CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 50591/S022

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number:NDA 50591/S022

Trade Name: Bactroban Ointment, 2%

Generic Name: (mupirocin)

Sponsor:SmithKline Beecham Pharmaceuticals

Approval Date: April 22, 1999

INDICATION: Provides for the following changes: a.Adds a "Pediatric Use" subsection as required by the December 13, 1994, Federal Register notice concerning pediatric labeling. b. Revises the labeling in accordance with suggestions in the approval letter for NDA 50-591/S-015 dated February 21, 1996.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number:NDA 50591/S022

APPROVAL LETTER

APR 2 2 1999

NDA 50-591/S-022

SmithKline Beecham Pharmaceuticals
Attention: Debra Hackett
Manager, U.S. Regulatory Affairs
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101-7929

Dear Ms. Hackett:

Please refer to your supplemental new drug application dated April 24, 1998, received April 27, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bactroban Ointment (mupirocin), 2%. We note that this application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your amendment dated April 13, 1999 (facsimile) which provides for revised draft labeling in accordance with the facsimile sent to you from this Division on January 21, 1999.

This supplemental new drug application provides for the following changes:

a. Adds a "Pediatric Use" subsection as required by the December 13, 1994, Federal Register notice concerning pediatric labeling.

b. Revises the labeling in accordance with suggestions in the approval letter for NDA 50-591/S-015 dated February 21, 1996.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted April 13, 1999).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 50-591/S-022." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have fulfilled the pediatric study requirement at this time.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Maureen Dillon-Parker, Project Manager, at (301) 827-2125.

Sincerely,

/S/

Janice Soreth, M.D.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50592/S022

MEDICAL REVIEW(S)

CLINICAL REVIEW OF AMENDMENT TO LABELING SUPPLEMENT
NDA 50-591/S-022

Date of Submission (by Fax): April 13, 1999

Date Assigned to Reviewer: April 15, 1999

Date Review Initiated: April 15, 1999

Date Review to Supervisor: April 19, 1999

Drug: Bactroban (mupirocin) Ointment, 2%.

Applicant: SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101

Indication: Bactroban Ointment (mupirocin ointment) 2% is indicated for the topical treatment of impetigo due to: *Staphyloccus aureus* and *Streptococcus pyogenes*.

Packaging: This product is available in 15 and 30 gram tubes.

Reason for Supplement: This supplement provides for a revised package insert, including responses to requests made by DAIDP in 1996 and a new "Pediatric Use" subsection.

Background: Please refer to the previous review of this supplement dated August 12, 1998. The conclusions of that review were faxed to the applicant, and the April 13, 1999 submission presents a revised label in response to our comments.

Related NDA's:
1. NDA 50-703, Bactroban Nasal 2% (mupirocin calcium ointment).
2. NDA 50-746, Bactroban Cream 2% (mupirocin calcium cream).

Material Reviewed: The August 12, 1998 clinical review, the April 13, 1999 Fax from the applicant, and the original supplement S-022, dated April 24, 1998 have been consulted in the review of this amendment.

Review: The following comments pertain to the draft label of April 13, 1999. If a labeling section is not mentioned, it should be presumed to be satisfactory as presented by the applicant.

1. CLINICAL PHARMACOLOGY

   a. In the second paragraph, the phrase) has been added following _ _ in the second sentence. This is satisfactory.

   b. In the Microbiology subsection, the words have been deleted from the end of the third sentence of the first paragraph of the FDA recommended version. This is also satisfactory.

2. INDICATIONS AND USAGE: The phrase _ has been added after _ This is satisfactory.

3. CLINICAL STUDIES: In the Pediatrics subsection, the total number of pediatrics patients has been changed from 88 to 91, as well as the numbers for the test groups: from 41 to 42 for Bactroban Ointment, and from 47 to 49 for vehicle placebo. The efficacy rates remain the same. The changes are satisfactory.

Conclusions and Recommendations:

The draft labeling submitted by fax on April 13, 1999 is satisfactory. This supplement may be approved.

/S/
David C. Bostwick

/S/ 4-16-99
Alexander Rakowsky, M.D.

For concurrence only:
Janice Soreth, M.D.,
Acting Divison Director /S/ 4/22/99

Original NDA
HFD-240
HFD-340
HFD-520
HFD-520/Bostwick
HFD-520/Rakowsky
HFD-520/Dillon-Parker
HFD-520/Micro/King
HFD-520/Pharm/Peters

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APPLICATION NUMBER: NDA 50591/S022

PHARMACOLOGY REVIEW(S)

1 Parke

MAY 19 1998

Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520

NDA #: 50591 (SLR-022)

SPONSOR: SmithKline Beecham Pharmaceuticals
Philadelphia, PA

AUTHORIZED REPRESENTATIVE: Debra Hackett
(215) 751-4455

DRUG NAMES: Bactroban Ointment (mupirocin) 2%

CATEGORY: Topical antimicrobial in a water miscible ointment

NUMBER OF VOLUMES: 1

DATE CDER RECEIVED: 4/27/97

DATE ASSIGNED: 5/4/98

DATE REVIEW STARTED: 5/15/98

DATE 1ST DRAFT COMPLETED: 5/19/98

DATE REVIEW ACCEPTED BY TEAM LEADER: May 19, 1998

REVIEW OBJECTIVES: To review the labeling for the pediatric use subsection.

TOXICOLOGY: No additional pharmacology/toxicology information is submitted.

RECOMMENDATION:
This reviewer has no additional data requests for this submission, and there are no significant pharmacology/toxicology issues outstanding at this time. Therefore, this discipline has no objection to approval for the pediatric indication.

/S/

Terry S. Peters, D.V.M., D.A.B.T.
VMO, HFD-520

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50591/S022

MICROBIOLOGY REVIEW(S)

/

520 Dillon. Parker

NDA 50-591
Bactroban
SKB

JUN 17 1998

Division of Anti-Infective Drug Products (HFD-520)
Clinical Microbiology Review Notes #1

NDA # 50-591 **DATE COMPLETED: 7 May,1998**

APPLICANT(NDA):

SMITHKLINE BEECHAM PHARMACEUTICALS
One Franklin Plaza
Box 7929
Philadelphia, PA 19101

CHEM/THER. TYPE: Topical

SUBMISSION REVIEWED: NDA 50-591
PROVIDING FOR: Update of Microbiology section of package insert

PRODUCT NAMES(S):

Proprietary: Bactroban®

Non-Proprietary/USAN: Mupirocin

DOSAGE FORMS(S) Ointment

STRENGTHS: 2%

ROUTE(S) OF ADMINISTRATION: Topical

PHARMACOLOGICAL CATEGORY: Antiinfective

DISPENSED: X Rx ___ OTC

INITIAL SUBMISSION:
Received by CDER: N/A
Received by Reviewer:
Review Completed:

AMENDMENT(S)
Received by CDER: 4/27/98
Received by Reviewer: 5/1/98
Review Completed: 5/7/98

NDA 50-591
Bactroban
SKB
REMARK(S):

From the microbiological perspective, this application involves no new basic microbiological information. This application provides microbiological labeling which is conceptually identical to other currently approved mupirocin products. While this product is labeled primarily for treatment of impetigo due to staphylococci and Lancefield's Group A streptococci, this application continues to carry an Indication for impetigo caused by " beta-hemolytic streptococci" . However, the Indications section should have the term " beta-hemolytic streptococci" deleted because the term includes several taxons which have no relationship to one another.

Since no conceptual labeling changes of microbiological significance were proposed for this application by the applicant, the proposed labeling should fully conform to the general format and content of more recently approved topical dosages forms of mupiricin. The Microbiology subsection of the package insert should be written as noted in the Conclusions and Recommendations Section below. In addition, the Indications section should have the term " beta-hemolytic streptococci" deleted.

CONCLUSIONS and/or RECOMMENDATIONS:

From the microbiological perspective, the Microbiology subsection of the package insert should be modified to read as noted below. In addition, the term " beta-hemolytic streptococci" should be deleted from the Indications Section.

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 as well. 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

NDA 50-591
Bactroban
SKB

clinical studies. (See INDICATIONS AND USAGE Section). 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*.

/S/ 6/17/98

James R. King
Microbiologist, HFD-520

SMicro/ASheldon
~~ADD#1 5/8/98 and Final 6/17/98 CMC~~
TS 6/17/98

DepDir/LGavrilovich LG 6/22/98

cc: Orig. NDA # 50-591
HFD-520/DepDir/LGavrilovich
HFD-635
HFD-520/SMicro/Asheldon
HFD-520
HFD-520/Micro/King
HFD-520/MO/Bostwick
HFD-520/Pharm/Peters
HFD-520/Chem/Timper
HFD-520/CSO/Dillon-Parker

Printed for signatures on 17 JUN 1998