%.

Reference is also made to your amendments dated June 1, 2010 and January 27, 2012.

The Division of Clinical Review has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **2** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Clinical Bioequivalence Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 201587 APPLICANT: Glenmark Generics Inc., USA

DRUG PRODUCT: Mupirocin Cream USP, 2%

The Division of Clinical Review has completed its review of the clinical endpoint bioequivalence study, and the following deficiencies have been identified:

1. The *Draft Guidance for Mupirocin Calcium Cream/Topical EQ 2% Base (revised October 2011)* recommends that "secondarily infected animal/human or insect bite" be excluded from clinical endpoint bioequivalence study for Mupirocin Cream USP, 2%. The study report for Study GLK 605 states that "infections resulting from the scratching of an insect bite were considered secondarily infected traumatic skin lesions." Infections resulting from the scratching of an insect bite are superficial and considered secondarily infected insect bite. Given that patients with secondarily infected insect bites cannot be identified from all clinical sites in order to exclude from the analysis populations, this study is not acceptable unless you can provide evidence to justify the inclusion of these patients in the analysis populations. If no such evidence is available, a new clinical endpoint bioequivalence study, which follows the recommendations provided in the *Draft Guidance for Mupirocin Calcium Cream/Topical EQ 2% Base (revised October 2011)*, should be conducted and submitted for agency review.

2. Clinical cure is defined as a Skin Infection Rating Scale (SIRS) score of 0 for all signs and symptoms on a 4-point scale. "Sustained improvement" is not part of the definition. The inclusion of patients with sustained improvement in the clinical cure group is not acceptable as it could reduce the sensitivity of the clinical endpoint study in distinguishing differences between drug products and placebo.

3. The inclusion criterion for baseline SIRS total score is a total sore of at least 8.

4. The exclusion criterion for the use of topical therapeutic agents is within 48 hours (not 24 hours) prior to study entry.

5. Patients with diabetes should be excluded from the study.

6. Compliance is generally defined as 75% to 125% of the scheduled applications.

7. Visit window is defined as ±4 days.

Sincerely yours,

{See appended electronic signature page}

John R. Peters, M.D.
Director, Division of Clinical Review
Office of Generic Drugs
Center for Drug Evaluation and Research

{See appended electronic signature page}

Barbara M. Davit, PhD, JD
Acting Director, Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SARAH H Seung
03/06/2012

JOHN R PETERS
03/06/2012

BARBARA M DAVIT
03/08/2012

BIOEQUIVALENCY INFORMATION REQUEST

ANDA 201587

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Glenmark Generics Inc., USA TEL: 201-684-8017

ATTN: William R. McIntyre FAX: 201-831-0080

FROM: Nitin K. Patel PROJECT MANAGER: (240) 276-8887
(240) 276-8966 (fax)

Dear Sir:

This facsimile is a request for information from the Division of Clinical Review, regarding your ANDA 201587 for Mupirocin Calcium Cream USP, 2%.

The information request is presented on the attached __1__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

Your cover letter should clearly indicate that the response is a " Clinical Bioequivalency Amendment". We also request that you include a copy of this communication with your response.

Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

MEMORANDUM

ANDA 201587

To: **Glenmark Generics Inc., USA**

Drug: **Mupirocin Calcium Cream USP, 2%**

From: **Sarah H. Seung, PharmD**
Clinical Reviewer
Office of Generic Drugs

Dena R. Hixon, MD
Acting Director, Division of Clinical Review
Office of Generic Drugs

Date: **October 17, 2011**

Re: **Request for Information**

In order to complete the review of a bioequivalence study with clinical endpoints for ANDA 201587 (GLK 605), please provide the following information:

In order to confirm the appropriate diagnosis and adequately compare treatment groups at baseline, the OGD requests that you review source documents and provide a description of the target treatment site for each patient in detail, including the nature of the wound at baseline (e.g., laceration, abrasion, sutured, insect bite, etc..), dimensions of the wound, site or location on the body (e.g., left arm, nose etc..) and any other available description of the target lesion at baseline. Please submit this data in electronic (.xpt) format. Additional information concerning the format of the electronic data can be found on the FDA website for *Individual Product Bioequivalence Recommendations: Draft Guidance on Mupirocin Calcium Cream, (June 2010).*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NITIN K PATEL
10/17/2011

SARAH H Seung
10/17/2011

DENA R HIXON
10/17/2011

QUALITY DEFICIENCY - MINOR

ANDA 201587

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Glenmark Generics Inc., USA

TEL: (201) 684-8017

ATTN: William R McIntyre

FAX: (201) 831-0080

FROM: Trang Q. Tran

FDA CONTACT PHONE: (240) 276-8518

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated February 22, 2010, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mupirocin Cream USP, 2%.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Effective 01-Aug-2010, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

Chemistry Comments to be provided to the Applicant.

ANDA: 201587 APPLICANT: Glenmark Generics Inc. USA

DRUG PRODUCT: Mupirocin Cream USP, 2%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)

2.

3.

4.

5.

6.

7.

8.

9.

10

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Information related to the bioequivalence and labeling is under review. After the reviews are completed, any deficiencies found will be communicated to you under separate covers.

2. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval.

3. Please provide all available long-term drug product stability data.

4. We note that your ANDA was submitted in hard copy paper format for Module 3. We encourage you to submit your future ANDAs (and amendments) using the electronic gateway in order to facilitate the prompt review of your applications.

Sincerely yours,

{See appended electronic signature page}

Paul Schwartz, Ph.D.
Acting Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES M FAN
07/07/2011
for Paul Schwartz

OFFICE OF GENERIC DRUGS EXPEDITED REVIEW REQUESTED

ANDA#/SUPPLEMENT#: 201587
DRUG: Mupirocin Cream USP, 2%

APPLICANT: Glenmark Generics Inc., USA
DATE OF SUBMISSION:2/24/2011

The Office of Generic Drugs may grant expedited review status to either an Original or Supplemental abbreviated new drug application for the following reasons (MaPP 5240.1,& MaPP 5240.3). At least one of the criteria must be met to receive Expedited Review Status:

1. PUBLIC HEALTH NEED. Events that affect the availability of a drug for which there is no alternative

2. EXTRAORDINARY HARDSHIP ON THE APPLICANT.

   a) Catastrophic events such as explosion, fire storms damage.

   b) Events that could not have been reasonably foreseen and for which the applicant could not plan. Examples include:

      - ♦ Abrupt discontinuation of supply of active ingredient, packaging material, or container closure; and
      - ♦ Relocation of a facility or change in an existing facility because of a catastrophic event (see item 2.a)

3. AGENCY NEED.
   a) Matters regarding the government's drug purchase program, upon request from the appropriate FDA office.
   b) Federal or state legal/regulatory actions, including mandated formation changes or labeling changes if it is in the Agency's best interest.
   c) Expiration-date extension or packaging change when the drug product is the subject of a government contract award.
   d) Request for approval of a strength that was previously tentatively approved (To be used in those cases where 180-day generic drug exclusivity prevented full approval of all strengths).
   e) MaPP 5240.3 conditions.

RECOMMENDATIONS:

DISCIPLINE	STATUS	SIGNATURE/DATE
Team Project Manager (PM must Endorse)	Grant☒ Deny☐	3/2/11
Chemistry Team Leader (sign as needed)	Grant☐ Deny☐	
Micro Team Leader (sign as needed)	Grant☐ Deny☐	
Labeling Team Leader (sign as needed)	Grant☐ Deny☐	
Chem. Div./Deputy Director (DO must Endorse)	Grant☐ Deny☐	
Office Director/Deputy Director (email concurrence) (Original ANDAs)	Grant☒ Deny☐	3/2/11

RETURN TO PROJECT MANAGER CHEMISTRY TEAM: SELECT TEAM #
a) When expedited review is denied, notify the applicant by telephone

ENTER FORM INTO DFS DATE

Paste Final Copy Below:

From: West, Robert L
Sent: Wednesday, March 02, 2011 1:01 PM
To: Tran, Trang
Cc: Fan, James M; Weitzman, Beverly; Patel, Nitin K. (CDER/OGD); CDER-DDR600; Ames, Timothy W; Inyard, April
Subject: RE: Expedited Review Granted for ANDA 201587 (Mupirocin Calcium Cream USP, 2% - Glenmark Generics Inc. USA) (RLD = Bactroban Cream/GSK)

Trang:

I agree that Glenmark's ANDA 201587 for Mupirocin Cream USP, 2% meets the criteria established in CDER MaPP 5240.3 for "expedited review" status; i.e., no generic approvals for this drug product and no patents or exclusivity listed in the "Orange Book".

Since the ANDA meets the established criteria, "expedited review" is granted. Please make any changes necessary in DARRTS to reflect this status and inform the review team.

Thank you,

Bob

(b) (4)

From: Tran, Trang
Sent: Tuesday, March 01, 2011 1:06 PM
To: West, Robert L
Cc: Ames, Timothy W; Fan, James M
Subject: Expedited Review Request for ANDA 201587 (Mupirocin Cream USP, 2% - Glenmark Generics Inc. USA)
Importance: High

Hi Bob,

Glenmark is requesting for expedited review for ANDA 201587 (Mupirocin Cream USP, 2%) in the submission dated 2/24/2011. This request is based upon the fact that this is the first generic product for which there is no blocking patents or exclusivity on the RLD (Bactroban). The RLD NDA # is 50-746. Please let me know if this request should be granted.

Thanks.

Trang

Trang Q. Tran, Pharm. D.
LT, U.S. Public Health Service
Chemistry Project Manager, Team 13
FDA/CDER/OGD/Division I
7500 Standish Place, MPN 2
Rockville, MD 20855
Phone: 240-276-8518
Fax: 240-276-8504
Email: Trang.Tran@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TRANG Q TRAN
03/02/2011

MEMORANDUM
Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: July 29, 2010

TO: C.T. Viswanathan, PhD
Associate Director - Bioequivalence, Division of Scientific Investigations
WO51, HFD-48

THROUGH: Dena R. Hixon, MD
Associate Director for Medical Affairs
Office of Generic Drugs
MPNI, HFD-600

FROM: Nitin K. Patel, PharmD
Medical Affairs Coordinator, Clinical Review Team
Office of Generic Drugs
MPNI, HFD-600
240-276-8887

SUBJECT: Compliance Program 7348.001 – In Vivo Bioequivalence

REQUEST FOR INSPECTION

REFERENCES:

ANDA#	201587
Product	Mupirocin Cream USP, 2 %
Sponsor: full address	Glenmark Generics Inc. USA 750 Corporate Drive Mahwah, NJ 07430
Phone	201-684-8017
Fax	201-831-0080
Sponsor Contact	William McIntyre, PhD, Executive Vice President
Phone	201-684-8017
Fax	201-831-0080
Submission Date	February 22, 2010

PRIORITY: C

A (highest) = ready for approval in the office
B = ready for approval, clinical study under review
C = pending clinical review

DUE DATE: October 29, 2010

REASON FOR REQUEST:

	Not inspected in the last three years
	For Cause/Violative History
X	New Sites
	Other

Clinical Endpoint Study

TITLE:	A multi-center, double-blind, randomized, vehicle-controlled, parallel-group study comparing generic Mupirocin Calcium Cream, 2% to Bactroban Cream® (mupirocin calcium cream), 2% and both active treatments to a vehicle control in the treatment of secondarily infected traumatic skin lesions
PROTOCOL #:	GLK 605
NUMBER OF STUDY SITES:	10
CROs/SMO:	Not provided with submission

SITES TO BE INSPECTED	
Site # 1	Daisy Blanco, MD (Site 04)
Address	Instituto Dermatológico Calle Federico Velásquez, Esq. Albert Thomas Ensanche Maria Auxiliadora Santo Domingo, Republica Dominicana
Phone	Tel: (809) 684-3257
Investigator (Name/Contact Info)	Daisy Blanco, MD
# of subjects	81
Site # 2	Josefina Fernandez, MD (Site 05)
Address	Departamento de Enfermedades Infecciosas Hospital Infantil Dr. Robert Reid Cabral Av. Abraham Lincoln #2 Santo Domingo, Republica Dominicana
Phone	Tel: (809) 532-5872
Investigator (Name/Contact Info)	Josefina Fernandez, MD
# of subjects	98
Site # 3	Ynca Nina Vasquez, MD (Site 13)
Address	Instituto Dermatololo'gico Unidad Sur Calle Padre Ayala #140 San Cristobal Santa Domingo, Republica Dominicana
Phone	Tel: (809) 528-4848
Investigator (Name/Contact Info)	Ynca Nina Vasquez, MD
# of subjects	72

COMMENTS/ADDITIONAL INFORMATION FOR INSPECTORS:

This ANDA is located in the Electronic Document Room (EDR).

CLINICAL STUDY STATUS:

	Study under review
	Study review completed
	Decision:
X	Other: Review not started.

CLINICAL REVIEWER/CONTACT INFORMATION: Not yet assigned to a clinical reviewer.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201587	ORIG-1	GLENMARK GENERICS INC USA	MUPIROCIN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NITIN K PATEL
07/29/2010

DENA R HIXON
07/29/2010

CLINICAL REVIEW TEAM CHECKLIST FOR GENERIC ANDA
FOR APPLICATION COMPLETENESS

ANDA# 201587___ **FIRM NAME**___Glenmark Generics limited _____

DRUG NAME __Mupirocin Cream, USP, 2%_____

DOSAGE FORM __topical cream_____

REFERENCE LISTED DRUG (RLD) _Bactroban® Cream, NDA 050746_____

Requested by: _Howard, Eda_____ Date: _3/19/10_____
Regulatory Support Team, (HFD-615)

	Summary of Findings by Clinical Review Team
X	**Study meets statutory requirements**
	Study does NOT meet statutory requirements
	Reason:
	Waiver meets statutory requirements
	Waiver does NOT meet statutory requirements
	Reason:

RECOMMENDATION: **_X__COMPLETE** **___INCOMPLETE**

Reviewed by:

_____ Date: _____
Reviewer
Carol Y. Kim, Pharm.D.
Clinical Reviewer

_____ Date: _____
Dena R. Hixon, M.D.
Associate Director for Medical Affairs

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	X				Protocol #GLK 605 Data in “CD4-module 5”
Summary of Study	X				
Clinical Site (s)	X				
Study Investigator (s)	X				
List of subjects included in PP/ (M)ITT populations per treatments	X				
List of subjects excluded/ from PP/ (M)ITT per treatments	X				
Reasons for discontinuation from the study if discontinued	X				
Adverse Events	X				
Concomitant Medications	X				
Individual subject’s scores/data per visit	X				
Pre-screening of Patients	X				
IRB Approval	X				
Consent Forms	X				
Randomization Schedule	X				
Protocol Deviations	X				
Case Report Forms	X				
PD Data Disk (or Elec Subm)	X				
Study Results	X				
Clinical Raw Data/ Medical Records	X				
Financial Disclosure	X				

Composition	X				
BioStudy Lot Numbers	X				
Date of Manufacture		X			Date of expiration was given instead. This is acceptable.
Exp. Date of RLD	X				
Statistical Reports	X				
Defined BE endpoints	X				
Summary results provided by the firm indicate studies pass BE criteria	X				See comments below
Summary results provided by the firm indicate superiority of the active treatments over the vehicle/placebo	X				
Waiver requests for other strengths / supporting data		X			n/a

Comments to be conveyed to the sponsor:

Your clinical endpoint bioequivalence study is acceptable for receiving your ANDA.

Comments <u>not to be conveyed</u> to the sponsor:

The sponsor conducted a bioequivalence study with a clinical endpoint in treatment of secondarily infected traumatic skin lesions (up to 10 cm in length or 100 cm^2 in area) to demonstrate bioequivalence between the test and the reference products. In this study, the sponsor enrolled patients who had a Skin Infection Rating Scale (SIRS) score of at least 4 and had white blood cells observed on Wright stain or Gram stain prepared from wound exudates. Patients applied the study drugs three times daily for 10 days.

According to the sponsor's analysis, the 90% CI of the difference between the test and reference products in the PP population with regard to the proportion of patients with clinical success at the follow-up visit 4 (Day 17-21) after completion of 10 days of treatment is (-0.066, 0.048), which is within acceptable BE limits of (-0.20 to +0.20). Both active drug products show superiority over the vehicle group in the MITT population ($P<0.001$). A clinical success was defined by the sponsor as "achieving complete resolution (SIRS scores of 0) or sustained improvement (SIRS scores of 0 for exudate/pus, crusting, tissue wamth, edema and pain; and 0 or 1 for erythema/inflammation and itching).

Reviewer's Comments: *The preferred definition of clinical success/cure is a Skin Infection Rating Scale (SIRS) score of 0 (absent) for all evaluated primary clinical signs and symptoms at the follow-up visit (visit 4) after completion of 10 days of treatment.*

The sponsor's summary of the primary endpoint analysis is shown below.

Table 11.5: Primary Efficacy Analysis: n (%) Clinical Success at Visit 4/Follow-up

Population	Clinical Response*	Mupirocin Calcium Cream, 2%	Bactroban® Cream 2%	Vehicle	90% CI for Bioequivalence of Mupirocin Calcium Cream, 2% to Bactroban® Cream 2%	p-values	
						Mupirocin Calcium Cream, 2% vs. Vehicle	Bactroban® Cream 2% vs. Vehicle
Per-Protocol Subjects		(N=175)	(N=170)	(N=165)			
	Success	158 (90.3%)	155 (91.2%)	117 (70.9%)	(-6.61%, 4.82%)[1]	<0.001[2]	<0.001[2]
Modified Intent-to-Treat Subjects		(N=181)	(N=181)	(N=176)			
	Success	164 (90.6%)	163 (90.1%)	124 (70.5%)	(-5.11%, 6.21%)[1]	<0.001[2]	<0.001[2]

Missing efficacy results were replaced using a last-observation carried forward (LOCF) approach for mITT subjects and for PP subjects who were discontinued early due to treatment failure.

*Clinical Success: achieving complete resolution (SIRS scores of 0) or sustained improvement (SIRS scores of 0 for exudate/pus, crusting, tissue warmth, edema and pain; and 0 or 1 for erythema/inflammation and itching) of signs and symptoms of infection. No additional antibiotic therapy required after End of Treatment.

[1]Confidence interval calculated using Wald's method with Yates' continuity correction.

[2]P-values for treatment comparisons from two-sided Z-test with Yates' continuity correction.

Reviewer's Comments: *Using the sponsor's primary dataset "STATMITT.XPT and STATPP.XPT", this reviewer evaluated the clinical success rate based on a SIRS score of 0 at visit 4. Using the preferred definition of a SIRS score of zero, the clinical success rate was 80% for the test product, 80% for the reference product and 59% for the vehicle in the sponsor's PP population. The clinical success rate was 80% for the test product, 79% for the reference product, and 70% for the vehicle in the sponsor's MITT population. Therefore, the sponsor's data appear to show bioequivalence between products.*

The sponsor's proposed formulation is shown below.

Sr. No.	Ingredient(s)	(b) (4)
1.	Mupirocin Calcium [1]	
2.	Benzyl Alcohol	
3.	Mineral Oil (b) (4)	
4.	Phenoxyethanol (b) (4)	
5.	Xanthan gum (b) (4)	
6.	Polyoxyl 20 cetostearyl ether (b) (4)	
7.	Glycerol monostearate (b) (4) (b) (4)	
8.	Purified water	

1 (b) (4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201587	ORIG-1	GLENMARK GENERICS INC USA	MUPIROCIN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CAROL Y KIM
05/10/2010

DENA R HIXON
05/10/2010
I concur.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 201587

Glenmark Generics Inc., USA
Attention: William McIntyre, Ph.D.
750 Corporate Drive
Mahwah, NJ 07430

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.

NAME OF DRUG: Mupirocin Cream USP, 2 %

DATE OF APPLICATION: February 22, 2010

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 23, 2010

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

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

Should you have questions concerning this application, contact:

Robert Gaines
Project Manager
240-276-8494

Sincerely yours,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201587	ORIG-1	GLENMARK GENERICS INC USA	MUPIROCIN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

IAIN MARGAND
05/18/2010
Signing for Wm Peter Rickman

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
*** **A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ ***

ANDA #: 201587 **FIRM NAME**: GLENMARK GENERICS LIMITED

PIV: NO **Electronic or Paper Submission:** CTD FORMAT PAPER

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: MUPIROCIN
DOSAGE FORM: CREAM USP, 2%

Review Team: (Bolded/Italicized & Checked indicate Assignment or DARRTS designation)

Quality Team: DC3 Team 11 ☒***Activity***	***Bio Team 1: Partha Chandaroy*** ☒***Activity***
ANDA/Quality RPM: Lisa Kwok ☒ ***FYI***	Bio PM: Jerome Lee ☐ ***FYI***
Quality Team Leader: Sriniasan, Aloka No assignment needed in DARRTS	***Clinical Endpoint Team Assignment: Random Clinical Team*** ☒***Activity***
Labeling Reviewer: Melaine Shin ☒***Activity***	***Micro Review (No)*** ☐***Activity***

*****Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s). *****

Letter Date: FEBRUARY 22, 2010 **Received Date**: FEBRUARY 23, 2010

Comments: EC- 1 YES **On Cards:** YES
Therapeutic Code: 4014100 ANTIBOITICS (TOPICAL)

Archival copy: CTD FORMAT PAPER **Sections** I
Review copy: YES E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Shannon Hill **Date May 12, 2010**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**

Supervisory Concurrence/Date: _____ **Date:** _____

1. Edit Application Property Type in DARRTS where applicable for
   a. First Generic Received
      ☐ Yes ☒ No
   b. Market Availability
      ☒ Rx ☐ OTC
   c. Pepfar
      ☐ Yes ☒ No
   d. Product Type
      ☐ Small Molecule Drug (usually for most ANDAs except protein drug products)
   e. USP Drug Product (at time of filing review)
      ☒ Yes ☐ No
2. Edit Submission Patent Records
   ☒ Yes
3. Edit Contacts Database with Bioequivalence Recordation where applicable
   ☒ Yes
4. Requested EER
   ☒ Yes

ADDITIONAL COMMENTS REGARDING THE ANDA:

1. Waiting for clinical review results; study meets statutory requirements 5/10/2010.

MODULE 1
ADMINISTRATIVE

ACCEPTABLE

1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: FEBRUARY 22, 2010	☒
1.2.1	**Form FDA 3674** **(PDF)** YES	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) NA	☒

1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s) 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☒ PIII ☐ PIV ☐ (Statement of Notification) ☐ 3. Expiration of Patent(s): NA a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES **Patent and Exclusivity Search Results from query on Appl No 050746 Product 001 in the OB_Rx list.** **There are no unexpired patents for this product in the Orange Book Database.** **There is no unexpired exclusivity for this product.**	☒
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient YES; (b) (4) Type II DMF No. b. Type III DMF authorization letter(s) for container closure YES; (b) (4) 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) (b) (4)	☒
1.12.11	**Basis for Submission** NDA# : 50-746 Ref Listed Drug: BACTROBAN Firm: GLAXO SMITHKLINE ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use SAME 2. Active ingredients SAME 3. Inactive ingredients JUSTIFIED 4. Route of administration SAME 5. Dosage Form SAME 6. Strength SAME	☒
1.12.14	**Environmental Impact Analysis Statement** YES SEE SECTION 1.12.14	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): NA	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) YES **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained YES **1.14.1.3** 1 package insert (content of labeling) submitted electronically YES ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such.) **HOW SUPPLIED** Mupirocin cream USP, 2% is supplied in 15 gram and 30 gram tubes. NDC 68462-564-17 (15 gram tube) NDC 68462-564-35 (30 gram tube)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained YES **1.14.3.3** 1 RLD label and 1 RLD container label YES	☒

MODULE 2
SUMMARIES ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** YES **Word Processed e.g., MS Word** YES A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** YES **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** YES **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P** **Drug Product** YES **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF** YES **Word Processed e.g., MS Word** YES **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary YES Table 4. Bioanalytical Method Validation YES; NO DATA Table 6. Formulation Data YES **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution YES; NO DATA **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies YES Table 3. Statistical Summary of the Comparative BA Data YES **2.7.1.4 Appendix** **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study YES **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies YES	☒

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) YES 2. Function or Responsibility YES 3. Type II DMF number for API YES; (b) (4) 4. CFN or FEI numbers YES; (b) (4) (b) (4)	☒
3.2.S.3	**Characterization**	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) YES **3.2.S.4.2 Analytical Procedures** YED **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples YES 2. Samples-Statement of Availability and Identification of: NOT FOUND a. Drug Substance b. Same lot number(s) **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) YES 2. Applicant certificate of analysis YES **3.2.S.4.5 Justification of Specification**	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems** refer to DMF # (b) (4)	☒
3.2.S.7	**Stability** refer to DMF (b) (4)	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition YES 2. Inactive ingredients and amounts are appropriate per IIG YES	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report YES	☒
3.2.P.3	**Manufacture** **3.2.P.3.1 Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. Function or Responsibility YES 4. CFN or FEI numbers YES Glenmark Generics Limited Plot No. S-7, Colvale Industrial Estate Colvale, Bardez, Goa 403 513, India CFN: 3004672766 Contact: Mr. Anil Agrawal, General Manager - Production Email: anil_a@glenmark-generics.com Telephone: 0091-832-2299833 Fax: 0091-832-2299857 **3.2.P.3.2 Batch Formula** YES **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES 3. If sterile product: Aseptic fill / Terminal sterilization N/A 4. Reprocessing Statement YES **3.2.P.3.4 Controls of Critical Steps and Intermediates** **3.2.P.3.5 Process Validation and/or Evaluation** 1. Microbiological sterilization validation N/A 2. Filter validation (if aseptic fill) N/A (b) (4)	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified YES **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) YES; except glycerol monostearate (b) (4) 2. Suppliers' COA (specifications and test results) YES **3.2.P.4.2 Analytical Procedures** **3.2.P.4.3 Validation of Analytical Procedures** **3.2.P.4.4 Justification of Specifications** Applicant COA YES	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

<table>
<tr>
<td>3.2.P.5</td>
<td>
Controls of Drug Product
3.2.P.5.1 Specification(s) YES
3.2.P.5.2 Analytical Procedures YES
3.2.P.5.3 Validation of Analytical Procedures
Samples - Statement of Availability and Identification of:
1. Finished Dosage Form YES
2. Same lot numbers
DRUG PRODUCT SAMPLES

The following drug product samples are being retained by Glenmark and will be supplied to the FDA upon request.

<table>
<tr><th>Product</th><th>Batch number</th><th>Packs</th><th>Samples</th></tr>
<tr><td rowspan="2">Mupirocin Cream USP, 2%</td><td rowspan="2">Q15748002</td><td>15 g</td><td>63 tubes</td></tr>
<tr><td>30 g</td><td>63 tubes</td></tr>
</table>
3.2.P.5.4 Batch Analysis
Certificate of Analysis for Finished Dosage Form YES
3.2.P.5.5 Characterization of Impurities
3.2.P.5.6 Justification of Specifications
</td>
<td>☒</td>
</tr>
<tr>
<td>3.2.P.7</td>
<td>
Container Closure System
1. Summary of Container/Closure System (if new resin, provide data) YES
2. Components Specification and Test Data YES
3. Packaging Configuration and Sizes YES
4. Container/Closure Testing YES
5. Source of supply and suppliers address YES
</td>
<td>☒</td>
</tr>
<tr>
<td>3.2.P.8</td>
<td>
3.2.P.8.1 Stability (Finished Dosage Form)
1. Stability Protocol submitted YES
2. Expiration Dating Period 24 MONTHS
3.2.P.8.2 Post-approval Stability and Conclusion
Post Approval Stability Protocol and Commitments YES
3.2.P.8.3 Stability Data
1. 3 month accelerated stability data YES
2. Batch numbers on stability records the same as the test batch Q15748002 (15 gm & 30 gm)
</td>
<td>☒</td>
</tr>
</table>

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available)** refer to DMF (b) (4) **3.2.R.2.S Comparability Protocols** N/A **3.2.R.3.S Methods Validation Package** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation YES SEE ATTACHED **3.2.R.1.P.2 Information on Components** 3.2.P.3.2 3.2.P.3.3 **3.2.R.2.P Comparability Protocols** N/A **3.2.R.3.P Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5

CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☒
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) N/A b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) YES **2. Lot Numbers of Products used in BE Study(ies):** ANDA: Q15748002 RLD: C328473 **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒

5.3.1.2 Comparative BA/BE Study Reports ☒

1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) within (+/- 20%)

Table 3 Statistical Summary of the Comparative Bioavailability Data

A multi-center, double-blind, randomized, vehicle-controlled, parallel-group study comparing generic Mupirocin Calcium Cream, 2% to Bactroban Cream® (mupirocin calcium cream), 2% and both active treatments to a vehicle control in the treatment of secondarily infected traumatic skin lesions

Study No. GLK 605

	Key Statistics and 90% Confidence Intervals				Superiority Testing	
Parameter	Test	Reference	Placebo	90% C.I.	Test vs. Placebo	Reference vs. Placebo
Clinical Success* Rates at Visit 4/Week 6 (PP)	90.3%	91.2%	70.9%	(-6.61%, 4.82%)[1]	<0.001[2]	<0.001[2]
Clinical Success* Rates at Visit 4/Week 6 (mITT)	90.6%	90.1%	70.5%	(-5.11%, 6.21%)[1]	<0.001[2]	<0.001[2]

Missing efficacy results were replaced using a last-observation carried forward (LOCF) approach for mITT subjects and for PP subjects who were discontinued early due to treatment failure.
*Clinical Success: achieving complete resolution (SIRS scores of 0) or sustained improvement (SIRS scores of 0 for exudate/pus, crusting, tissue warmth, edema and pain; and 0 or 1 for erythema/inflammation and itching) of signs and symptoms of infection. No additional antibiotic therapy required after End of Treatment.
[1]Confidence interval calculated using Wald's method with Yates' continuity correction.
[2]P-values for treatment comparisons from two-sided Z-test with Yates' continuity correction.

2. Summary Bioequivalence tables:
   - Table 10. Study Information YES
   - Table 12. Dropout Information YES
   - Table 13. Protocol Deviations YES

5.3.1.3
In Vitro-In-Vivo Correlation Study Reports

1. Summary Bioequivalence tables:
   - Table 11. Product Information YES
   - Table 16. Composition of Meal Used in Fed Bioequivalence Study YES; NO DATA

5.3.1.4
Reports of Bioanalytical and Analytical Methods for Human Studies

1. Summary Bioequivalence table:
   - Table 9. Reanalysis of Study Samples YES; NO DATA
   - Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses YES; NO DATA
   - Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples YES; NO DATA

5.3.7
Case Report Forms and Individual Patient Listing YES

5.4 **Literature References** ☐

Possible Study Types:

Study Type

IN-VIVO BE STUDY(IES) with PK ENDPOINTS (i.e., fasting/fed/sprinkle) NA ☐

1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC)
2. EDR Email: Data Files Submitted: YES SENT TO EDR
3. In-Vitro Dissolution: NA

Study Type

IN-VIVO BE STUDY with CLINICAL ENDPOINTS YES/BIO ☒

1. Properly defined BE endpoints (eval. by Clinical Team) YES
2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). YES
3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) MEMO SENT TO CLINICAL TEAM FOR REVIEW 3/19/10
4. EDR Email: Data Files Submitted YES SENT TO EDR

Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 10/19/2009

Active Ingredient Search - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Search Favorites

Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm

Go Links

U.S. Department of Health & Human Services www.hhs.gov

U.S. Food and Drug Administration A-Z Index Search go

Home | Food | Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Radiation-Emitting Products | Tobacco Products

FDA Home

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Active Ingredient Search Results from "OB_Rx" table for query on "MUPIROCIN."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
A065192	AB	No	MUPIROCIN	OINTMENT; TOPICAL	2%	MUPIROCIN	ALTANA
N050591	AB	Yes	MUPIROCIN	OINTMENT; TOPICAL	2%	BACTROBAN	GLAXOSMITHKLINE
N050788	BX	No	MUPIROCIN	OINTMENT; TOPICAL	2%	CENTANY	PERRIGO NEW YORK
A065123	AB	No	MUPIROCIN	OINTMENT; TOPICAL	2%	MUPIROCIN	PERRIGO NEW YORK
A065170	AB	No	MUPIROCIN	OINTMENT; TOPICAL	2%	MUPIROCIN	TARO
A065085	AB	No	MUPIROCIN	OINTMENT; TOPICAL	2%	MUPIROCIN	TEVA
N050746		Yes	MUPIROCIN CALCIUM	CREAM, AUGMENTED; TOPICAL	EQ 2% BASE	BACTROBAN	GLAXOSMITHKLINE
N050703		Yes	MUPIROCIN CALCIUM	OINTMENT; NASAL	EQ 2% BASE	BACTROBAN	GLAXOSMITHKLINE

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support

Local intranet

Orange Book Detail Record Search - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Search Favorites

Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=050591&TABLE1=OB_Rx

Go Links

U.S. Department of Health & Human Services www.hhs.gov

U.S. Food and Drug Administration A-Z Index Search go

Home | Food | Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Radiation-Emitting Products | Tobacco Products

FDA Home

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Search results from the "OB_Rx" table for query on "050591."

Active Ingredient:	MUPIROCIN
Dosage Form;Route:	OINTMENT; TOPICAL
Proprietary Name:	BACTROBAN
Applicant:	GLAXOSMITHKLINE
Strength:	2%
Application Number:	N050591
Product Number:	001
Approval Date:	Dec 31, 1987
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AB**
Patent and Exclusivity Info for this product:	View

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:

Orange Book Data - **Monthly**

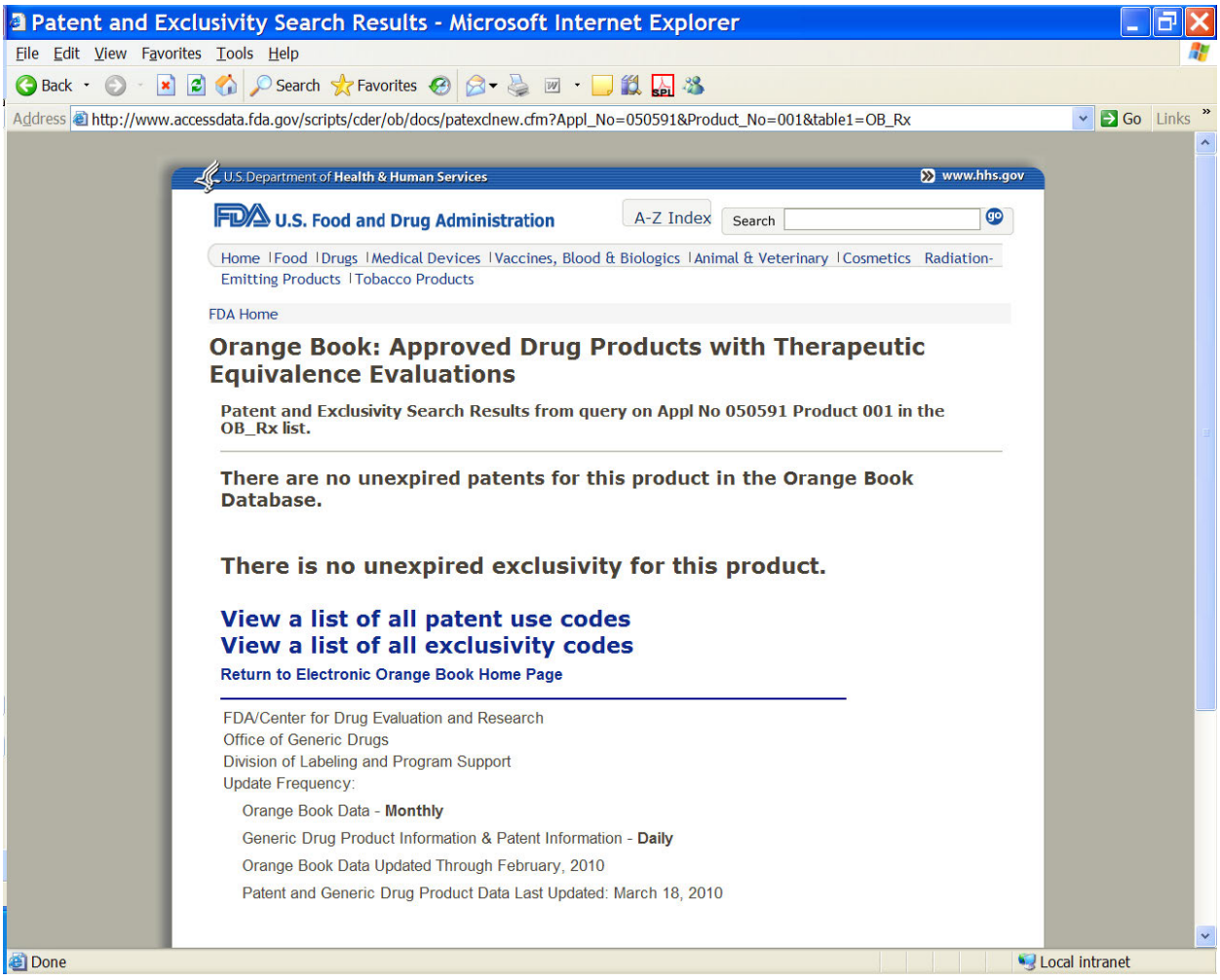
Generic Drug Product Information & Patent Information - **Daily**

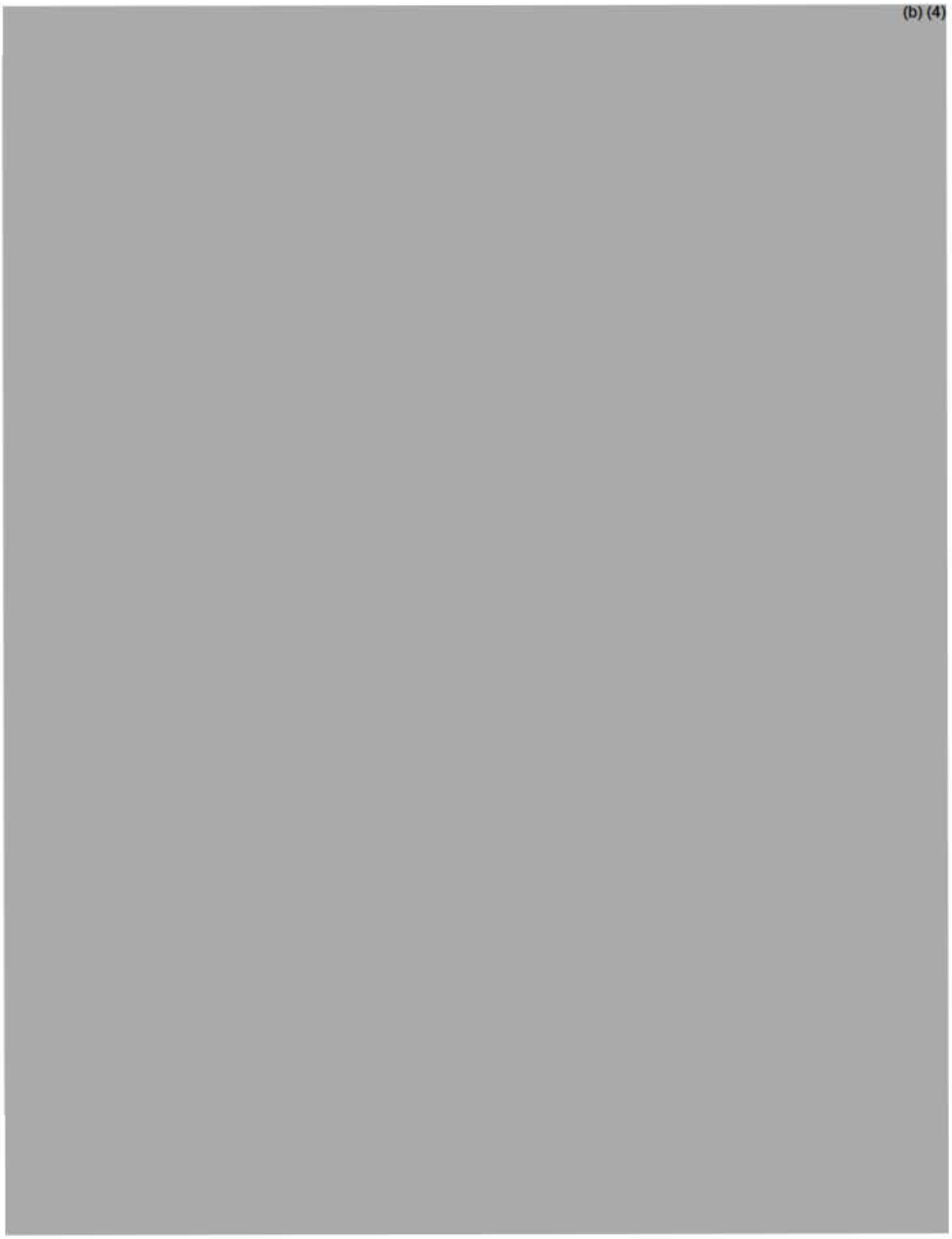
Orange Book Data Updated Through February, 2010

Patent and Generic Drug Product Data Last Updated: March 18, 2010

Done

Local intranet


Patent and Exclusivity Search Results - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=050591&Product_No=001&table1=OB_Rx
Go Links
U.S. Department of Health & Human Services
www.hhs.gov
U.S. Food and Drug Administration
A-Z Index
Search
go
Home | Food | Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Radiation-Emitting Products | Tobacco Products
FDA Home
Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
Patent and Exclusivity Search Results from query on Appl No 050591 Product 001 in the OB_Rx list.
There are no unexpired patents for this product in the Orange Book Database.
There is no unexpired exclusivity for this product.
View a list of all patent use codes
View a list of all exclusivity codes
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through February, 2010
Patent and Generic Drug Product Data Last Updated: March 18, 2010
Done
Local intranet


(b) (4)

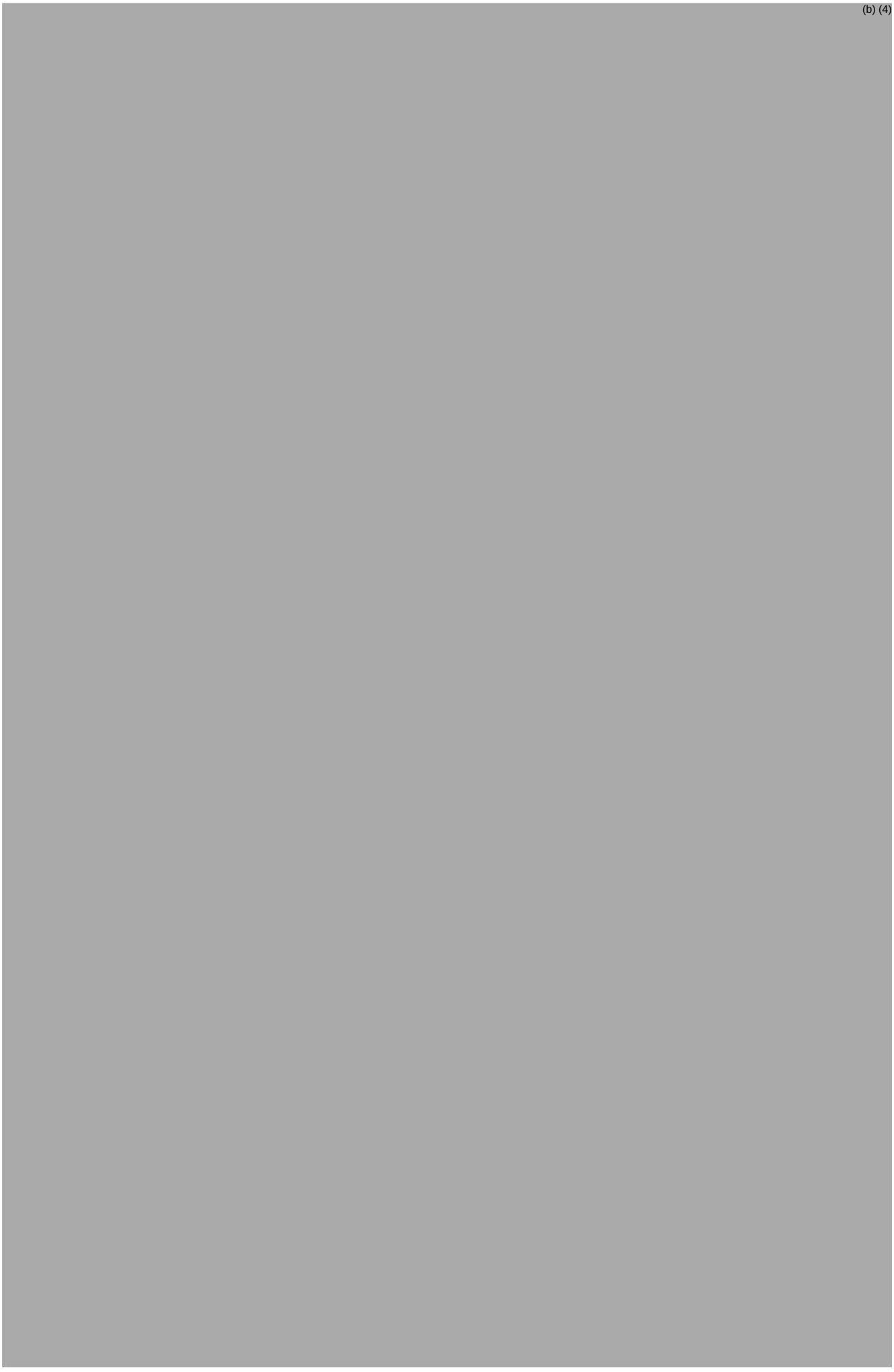


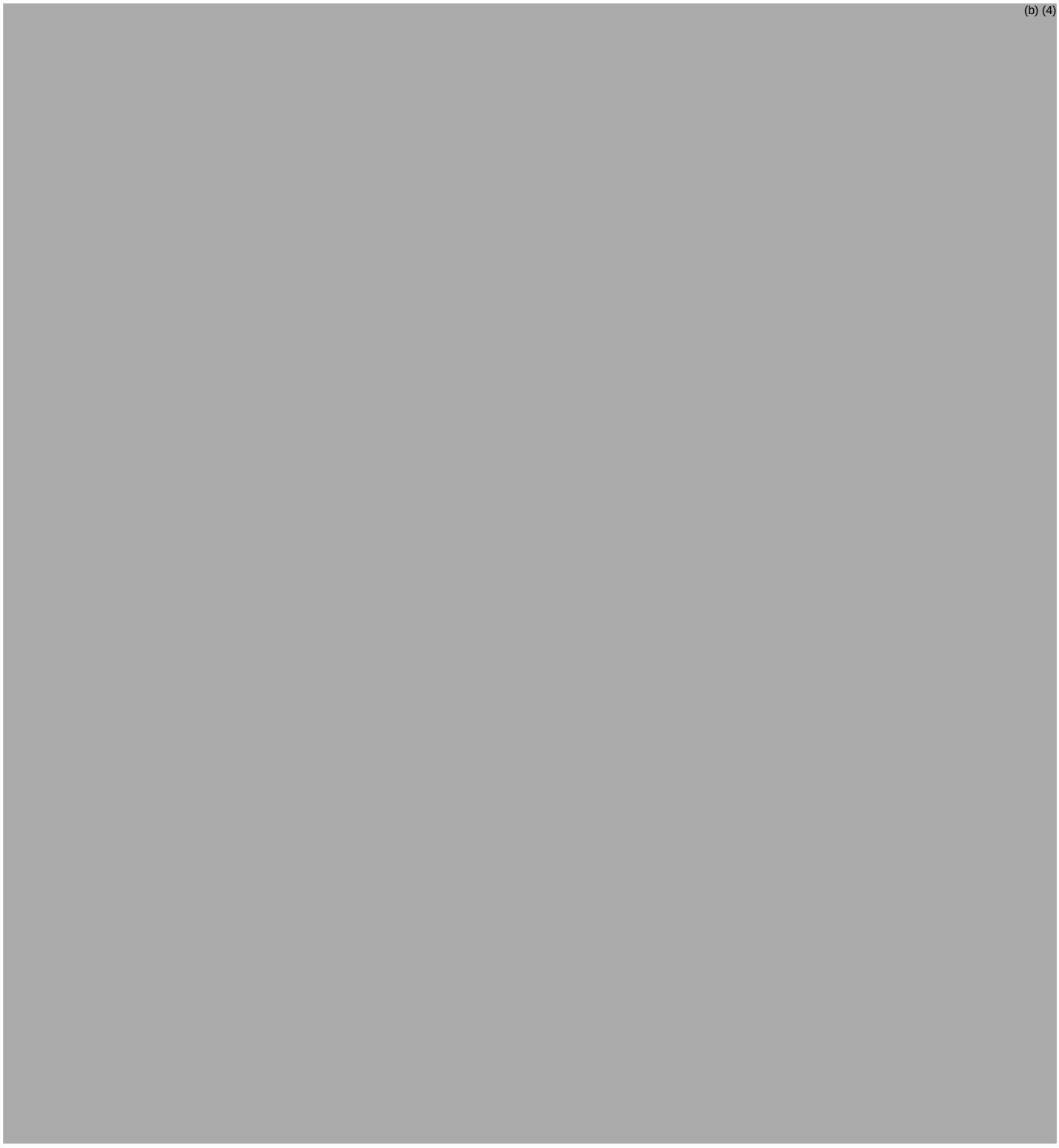
Table 6 Formulation Data

Sr. No.	Ingredient(s)	Quality Standard	Quantity (%w/w)
1.	Mupirocin Calcium [1]	USP	2.365
2.	Benzyl Alcohol	(b) (4)	
3.	Mineral Oil (b) (4)		
4.	Phenoxyethanol (b) (4)		
5.	Xanthan gum (b) (4)		
6.	Polyoxyl 20 cetostearyl ether (b) (4)		
7.	Glycerol monostearate 40 – 55 (b) (4)		
8.	Purified water		

(b) (4)

Sr. No.	Ingredients	Quantity	Exhibit batch size (b) (4)	Intended commercial production batch size (b) (4)
		(% w/w)	(kg)	(kg)
1.	Mupirocin Calcium, USP[1,2]	2.365	(b) (4)	
2.	Benzyl alcohol, NF	(b) (4)		
3.	Mineral oil, USP (b) (4)			
4.	Phenoxyethanol, NF (b) (4)			
5.	Xanthan gum, NF (b) (4)			
6.	Polyoxyl 20 cetostearyl ether, NF (b) (4)			
7.	Glycerol monostearate (b) (4) (b) (4)			
8.	Purified water, USP[3]			

(b) (4)


(b) (4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201587	ORIG-1	GLENMARK GENERICS INC USA	MUPIROCIN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHANNON L HILL
05/17/2010

IAIN MARGAND
05/18/2010
Signing for Martin Shimer

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : March 19, 2010

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 201587 for Mupirocin Cream USP, 2% to determine if the application is substantially complete for filing.

Glenmark Generics Limited has submitted ANDA 201587 for Mupirocin Cream USP, 2%. In order to accept an ANDA the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Glenmark Generics Limited on February 22, 2010 for its Mupirocin product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201587	ORIG-1	GLENMARK GENERICS INC USA	MUPIROCIN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EDA E HOWARD
03/19/2010