CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

65-123

Generic Name: Mupirocin Ointment USP, 2%

Sponsor: Clay-Park Labs Inc.

Approval Date: November 7, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-123

CONTENTS

Reviews / Information Included in this ANDA Review.

Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	X
Medical Officer Review(s)	
Chemistry Review(s)	X
Microbiology Review(s)	
Bioequivalence Review(s)	X
Administrative Document(s)	
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-123

APPROVAL LETTER

ANDA 65-123

NOV 7 2003

Clay-Park Labs, Inc.
Attention: Candis Edwards
1700 Bathgate Avenue
Bronx, NY 10457

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated January 4, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Mupirocin Ointment USP, 2%. We note that this product is subject to the exception provisions of Section 125(d)(2) of Title I of the Food and Drug Administration Modernization Act of 1997.

Reference is also made to your amendments dated September 5, and September 11, 2002; and January 24, January 27, and October 30, 2003.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Mupirocin Ointment USP, 2%, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Bactroban® Ointment, 2%, of GlaxoSmithKline.

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

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Robert Lumpkin/for 11/1/2003

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-123

FINAL PRINTED LABELING

MUPIROCIN OINTMENT USP, 2%

For Dermatologic Use

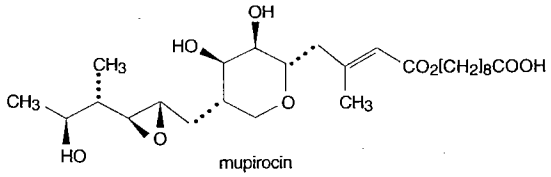
Rx only

APPROVED

NOV - 7 2003

DESCRIPTION

Each gram of Mupirocin Ointment USP, 2% contains 20 mg mupirocin in a bland water miscible ointment base (polyethylene glycol ointment, N.F.) consisting of polyethylene glycol 400 and polyethylene glycol 3350. Mupirocin is a naturally occurring antibiotic. The chemical name is (*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-2 *H*-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid. The molecular formula of mupirocin is $C_{26}H_{44}O_9$ and the molecular weight is 500.62. The chemical structure is:



mupirocin

CLINICAL PHARMACOLOGY

Application of ^{14}C-labeled mupirocin ointment to the lower arm of normal male subjects followed by occlusion for 24 hours showed no measurable systemic absorption (<1.1 nanogram mupirocin per milliliter of whole blood). Measurable radioactivity was present in the stratum corneum of these subjects 72 hours after application.

Following intravenous or oral administration, mupirocin is rapidly metabolized. The principal metabolite, monic acid, is eliminated by renal excretion, and demonstrates no antibacterial activity. In a study conducted in seven healthy adult male subjects, the elimination half-life after intravenous administration of mupirocin was 20 to 40 minutes for mupirocin and 30 to 80 minutes for monic acid. The pharmacokinetics of mupirocin has not been studied in individuals with renal insufficiency.

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 *S. aureus* and coagulase-negative staphylococci.

Mupirocin is bactericidal at concentrations achieved by topical administration. However, the minimum bactericidal concentration (MBC) against relevant pathogens is generally eight-fold to thirty-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 *Staphylococcus 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 Ointment USP, 2% is indicated for the topical treatment of impetigo due to: *Staphylococcus aureus* and *Streptococcus pyogenes*.

CONTRAINDICATIONS

This drug is contraindicated in individuals with a history of sensitivity reactions to any of its components.

WARNINGS

Mupirocin Ointment USP, 2% is not for ophthalmic use.

PRECAUTIONS

If a reaction suggesting sensitivity or chemical irritation should occur with the use of Mupirocin Ointment USP, 2%, treatment should be discontinued and appropriate alternative therapy for the infection instituted.

As with other antibacterial products, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Mupirocin Ointment USP, 2% is not formulated for use on mucosal surfaces. Intranasal use has been associated with isolated reports of stinging and drying. Bactroban®* Nasal (mupirocin calcium ointment) - is available for intranasal use.

Polyethylene glycol can be absorbed from open wounds and damaged skin and is excreted by the kidneys. In common with other polyethylene glycol-based ointments, Mupirocin Ointment USP, 2% should not be used in conditions where absorption of large

quantities of polyethylene glycol is possible, especially if there is evidence of moderate or severe renal impairment.
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 medication should be stopped and your healthcare practitioner contacted if irritation, severe itching, or rash occurs. If impetigo has not improved in 3 to 5 days, contact your healthcare practitioner.

Drug Interactions: The effect of the concurrent application of Mupirocin Ointment USP, 2% and other drug products has not been studied.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals to evaluate carcinogenic potential of mupirocin 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 genotoxicity: 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.

Reproduction studies were performed in male and female rats with mupirocin administered subcutaneously at doses up to 14 times a human topical dose (approximately 60 mg mupirocin per day) on a mg/m^2 basis and revealed no evidence of impaired fertility and reproductive performance from mupirocin.

Pregnancy
Teratogenic Effects.
Pregnancy Category B: Reproduction studies have been performed in rats and rabbits with mupirocin administered subcutaneously at doses up to 22 and 43 times, respectively, the human topical dose (approximately 60 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 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 Ointment USP, 2% is administered to a nursing woman.
Pediatric Use: The safety and effectiveness of Mupirocin Ointment USP, 2% have been established in the age range of 2 months to 16 years. Use of Mupirocin Ointment USP, 2% in these age groups is supported by evidence from adequate and well-controlled studies of Mupirocin Ointment USP, 2% in impetigo in pediatric patients studied as a part of the pivotal clinical trials. (See **CLINICAL STUDIES.**)

ADVERSE REACTIONS
The following local adverse reactions have been reported in connection with the use of Mupirocin Ointment USP, 2%: burning, stinging, or pain in 1.5% of patients; itching in 1% of patients; rash, nausea, erythema, dry skin, tenderness, swelling, contact dermatitis, and increased exudate in less than 1% of patients.

DOSAGE AND ADMINISTRATION
A small amount of Mupirocin Ointment USP, 2% should be applied to the affected area three times daily. The area treated may be covered with a 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 Ointment USP, 2% in impetigo was tested in two studies. In the first, patients with impetigo were randomized to receive either Mupirocin Ointment USP, 2% or vehicle placebo t.i.d. for 8 to 12 days. Clinical efficacy rates at end of therapy in the evaluable populations (adults and pediatric patients included) were 71% for Mupirocin Ointment USP, 2% (n=49) and 35% for vehicle placebo (n=51). Pathogen eradication rates in the evaluable populations were 94% for Mupirocin Ointment USP, 2% and 62% for vehicle placebo. There were no side effects reported in the group receiving Mupirocin Ointment USP, 2%.
In the second study, patients with impetigo were randomized to receive either Mupirocin Ointment USP, 2% t.i.d. or 30 to 40 mg/kg oral erythromycin ethylsuccinate per day (this was an unblinded study) for 8 days. There was a follow-up visit 1 week after treatment ended. Clinical efficacy rates at the follow-up visit in the evaluable populations (adults and pediatric patients included) were 93% for Mupirocin Ointment USP, 2% (n=29) and 78.5% for erythromycin (n=28). Pathogen eradication rates in the evaluable patient populations were 100% for both test groups. There were no side effects reported in the Mupirocin Ointment USP, 2% group.
Pediatrics
There were 91 pediatric patients aged 2 months to 15 years in the first study described above. Clinical efficacy rates at end of therapy in the evaluable populations were 78% for Mupirocin Ointment USP, 2% (n=42) and 36% for vehicle placebo (n=49). In the second study described above, all patients were pediatric except two adults in the group receiving Mupirocin Ointment USP, 2%. The age range of the pediatric patients was 7 months to 13 years. The clinical efficacy rate for Mupirocin Ointment USP, 2% (n=27) was 96%, and for erythromycin it was unchanged (78.5%).

HOW SUPPLIED
Mupirocin Ointment USP, 2% is supplied in 15 gram, 22 gram and 30 gram tubes.
Store at controlled room temperature 20° to 25°C (68° to 77°F).
* Bactroban® Nasal is a registered trademark of SmithKline Beecham Pharmaceuticals.

Mfg. By: **CLAY-PARK LABS, INC.**, Bronx, NY 10457

I112-2X N0802

TUBE MASTER 3/4 X 4

SHOULDER | TUBE LENGTH 4 | B.M. I/16 | OPEN END

MUPIROCIN OINTMENT USP, 2%

Rx only

NDC 45802-112-37

Net Wt 15 g

Store at controlled room temperature 20° to 25°C (68° to 77°F).
Each gram contains 20 mg mupirocin in a polyethylene glycol ointment, NF base.
Dosage: For dermatologic use only. Apply a small amount of ointment to the affected area three times daily. Patients not showing a clinical response within 3 to 5 days should be re-evaluated.
See accompanying prescribing information.
Mfg. By: **CLAY-PARK LABS, INC.**
Bronx, NY 10457

TM11215CPL-2x N1001

APPROVED NOV - 7 2003

PHARMA CODE PMC

[redacted]

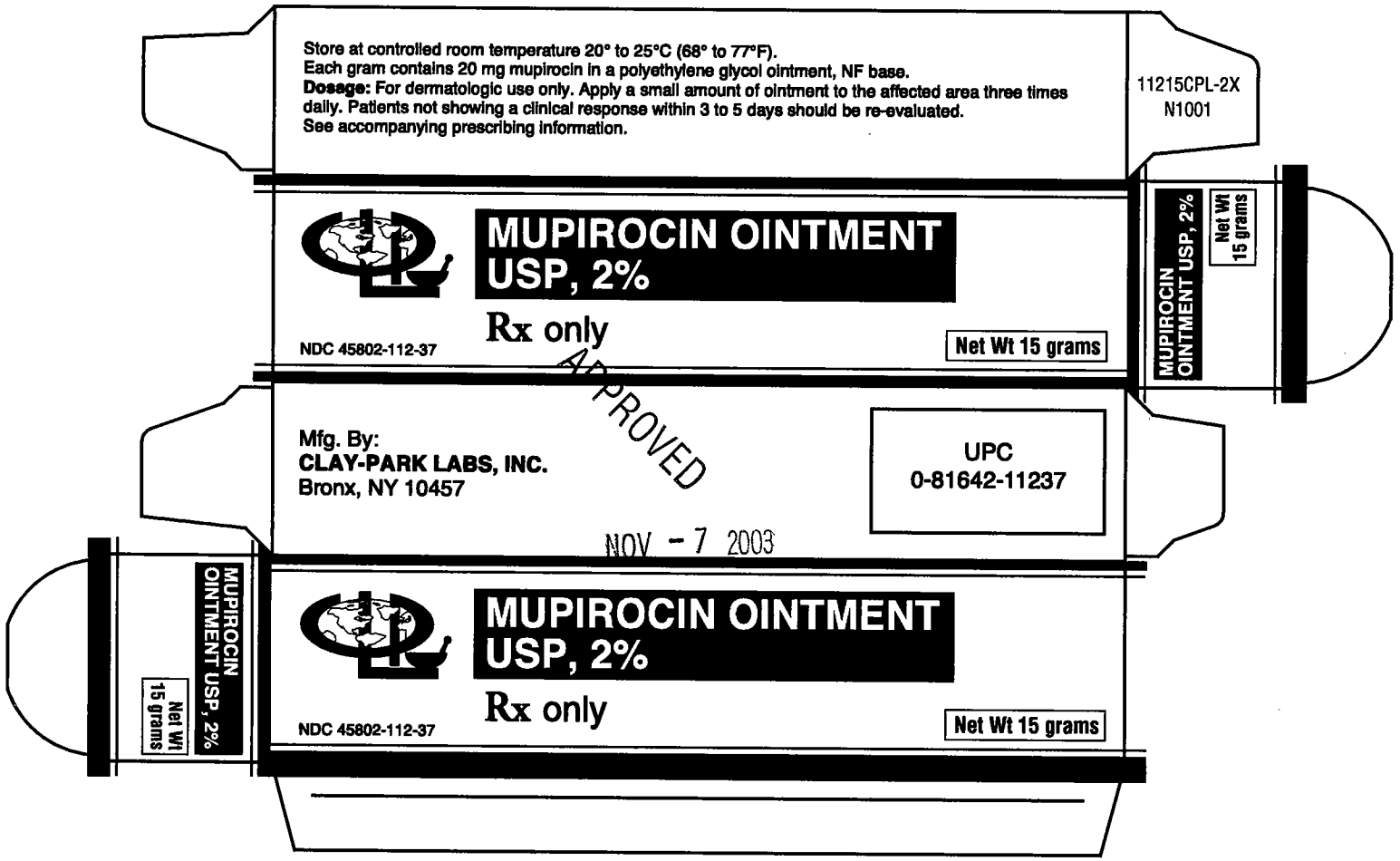
0059-4

Statement of identity			Disclaimer			Size (Tube, Label, Box)		
Net Wt.			UPC			Tamper		
Compare to...			Dist By.					

Clay Park Labs,Inc. Graphics Dept. (Ph 718 960-9967)

DIE# 8016 **PHARMACODE#** 000	**COLORS:** 541 Black	**PRODUCT NO:** 112 **MAC ARTIST:** Angel

**Please see the Pantone® Color Guide to verify colors.



4-6900

Statement of Identity			Disclaimer			Size (Tube, Label, Box)			
Net Wt.			UPC			Tamper			
Compare to...			Dist By.						

Clay Park Labs, Inc. Graphics Dept. (Ph 718 960-9967)		
DIE# 8016 PHARMACODE# 000	COLORS: 541 Black	PRODUCT NO: 112 MAC ARTIST: Angel

**Please see the Pantone® Color Guide to verify colors.

TUBE MASTER 7/8 X 4 1/2

SHOULDER | TUBE LENGTH 4 1/2 | OPEN END

B.M. I/16

MUPIROCIN OINTMENT USP, 2%

Rx only

NDC 45802-112-22

Net Wt 22 g

APPROVED NOV - 7 2003

PHARMA CODE PPD [redacted]

Store at controlled room temperature 20° to 25°C (68° to 77°F).
Each gram contains 20 mg mupirocin in a polyethylene glycol ointment, NF base.
Dosage: For dermatologic use only. Apply a small amount of ointment to the affected area three times daily. Patients not showing a clinical response within 3 to 5 days should be re-evaluated.
See accompanying prescribing information.
Mfg. By: **CLAY-PARK LABS, INC.**
Bronx, NY 10457

TM11222CPL-2X N1001

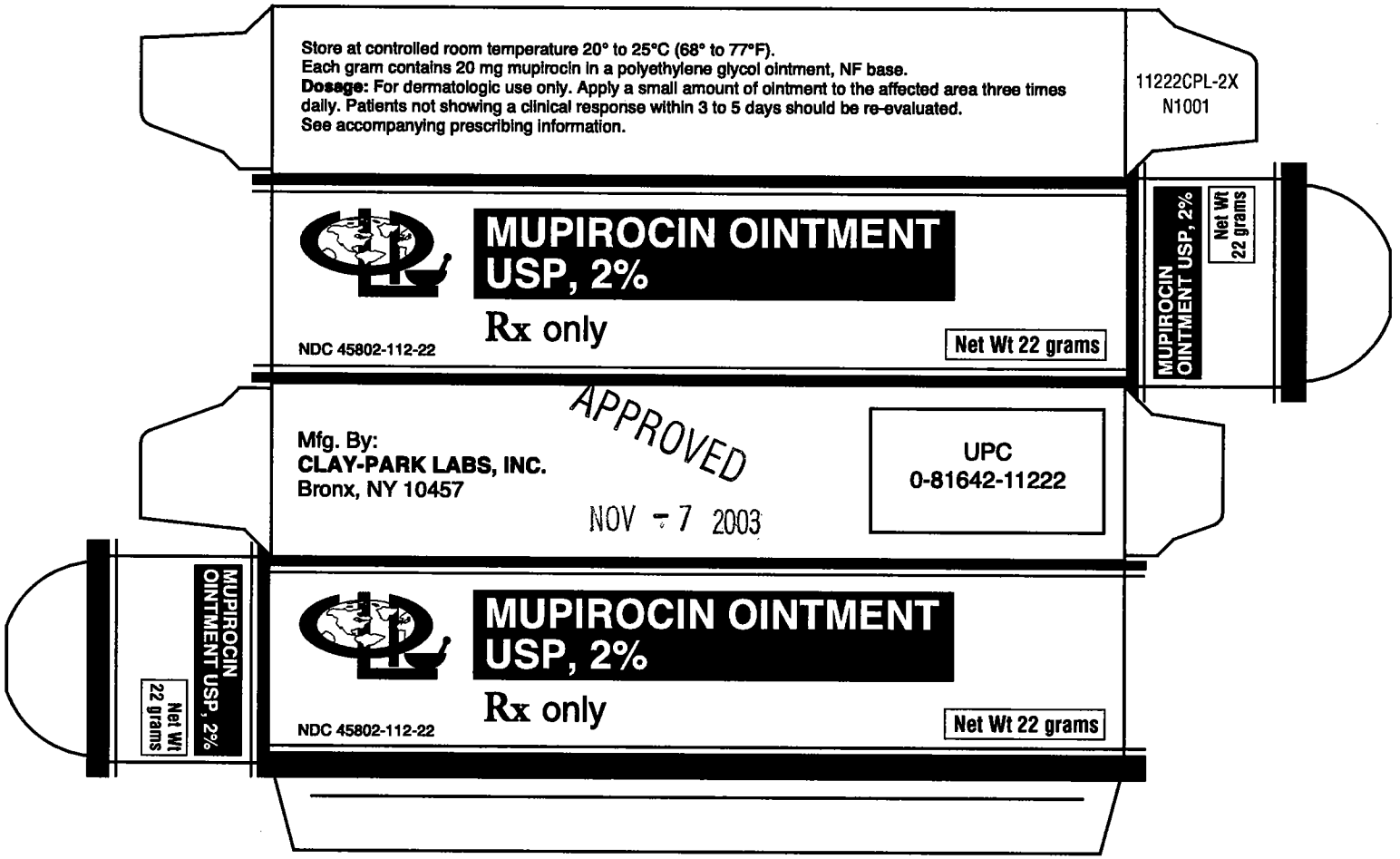
9-1900

Statement of Identity			Disclaimer			Size (Tube, Label, Box)		
Net Wt.			UPC			Tamper		
Compare to...			Dist By.					

Clay Park Labs,Inc. Graphics Dept. (Ph 718 960-9967)

DIE# 8016 **PHARMACODE#** 000	**COLORS:** 541 Black	**PRODUCT NO:** 112 **MAC ARTIST:** Angel

**Please see the Pantone® Color Guide to verify colors.



0067-9

Statement of identity				Disclaimer				Size (Tube, Label, Box)		
Net Wt.				UPC				Tamper		
Compare to...				Dist By.						

Clay Park Labs, Inc. Graphics Dept. (Ph 718 960-9967)		
DIE# 8016 PHARMACODE# 000	COLORS: 541 Black	PRODUCT NO: 112 MAC ARTIST: Angel

**Please see the Pantone® Color Guide to verify colors.

TUBE MASTER 7/8 X 5 1/8

SHOULDER | TUBE LENGTH 5 1/8 | OPEN END

B.M. I/16

NOV - 7 2003

MUPIROCIN OINTMENT USP, 2%

Rx only

NDC 45802-112-11

Net Wt 30 g

APPROVED

Store at controlled room temperature 20° to 25°C (68° to 77°F).
Each gram contains 20 mg mupirocin in a polyethylene glycol ointment, NF base.
Dosage: For dermatologic use only. Apply a small amount of ointment to the affected area three times daily. Patients not showing a clinical response within 3 to 5 days should be re-evaluated.
See accompanying prescribing information.
Mfg. By: **CLAY-PARK LABS, INC.**
Bronx, NY 10457

TM11230CPL-2X N1001

PHARMA CODE FPO

[redacted]

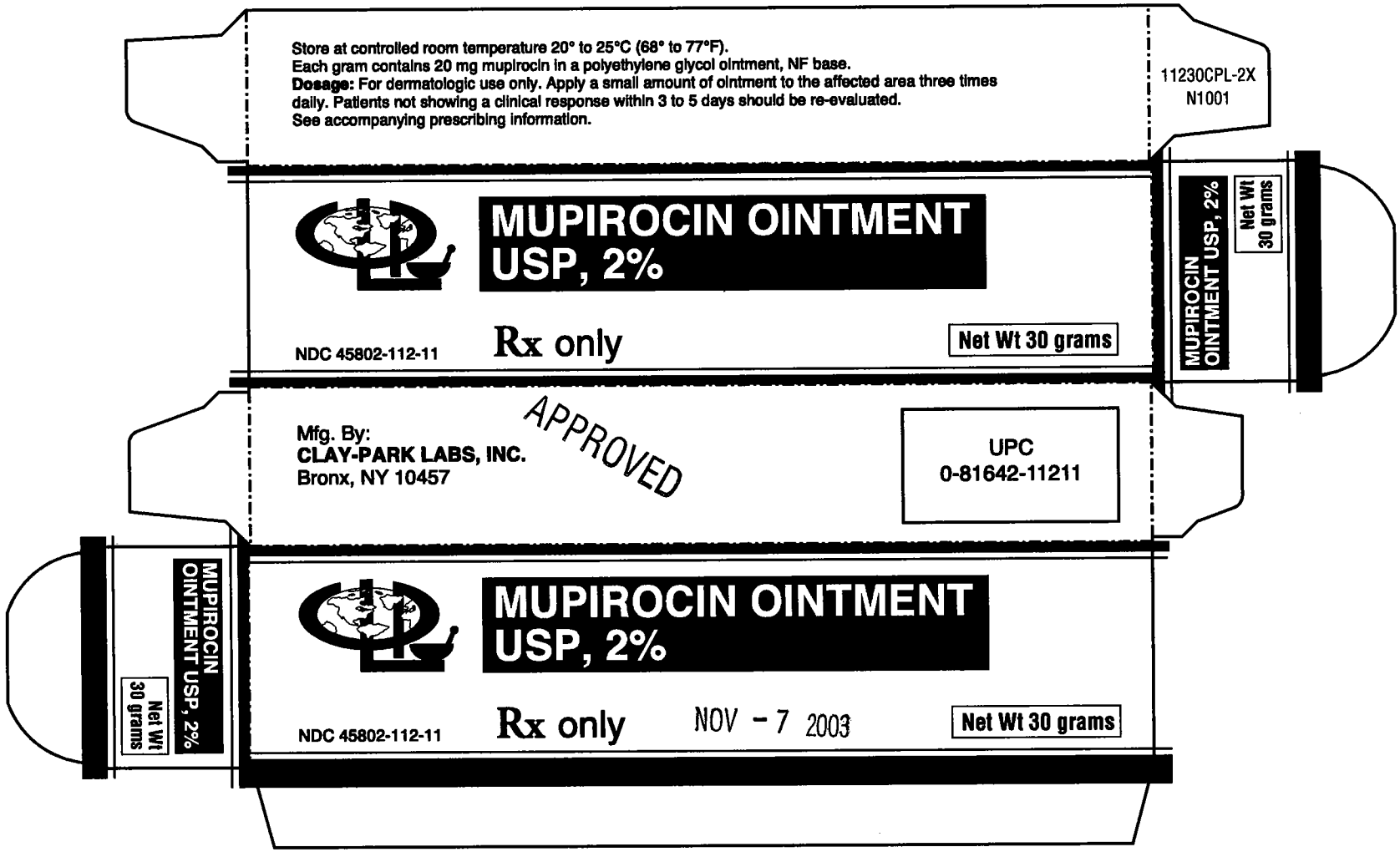
4-0300

Statement of Identity			Disclaimer			Size (Tube, Label, Box)			
Net Wt.			UPC			Tamper			
Compare to...			Dist By.						

Clay Park Labs,Inc. Graphics Dept. (Ph 718 960-9967)

DIE# 8016 **PHARMACODE#** 000	**COLORS:** 541 Black	**PRODUCT NO:** 112 **MAC ARTIST:** Angel

**Please see the Pantone® Color Guide to verify colors.



9-6900

Statement of Identity			Disclaimer			Size (Tube, Label, Box)		
Net Wt.			UPC			Tamper		
Compare to...			Dist By.					

Clay Park Labs, Inc. Graphics Dept. (Ph 718 960-9967)		
DIE# 1521Q1A PHARMACODE# 000	COLORS: 541, Black	PRODUCT NO: 112 MAC ARTIST: Angel

**Please see the Pantone® Color Guide to verify colors.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-123

CSO LABELING REVIEW(S)

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

ANDA Number: 65-123

Dates of Submissions: September 5, 2002

Applicant's Name: Clay-Park Labs, Inc.

Established Name: Mupirocin Ointment USP, 2%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 15 gram, 22 gram and 30 gram
Satisfactory in FPL as of the January 4, 2002 submission. [Vol. 1.1, Attachment 6.]

Carton Labeling: 1 x 15 gram, 1 x 22 gram and 1 x 30 gram
Satisfactory in FPL as of the January 4, 2002 submission. [Vol. 1.1, Attachment 6.]

Professional Package Insert Labeling:
Satisfactory in FPL as of the September 5, 2002, [Vol. 2.1, Attachment I, Code I112-2X N0802]

Revisions needed post-approval:
GENERAL
Add "[see USP Controlled Room Temperature] to your container labels, carton and insert labeling.
Revise ——— to read "Usual Dosage" on your container and carton labeling.

PRECAUTIONS - Start a new paragraph with the sentence, "Mupirocin Ointment . . .surfaces"

BASIS OF APPROVAL:

Patent Data – NDA 50-591

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 50-591

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Bactroban® Ointment
NDA Number: 50-591
NDA Drug Name: Bactroban® (mupirocin 2%) Ointment
NDA Firm: SmithKline Beecham

Date of Approval of NDA Insert and supplement #: 4/22/99 (SE8-022)
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-sides
Basis of Approval for the Carton Labeling: side-by-sides
Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N/A
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 25	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? NO Issues for FTR: Innovator individually cartoned? YES Light sensitive product which might require cartoning? NO Must the package insert accompany the product? YES *RLD packages the drug product in a carton			
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label)		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult, Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by..." statement needed?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e. benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			X
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

In the CLINICAL PHARMACOLOGY/Microbiology section the firm indicates that, "Mupirocin is an antibacterial agent produced by fermentation using the organism *Pseudomonas fluorescens*."

Is this information accurate for this ANDA? Yes, the same DMF was used for ANDA 65-085. Dr. Furness verified that the species is accurate for ANDA 65-085.

FOR THE RECORD:

1. Review based on the labeling of Bactroban® Ointment, approved 4/22/99 in draft (NDA 50-591/SE8-022).

2. Patent/ Exclusivities:

   There are no active patents or exclusivities for this drug product.

3. Storage Conditions:

   NDA – Store at controlled room temperature 20° and 25°C (68° and 77°F).
   ANDA – Store at controlled room temperature 20° and 25°C (68° and 77°F).
   USP – Preserve in collapsible tubes or in well-closed containers.

4. Product Line:

   RLD – 15 g and 30 g
   ANDA – 15 g, 22 g, and 30 g

4. Clay-Park Labs, Inc. is the manufacturer.
   [Vol. B1.2, p. 1304]

6. Inactive Ingredients:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 1166 (Volume B1.2).

7. Container/Closure:

   Lined aluminum [redacted] end tube with a white pointed HDPE cap.
   [Vol. B1.2, p. 1447]

Date of Review: 12/23/02

Date of Submission: 9/5/02

Primary Reviewer:
Michelle Dillahunt M Dillahunt Date: 12/26/02

Acting Team Leader
Lillie Golson L M Golson Date: 12/26/02

---

cc: ANDA 65-123
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
V:\FIRMSAM\CLAYPARK\LTRS&REV\65123AP L.doc
Review

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

ANDA Number: 65-123

Date of Submission: January 4, 2002

Applicant's Name: Clay-Park Labs, Inc.

Established Name: Mupirocin Ointment USP, 2%

Labeling Deficiencies:

1. INSERT

   a. General Comment

      We consider your insert labeling printer's proof and not final print. Final printed labeling is the true size, print and color that you plan to use in the marketplace.

   b. DESCRIPTION

      Revise the molecular weight to be in accord with USP 25, "500.62".

   c. PRECAUTIONS

      i. Start a new paragraph with the sentence, "Mupirocin Ointment ...surfaces". At the end of this paragraph add the text, "Bactroban®* Nasal (mupirocin calcium ointment) – is avaiable for intranasal use".

      ii. Start a new paragraph with the sentence, "Polyethylene glycol ...".

   d. HOW SUPPLIED
      At the end of this section, add the statement "*Bactroban® Nasal is a registered trademark of SmithKline Beecham Pharmaceuticals."

Please revise your insert labeling, as instructed above, and submit in final print.

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

APPEARS THIS WAY
ON ORIGINAL

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

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

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:
Container Labels: 15 gram and 30 gram
Carton Labeling: 1 x 15 gram and 1 x 30 gram
Professional Package Insert Labeling:
Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Bactroban® Ointment
NDA Number: 50-591
NDA Drug Name: Bactroban® (mupirocin 2%) Ointment
NDA Firm: SmithKline Beecham
Date of Approval of NDA Insert and supplement #: 4/22/99 (SE8-022)
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-sides
Basis of Approval for the Carton Labeling: side-by-sides
Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N/A
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured: USP 25	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? NO Issues for FTR: Innovator individually cartoned? YES Light sensitive product which might require cartoning? NO Must the package insert accompany the product? YES *RLD packages the drug product in a carton			
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label)		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult, Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			

Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values, insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			X
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR. Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

In the CLINICAL PHARMACOLOGY/Microbiology section the firm indicates that, "Mupircin is an antibacterial agent produced by fermentation using the organism *Pseudomonas fluorescens*."

Is this information accurate for this ANDA?

APPEARS THIS WAY
ON ORIGINAL

FOR THE RECORD:

1. Review based on the labeling of Bactroban® Ointment, approved 4/22/99 in draft (NDA 50-591/SE8-022).

2. Patent/ Exclusivities:

   There are no active patents or exclusivities for this drug product.

3. Storage Conditions:

   NDA – Store at controlled room temperature 20° and 25°C (68° and 77°F).
   ANDA – Store at controlled room temperature 20° and 25°C (68° and 77°F).
   USP – Preserve in collapsible tubes or in well-closed containers.

4. Product Line:

   RLD – 15 g and 30 g
   ANDA – 15 g, 22 g and 30 g

4. Clay-Park Labs, Inc. is the manufacturer.
   [Vol. B1.2, p. 1304]

6. Inactive Ingredients:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 1166 (Volume B1.2).

7. Container/Closure:

   Lined aluminum ——— tube with a white pointed HDPE cap
   [Vol. B1.2, p. 1447]

Date of Review: 6/21/02

Date of Submission: 2/4/02

Primary Reviewer: Jacqueline Council, Pharm.D. Date: 7-1-02

Acting Team Leader: Captain Lillie Golson Date: 7/1/02

---

cc: ANDA: 65-085
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
V:\FIRMSAM\CLAYPARK\LTRS&REV\65123NA1 L.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-123

CHEMISTRY REVIEW(S)

ANDA 65-123

Mupirocin Ointment USP, 2%

Clay-Park Labs, Inc.

Ruth Ganunis
Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 65-123

2. REVIEW # 1

3. REVIEW DATE: 7/10/02

4. REVIEWER: Ruth Ganunis

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Acceptable for Filing	3/7/02

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	1/4/02
New Correspondence (Electronic submission and corrections)	2/8/02
New Correspondence (composition statement)	3/6/02
New Correspondence (corrected 356H form)	3/7/02

An electronic CMC section was submitted for this application. However, since the reviewer document failed generation, the electronic submission was not reviewed.

APPEARS THIS WAY
ON ORIGINAL

7. NAME & ADDRESS OF APPLICANT:

Name:	Clay-Park Labs, Inc.
Address:	1700 Bathgate Avenue Bronx, NY 10457
Representative:	Candis Edwards
Telephone:	718-960-9976

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS FOR SUBMISSION: The application is based on Bactroban® Ointment manufactured by SmithKline Beecham Pharmaceuticals (NDA# 50-591). The firm states that no effective patents or exclusivity periods are in force for the referenced product (p. 14-15).

10. PHARMACOL. CATEGORY: Antibiotic

11. DOSAGE FORM: Ointment

12. STRENGTH/POTENCY: 2%, in 15 g, 22 g, and 30 g tube sizes

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: _X_Rx ___OTC

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

_____SPOTS product – Form Completed

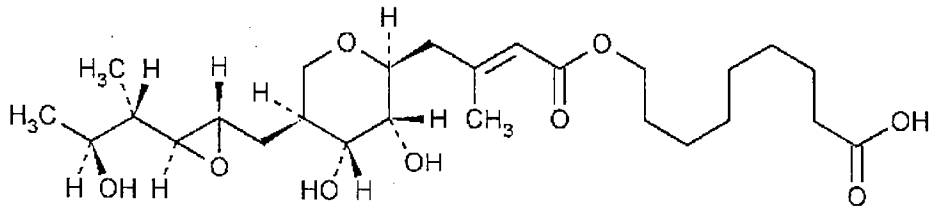
__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

$C_{26}H_{44}O_9$ 500.62

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]-, [2 S-2a(E),3b,4b,5a[2 R*, 3 R*(1 R*,[2R*)]]]-.

(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-b- methyl-2 H-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid. [12650-69-0].



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	3	NA	12/10/01	The firm's response to the 12/10/01 deficiency letter has been reviewed and found inadequate. The deficiencies will be communicated to the firm by S. Furness.
[redacted]	III	[redacted]	[redacted]	3	A	8/11/02	6/15/01 Update provides for no changes to the DMF

[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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

APPEARS THIS WAY
ON ORIGINAL

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	3/25/02	J. D Ambrogio
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Pending		
EA	Acceptable		
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:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 65-123

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable (Minor)

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

N/A

II. Summary of Chemistry Assessments

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

At present, there are no approved generic Mupirocin Ointments USP, 2%.

Mupirocin is a direct fermentation product. The drug substance is a white to off-white crystalline powder. The drug substance, obtained from ——— conforms to the USP monograph, and meets additional tests for related substances and residual solvents.

The drug product ——— The firm monitors ——— , adequately controlling the manufacturing process. The drug product conforms to the USP monograph. In addition to the USP requirements, the firm monitors related substances, viscosity, and microbial limits for finished product and stability.

The drug product is packaged into 15 g and 30 g tubes. Accelerated stability studies support the firm's proposed 24 month expiration period. In addition, the firm has conducted thermal cycling stability studies on the drug product. At completion of the cycling studies, the drug product conforms to the firm's proposed specifications.

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

N/A

C. Basis for Approvability or Not-Approval Recommendation

The application is not approvable for minor CMC issues. The deficiencies are related to the specifications, and for use of [redacted] without justification.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-643/RGanunis/7/10/02; 8/1/02 (as revised) R. Ganunis 8/1/02

HFD-643/RAdams/7/14/02 R. C. Adams 8/2/02

C. CC Block

ANDA
ANDA DUP
DIV FILE
Field Copy

APPEARS THIS WAY
ON ORIGINAL

Redacted 11

Page(s) of trade secret and /or confidential commercial information

ANDA 65-123

Mupirocin Ointment USP, 2%

Clay-Park Labs, Inc.

M. Scott Furness
Division of Chemistry II
Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. ANDA **65-123**

2. REVIEW # 2

3. REVIEW DATE: 1/29/03

4. REVIEWER: Scott Furness

5. PREVIOUS DOCUMENTS:

Previous Documents	**Document Date**
Original	1/4/02
New Correspondence (Electronic submission and corrections)	2/8/02
New Correspondence (composition statement)	3/6/02
New Correspondence (corrected 356H form)	3/7/02
Acceptable for Filing	3/7/02
Labeling Deficiency	7/1/02
CMC Review #1 – N/A Major	8/02/02
Labeling Acceptance	12/26/02

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	**Document Date**
Major CMC Amendment	9/5/02
Telephone Amendment #1	1/24/03
Telephone Amendment #2	1/27/03

7. NAME & ADDRESS OF APPLICANT:

Name:	Clay-Park Labs, Inc.
Address:	1700 Bathgate Avenue Bronx, NY 10457
Representative:	Candis Edwards
Telephone:	718-960-9976

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS FOR SUBMISSION: The application is based on Bactroban® Ointment manufactured by SmithKline Beecham Pharmaceuticals (NDA# 50-591). The firm states that no effective patents or exclusivity periods are in force for the referenced product (p. 14-15).

10. PHARMACOL. CATEGORY: Antibiotic

11. DOSAGE FORM: Ointment

12. STRENGTH/POTENCY: 2%, in 15 g, 22 g, and 30 g tube sizes

13. ROUTE OF ADMINISTRATION: Topical

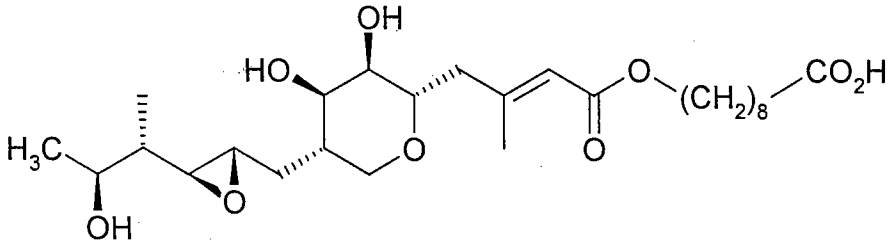
14. Rx/OTC DISPENSED: ✓ Rx ___ OTC

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

_____ SPOTS product – Form Completed

✓ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Name: (*E*)-(2S,3R,4R,5S)-5-[(2S,3S,4S,5S)-2,3-Epoxy-5-hydroxy-4-methylhexyl]tetrahydro-3,4-dihydroxy-b-methyl-2H-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid
Molecular Formula: $C_{26}H_{44}O_9$
Molecular Weight: 500.62

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	1	Adequate	1/21/03	-
[redacted]	III	[redacted]	[redacted]	3	A	11/27/02	-

[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
EES	Acceptable	3/25/02	J. D Ambrogio
Labeling	Acceptable	12/26/02	Michelle Dillahunt
Bioequivalence	Acceptable	10/14/03	Carol Kim
EA	Acceptable		

19. ORDER OF REVIEW:

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

The Chemistry Review for ANDA 65-123

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval is recommended.

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

N/A

II. Summary of Chemistry Assessments

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

At present, there are no approved generic Mupirocin Ointments USP, 2%.

Mupirocin is a direct fermentation product. The drug substance is a white to off-white crystalline powder. The drug substance, obtained from [redacted], conforms to the USP monograph, and meets additional tests for related substances and residual solvents.

The drug product [redacted]. The firm monitors [redacted], adequately controlling the manufacturing process. The drug product conforms to the USP monograph. In addition to the USP requirements, the firm monitors related substances, viscosity, and microbial limits for finished product and stability.

The drug product is packaged into 15 g, 22 g, and 30 g tubes. Accelerated stability studies support the firm's proposed 24 month expiration period. In addition, the firm has conducted thermal cycling stability studies on the drug product. At completion of the cycling studies, the drug product conforms to the firm's proposed specifications.

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

N/A

C. Basis for Approvability or Not-Approval Recommendation

The application is approvable. The drug product related substances stability specification and assay sampling issues were resolved by means of a series of telephone calls (and subsequent telephone amendments).

III. Administrative

cc: ANDA 65-123
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-643/SFurness/1/29/03; 10/21/03 (as revised upon completion of bio review) M. Doll Zumer 10/21/03

HFD-643/RAdams/2/1/03; 10/21/03 R. C. Adams 10/21/03

V:\firmsam\CLAYPARK\ltrs&rev\65135ap.doc

F/T by: mda/10/21/03

TYPE OF LETTER: APPROVAL

APPEARS THIS WAY ON ORIGINAL

Redacted 13

Page(s) of trade secret and /or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-123

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:65-123 APPLICANT:Clay-Park Labs. Inc.

DRUG PRODUCT: Mupirocin Ointment USP, 2%

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

The data submitted to ANDA 65-123, using the primary endpoint of clinical success rate at the 7-day follow-up visit (visit 4), are adequate to demonstrate bioequivalence of Clay-Park's Mupirocin Ointment USP, 2%, with the reference listed drug, SmithKline Beecham Pharmaceuticals' Bactroban® Ointment, 2%.

Regarding bioequivalence testing sample issue, it is the sponsor's responsibility to assure that the clinical sites for all future BE studies comply with the requirements for retention of study drugs as per 21 CFR 210.38 and 320.63. The Final Rule requires that retention samples be randomly collected and retained from each shipment received by the clinical site. If the sponsor fails to comply with the Agency's regulation in any subsequent study, the study may be found unacceptable and a new bioequivalence study may be requested.

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

Sincerely yours,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-123

CORRESPONDENCE

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

NEW CORRESP

AM

AC

Hard Copy To Fax

October 30, 2003

Mark Anderson, Project Manager
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II, HFD-615
7500 Standish Place, Room 150
Rockville, MD 20855

Noted: NAE
This piece found acceptable by Dr. Sayeed.
M Anderson
11/7/03

TELEPHONE AMENDMENT

Submitted By Fax – Hard Copy to follow

Re: ANDA #65-123 Mupirocin Ointment USP, 2%

Dear Mr. Anderson:

Pursuant to our telephone conversation with the Agency on October 29, 2003, in reference to our ANDA # 65-123 for Mupirocin Ointment USP, 2%, Clay-Park Labs, Inc. hereby submits our response to the following comments, designated as a Telephone Amendment:

Comment #1:

What is the difference between the two viscosity test methods (STP#D1120-8 and STP#D1121-7)?

Response #1:

The two viscosity test methods are identical. STP #D1120-8 is the number for the method in the Finished Product Test Monograph whereas STP #D1121-7 is the method number in the Stability Product Test Monograph. The difference in numbers reflects our internal numbering system.

Comment #2:

How is the product sampled for viscosity testing?

RECEIVED
NOV 0 3 2003
OGD/CDER

11/3/03

Response #2:

Viscosity testing is performed on a composite sample. The sampling plan is described in the revised finished product and stability product test monographs (See **Attachment A**).

Comment #3:

Why does the viscosity change over storage?

Response #3:

Based on the review of the 24 month Controlled Room Temperature (CRT) stability data for Mupirocin Ointment USP, 2%, Lot # RX123, 15 g, 22 g and 30 g tubes, the observed viscosity change is from [redacted]. This change is representative of the product. The product maintains its physical attributes throughout the 24 month period. There is no separation observed in the stability samples. The [redacted] in the [redacted]

We hereby propose to revise the Finished Drug Product and Stability Specifications for viscosity as follows:

	Old Specification	New Specification
Finished Product Monograph	[redacted]	[redacted]
Stability Product Monograph	[redacted]	[redacted]

See **Attachment A** for the revised Finished Product and Stability Test Monographs.

Please note that in order to update the application, Clay-Park Labs, Inc. hereby submits the CRT stability summary data report for Mupirocin Ointment USP, 2%, Lot # RX118, 22 g tube, accrued to date (see **Attachment B**).

Additionally, the Post Approval Stability Protocols for Mupirocin Ointment USP, 2% were revised to reflect the changes in the viscosity specifications and are presented in **Attachment C**.

We hope this will satisfy the Agency's request. Should you require further assistance, please contact the undersigned as follows:

Telephone: (718) 960-9976 **Fax: (718)960-0111**

Sincerely,

for Candis Edwards
Vice President Regulatory Affairs
Clay-Park Labs, Inc.

APPEARS THIS WAY
ON ORIGINAL

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

January 27, 2003

N/AM.

Mark Anderson, Project Manager
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II, HFD-615
7500 Standish Place, Room 150
Rockville, MD 20855

Telephone Amendment
Submitted via Fax – Hard Copy to Follow

Re: ANDA # 65-123 Mupirocin Ointment USP, 2%

Dear Mr. Anderson:

In response to our telephone conversation with Scot Furness today, January 27, 2003, in reference to the Telephone Amendment submitted January 24, 2003, on ANDA # 65-123 for Mupirocin Ointment USP, 2%, Clay-Park Labs, Inc. hereby re-submits the following requested documents:

- The revised Stability Product Monograph for Mupirocin Ointment USP, 2% is presented as **Attachment A**. The monograph was revised to change the specification for Total Related Substances from [redacted]

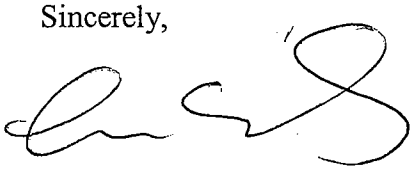
- The Post Approval Stability Protocols for 15 g, 22 g and 30 g tubes, previously submitted on Friday, January 24, 2003, designated as a Telephone Amendment, have been revised to incorporate the specifications for Total Related Substances and Individual Impurities in Mupirocin Ointment USP, 2%, which were omitted (**See Attachment B** for the revised Approval Stability Protocols). We hope that this will satisfy the agency's request.

The change in the specifications for Total Related Substances was made at the FDA's request in order to meet the standard set by the reference listed drug. We continue to believe that there is significant risk in adopting the [redacted] standard in light of the [redacted] value that was obtained during the 24 month Room Temperature Stability Study. However, we defer to the agency's judgment on this issue.

Should you require any further assistance, please contact the undersigned as follows:

Telephone: **(718) 960-9976** **Fax:** **(718) 960-0111**

Sincerely,



Candis Edwards
Vice President of Regulatory Affairs
Clay-Park Labs, Inc.

APPEARS THIS WAY
ON ORIGINAL

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

January 24, 2003

Mark Anderson, Project Manager
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II, HFD-615
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N/AM

Submitted by FAX – Hard Copy to Follow

Telephone Amendment

Re: ANDA # 65-123 Mupirocin Ointment USP, 2%

Dear Mr. Anderson:

As per our telephone conversation on January 21, 2003, for clarification purposes, Clay-Park Labs, Inc. hereby submits the requested documents.

The Revised Finished Product and Stability Product Monographs for Mupirocin Ointment USP, 2% are presented as **Attachment A.** The monographs were revised to include the specifications for Total Related Substances and Individual Impurities

The Finished Product Monograph was revised to include the specifications for Total Related Substances and Individual Impurities under Test for Related Substances.

The Stability Product Monograph was revised to include the specifications for [redacted] Individual Impurities and Total Related Substances.

The Revised Post Approval Stability Protocols for Mupirocin Ointment USP, 2% for the 15 g, 22 g and 30 g package sizes are presented as **Attachment B.** The Post Approval Protocols were revised to specify that the product assay is to be performed from samples each taken from the cap, middle and crimp positions of the tubes.

We hope this will satisfy the agency's request.

RECEIVED
JAN 28 2003
OGD / CDER

Should you require further assistance, please contact the undersigned as follows:

Telephone: (718) 960-9976 **Fax: (718) 960-0111**

Sincerely,

Candis Edwards
Vice President Regulatory Affairs
Clay-Park Labs, Inc.

APPEARS THIS WAY
ON ORIGINAL

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

September 11, 2002

ORIG AMENDMENT
NAA

Candis Edwards
718-960-9976
Fax: 718-960-0111
CEdwards@agis-group.co.il

NAE Mark Anderson
11/7/03

Mr. Gary J. Buehler (HFD-600)
Director, Office of Generic Drugs
Center for Drug Evaluation & Research
US Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-1706

RE: Clay-Park Labs, Inc.
ANDA #65-123 for Mupirocin Ointment USP, 2%
22 gm Tube Data Request Should Be a Minor Amendment

Dear Mr. Buehler:

I wanted to bring to your attention a classic, transparent attempt by a brand name company to manipulate the approval process to prevent and delay generic products from reaching the market.

On January 4, 2002, Clay-Park Labs, Inc. (CPL), filed an ANDA for Mupirocin Ointment USP, 2%. As part of that filing, we submitted stability data on the 15 g and 30 g tube sizes and requested approval of the 22 g tube based on a bracketing protocol. When CPL conducted its bioequivalence and stability testing, the reference listed drug (RLD) was marketed only in 15 g and 30 g tube sizes. Just prior to the filing of our ANDA, however, the RLD sponsor discontinued the 15 and 30 g tube sizes and introduced the 22 g tube, so that now the 22 g tube is the only product currently in the market. Assuming that the RLD sponsor's tube size change was an attempt to delay eventual generic substitution, CPL submitted its 15 g and 30 g data along with a bracketing protocol for its 22 g tube expecting that this would be sufficient for CPL to obtain timely approval of its generic product.

Our concern is that the Office of Generic Drugs ("OGD") has denied our request that FDA consider the bracketing protocol, and has indicated it would require new data on the 22 g tube size and that this would be a Major Amendment. This is in spite of the fact that the lots of ointment were identical, as noted by the batch records. The only change is the crimping placement, so that 30 g tube is shorter to hold 22 g of product. There are no other differences. (See attached cover letter to Major Amendment to ANDA 65-123 for additional description.) In

RECEIVED
SEP 12 2002
OGD / CDER

this circumstance, to place this application back in the 180-day queue as a Major Amendment appears unreasonable and rewards precisely the kinds of manipulating of the generic approval process attempted by the brand name companies.

We believe that the middle tube size should be the subject of a bracketing exception. The ointment was manufactured using the same controls as in the ANDA batch, the tube is identical, and the headspace or internal container's open space is the same since the tube is crimped based on 22 g, not 30 g. These limitations are actually better than the solid oral dosage limitation required in a bracketing situation with tablets/capsules, where the headspace can actually be different, thereby affecting the potential for degradation due to the presence of additional atmospheric conditions in the container.

There is no logical reason for the FDA and CPL to find themselves burdened with a six-month Major Amendment review when all of the data is available for approval of the generic. Requiring a Major Amendment in this case is to reward the manipulation of the RLD sponsor with extra monopoly time for an inconsequential change in container closure systems, which delays CPL's approval.

We respectfully request that OGD review this issue and conclude that the bracketing protocol is acceptable and therefore, a Minor Amendment and not a Major Amendment is appropriate.

Very truly yours,

Candis Edwards
Director of Regulatory Affairs

Cc: Gary Yingling, Kirkpatrick & Lockhart, L.L.P.
Richard Adams, Team Leader - FDA Division of Chemistry II
Mark Anderson, Project Manager - FDA Division of Chemistry II

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

September 5, 2002

Thomas Hinchliffe, Project Manager
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room,
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AM

MAJOR AMENDMENT

RE: ANDA # 65-123 Mupirocin Ointment USP, 2%

Dear Mr. Hinchliffe:

In reference to the deficiency letter dated August 2, 2002 **(Attachment A)** on our abbreviated new drug application for Mupirocin Ointment, 2%, ANDA # 65-123, Clay-Park Labs, Inc. hereby submits the deficiency response for Chemistry and Labeling sections, designated as a Major Amendment.

As requested by the Agency, Clay-Park Labs, Inc. hereby withdraws the bracketing protocol submitted in ANDA # 65-123 and provides new exhibit batch data to support the 22 g tube size. Hence, this Amendment changes from Minor to Major.

While the information provided in this Major Amendment is under review by the Agency, we respectfully request that you consider revisiting the acceptance of the pre-approval bracketing protocol for this product, especially when circumstances exist that may warrant special consideration based on scientific justification as described below.

Clay-Park Labs, Inc. submitted the protocol for the 22 g tube size in response to the reference listed drug sponsor's action of introducing a 22 g tube size while simultaneously limiting production on the 15 g and 30 g tube sizes. This action by the listed drug sponsor appears to have been marketing driven, in that it served to restrict generic substitutability.

Regarding the issue of the acceptance of the comparability protocol, Clay-Park Labs, Inc. explained in a teleconference with the Office of Generic Drugs that the tube used to fill the 22 g product was identical to the tube used to fill the 30 g product. The only

RECEIVED
SEP 0 6 2002
OGD / CDER

9-10-02

difference is the amount of product filled into the tubes and the fact that the 22 g tube is crimped at a higher position than the 30 g tube, due to the lower fill volume. Additionally, the same lot of tubes was used to package the 22 g and 30 g product.

Accordingly, there is no scientific reason to expect that the product packaged in a 22 g tube would provide a different safety, efficacy or stability profile when the same batch of the drug product is used to fill the different-sized tubes (i.e., 15 g, 22 g and 30 g), the same lot of tubes is used for the 30 g and 22 g product packaging, and the same controls are used in packaging the three tube sizes. With the Agency's concurrence, Clay-Park Labs, Inc. would propose to provide justification for these particulars via a Minor Amendment.

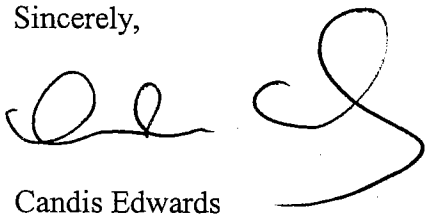
Moreover, we respectfully suggest that acceptance of this data as a Minor Amendment by the Office of Generic Drugs would comport with FDA's oft-stated policy that more ANDA amendments will be categorized as Minor Amendments and fewer will be categorized as Major Amendments, for the purpose of reducing the total time for approval of ANDAs.

Please note that this request is made as an adjunct to our submission of this Major Amendment, and not as a substitute for it. Above all, we are concerned that review of this product be as expeditious as possible.

Should you have any comments or require any further clarifications on this Major Amendment, please contact the undersigned as follows:

Telephone: 718-960-9976 **Fax: 718-960-0111**

Sincerely,



Candis Edwards
Director of Regulatory Affairs

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

March 7, 2002

Mr. Gary Buehler, Director
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

Re: CORRESPONDENCE TO ANDA # 65-123 FOR MUPIROCIN OINTMENT USP, 2%

Dear Mr. Buehler:

Clay-Park Labs, Inc. hereby submits a Correspondence to ANDA # 65-123 for Mupirocin Ointment USP, 2% submitted on January 4, 2002.

On February 8, 2002, Clay-Park Labs, Inc. submitted a correspondence to ANDA # 65-123, which contained a corrected Form FDA 356h where the marketing status was corrected from over the counter (OTC) to prescription product (℞).

Upon reviewing the correspondence dated February 8, 2002, we found that a typographical error was made in the number of volumes of the submitted ANDA. The correct number of volumes should be nine (9), instead of zero (0), which was correctly represented in the original Form FDA 356h, submitted on January 4, 2002.

We respectfully request that you disregard all previous incorrect Forms FDA 356h, submitted on January 4, 2002 and February 8, 2002, and replace them with the Form attached with this letter (**See Attachment 1**). We apologize for any inconvenience this may have caused you.

RECEIVED

MAR 0 8 2002

OGD / CDER

Should you have any questions, please contact the undersigned as follows:

Telephone: (718) 960-9976 **Fax: (718) 960-0111**

Sincerely,

FOR Candis Edwards
Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

ANDA 65-123

Clay-Park Labs, Inc.
Attention: Candis Edwards
1700 Bathgate Avenue
Bronx, NY 10457

MAR -7 2002

Dear Madam:

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

Reference is made to the telephone conversation dated March 6, 2002 and your correspondence dated March 6, 2002.

NAME OF DRUG: Mupirocin Ointment USP, 2%

DATE OF APPLICATION: January 4, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: January 8, 2002

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:

Mark Anderson
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

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

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

March 6, 2002

NC

NEW CORRESP

Mr. Gary Buehler, Director
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Amendment to ANDA # 65-123 for Mupirocin Ointment USP, 2% to Complete ANDA File

Dear Mr. Buehler:

As per a telephone request from Martin Shimer, Regulatory Management Officer on March 6, 2002, Clay-Park Labs, Inc. hereby submits the following information to complete the file for Mupirocin Ointment USP, 2%, ANDA #65-123:

1) A copy of the revised Quantitative Statement, **(See Attachment A)**, which reflects the removal of the scale up batch (———) that was referenced on page 1167 of the original submission. In the eventuality of approval of the drug product, Clay-Park Labs, Inc. does not commit to manufacture the scale-up batch because we do not have the appropriate manufacturing equipment. However in the event a scale-up batch is required, Clay-Park Labs, Inc. commits to manufacture the scale-up batch based on the commitment statement presented on page 1382 of the original submission. For ease of review page #1383 is presented **(See Attachment B)**.

APPEARS THIS WAY
ON ORIGINAL

RECEIVED
MAR 0 7 2002
OGD / CDER

2) A copy of the Post Approval Stability Protocol for the 22 g tube **(Attachment C)**.

Should you have any comments or require any further clarification on this ANDA, please contact the undersigned as follows:

Telephone: (718) 960-9976 **Fax: (718) 960-0111**

Sincerely,

For Candis Edwards
Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

February 8, 2002

Mr. Gary Buehler, Director
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Electronic Submission for Mupirocin Ointment USP, 2%, ANDA

Dear Mr. Buehler:

In support of the hard copy of the ANDA for Mupirocin Ointment, USP, 2%, we are hereby submitting two copies of the electronic submission of the Chemistry, Manufacturing and Control (CMC) section. The CMC electronic submission includes the following files, which are contained on one (1) diskette:

File Name	Document
Cpl0006.003	CMC ESD File
Cpl0006.004	Log File
Cpl0006.lgc	Companion Document including Table of Contents

The diskette and a Declaration Statement are contained in the blue (Archival Copy) jacket, Form FDA 2626.

Clay-Park Labs, Inc. submitted an original Abbreviated New Drug Application (ANDA) for Mupirocin Ointment USP, 2% in the hard copy format on January 4, 2002. During the data entry in the Entry Validation Application (EVA) for the electronic submission, discrepancies were

noted. They have been corrected in the electronic submission document (ESD) and referenced in the companion document.

Clay-Park Labs, Inc. is hereby submitting the corrections to the following discrepancies to update the hard copy of ANDA for Mupirocin Ointment USP, 2%:

1. On page 0002 of the hard copy, the proposed marketing status of the Form FDA 356h was incorrectly marked as over the counter (OTC) instead of prescription product (RX). The revised Form FDA 356h is presented as **Attachment A**.

2. On page 1275 of the hard copy, the test results for Average Molecular weight was incorrectly reported as 403 instead of 404 on the Certificate of Analysis for Polyethylene Glycol 400, NF. The corrected Certificate of Analysis is presented in **Attachment B**.

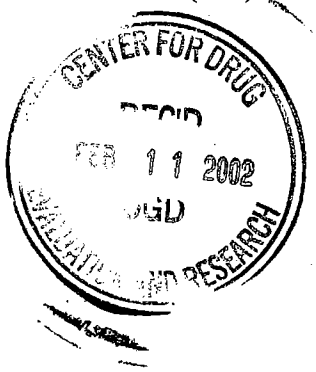
3. On Page 1731 of the hard copy, the microbiologist name was incorrectly reported as [redacted], instead of [redacted] for the Microbial Limit Test on the Certificate of Analysis for Mupirocin Ointment USP, 2%-Placebo. The corrected Certificate of Analysis is presented in **Attachment C**.

Should you have any questions, please contact the undersigned as follows:

Telephone: (718) 960-9976 **Fax: (718) 960-0111**

Sincerely,

Candis Edwards
Director of Regulatory Affairs



65123

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

February 8, 2002

RW 8/26/02
MB

Mr. Gary Buehler, Director
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NC
NEW CORRESP

RE: CORRESPONDENCE TO ANDA FOR MUPIROCIN OINTMENT USP, 2%

Dear Mr. Buehler:

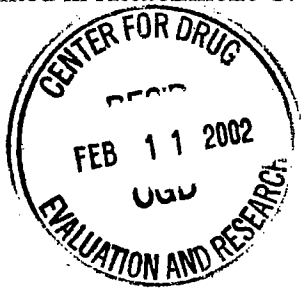
Clay-Park Labs, Inc. submitted an original Abbreviated New Drug Application (ANDA) for Mupirocin Ointment USP, 2% in the hard format on February 4, 2002. During the data entry in Entry Validation Application (EVA) for the electronic submission, discrepancies were noted in the hard copy of the ANDA. They have been corrected in the electronic submission (ESD).

Clay-Park Labs, Inc. is hereby submitting the corrections to the following discrepancies to update the hard copy of ANDA for Mupirocin Ointment USP, 2%:

1. On page 0002 of the hard copy, the proposed marketing status of the Form FDA 356h was incorrectly marked as over the counter (OTC) instead of prescription product (℞). The revised Form FDA 356h is presented as **Attachment A**.

2. On page 1275 of the hard copy, the test results for Average Molecular Weight was incorrectly reported as 403 instead of 404 on the Certificate of Analysis for Polyethylene Glycol 400, NF. The corrected Certificate of Analysis is presented in **Attachment B**.

3. On page 1731 of the hard copy, the microbiologist's name was incorrectly reported as [redacted], instead of [redacted] for the Microbial Limit Test on the Certificate of Analysis for Mupirocin Ointment USP, 2% - Placebo. The corrected Certificate of Analysis is presented in **Attachment C**.



Should you have any questions, please contact the undersigned as follows:

Telephone: (718) 960-9976 **Fax: (718) 960-0111**

Sincerely,

Candis Edwards
Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

505(b)(2) OK
07-MAR-2002
Gregory S. Davis

January 4, 2002

Part of this application was received by the DR on 1/7/02. However the balance was received 1/8/02.

The received date for the entire appl. will be 1/8/02.

08-JAN-2002
Gregory S. Davis

Mr. Gary Buehler, Director
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA for Mupirocin Ointment USP, 2%

Dear Mr. Buehler:

Clay-Park Labs, Inc. hereby submits an original abbreviated new drug application (ANDA) in hard copy format to be followed by electronic format, to seek approval to market Mupirocin Ointment USP, 2% that is bioequivalent to the reference listed drug Bactroban® Ointment (Mupirocin Ointment, 2%), distributed by SmithKline Beecham to NDA # 050591.

This ANDA consists of nine (9) volumes. Clay-Park Labs, Inc. is filing an archival copy (in blue folders) of the ANDA that contains all the information required in the ANDA and a technical review copy (in red folders) that contains all the information in the archival copy with the exception of the bioequivalence section (VI). A separate copy of the bioequivalence section is provided in orange folders.

This also certifies that, concurrently with the filing of this ANDA, a true copy of the technical sections of the ANDA (including a copy of the 356h form and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) is being sent to our local district office. This "field copy" is contained in burgundy folders.

For more detailed information on the organization of this ANDA, please refer to the "Executive Summary" attached after the Table of Contents.

Clay-Park Labs, Inc will submit CMC ESD electronic submission (diskettes) for Mupirocin Ointment USP, 2% as a new correspondence within the 30 day grace period.

Should you have any comments or require any further clarification on this ANDA, please contact the undersigned as follows:

Telephone: (718) 960-9976 **Fax:** (718(960-0111

Sincerely,

Candis Edwards
Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL