CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-055

CHEMISTRY REVIEW(S)
NDA 22-055

ALTABAX
(retapamulin ointment), 1%

GlaxoSmithKline

Dorota Matecka

Division of Pre-Marketing Assessment II, Branch IV
ONDQA
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Chemistry Review Data Sheet

1. NDA 22-055

2. REVIEW # 1

3. REVIEW DATE: 25-Feb-2007

4. REVIEWER: Dorota Matecka

5. PREVIOUS DOCUMENTS:

<table>
<thead>
<tr>
<th>Previous Documents</th>
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6. SUBMISSION(S) BEING REVIEWED:

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7. NAME & ADDRESS OF APPLICANT:

<table>
<thead>
<tr>
<th>Name:</th>
<th>GlaxoSmithKline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address:</td>
<td>One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19101-7929</td>
</tr>
<tr>
<td>Representative:</td>
<td>Deborah E. Zuber, R. Ph., CMC Global Regulatory Affairs</td>
</tr>
<tr>
<td>Telephone:</td>
<td>(610) 917-6884</td>
</tr>
</tbody>
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8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Altabax
b) Non-Proprietary Name (USAN): retapamulin ointment
c) Code Name/# (ONDC only): SB-275833

d) Chem. Type/Submission Priority:
   • Chem. Type: 1
   • Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: antibacterial

11. DOSAGE FORM: Ointment

12. STRENGTH/POTENCY: 1%

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:

   Chemical name: Retapamulin; Acetic acid, [(3-exo)-8-methyl-8-azabicyclo[3.2.1]oct-3-y1]thio]-,(3aS,4R,5S,6S,8R,9R,9aR,10R)-6-ethenyldecahydro-5-hydroxy-4,6,9,10-tetramethyl-1-oxo-3a,9-propano-3aH/cyclopentacycloocten-8-y1 ester (9CI) (CAS name)

   Molecular weight: 517.78

   Molecular formula: C_{30}H_{47}NO_{4}S
Chemical structure:

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

<table>
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<th>DMF #</th>
<th>TYPE</th>
<th>HOLDER</th>
<th>ITEM REFERENCED</th>
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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:

<table>
<thead>
<tr>
<th>DOCUMENT</th>
<th>APPLICATION NUMBER</th>
<th>DESCRIPTION</th>
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<tr>
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<td>GSK’s IND for retapamulin ointment, 1%</td>
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<td>GSK’s NDA for retapamulin ointment, 1%</td>
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18. STATUS:

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<th>CONSULTS/CMC RELATED REVIEWS</th>
<th>RECOMMENDATION</th>
<th>DATE</th>
<th>REVIEWER</th>
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<tr>
<td>Biometrics</td>
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<td>EES</td>
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<td>17-Aug-2006</td>
<td>Shawnie Adams</td>
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<td>Pharm/Tox</td>
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<td>DMETS</td>
<td>ACCEPTABLE (name: Altabax)</td>
<td>2-Aug-2006</td>
<td>Todd Bridges</td>
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<td>EA</td>
<td>N/A (request for a categorical exclusion)</td>
<td>N/A</td>
<td>Anastasia Lolas</td>
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<td>Microbiology</td>
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<td>14-Jun-2006</td>
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The Chemistry Review for NDA

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval.

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)

This NDA provides for a new indication of Altabax (retapamulin ointment), 1%, which is the treatment of primary impetigo. For the chemistry, manufacturing and controls information, the applicant has made a reference to __________________________. However, from the chemistry, manufacturing and controls standpoint, it was found acceptable (per review dated 25-Sep-2006).

The retapamulin drug substance, a new molecular entity (NME), is a novel semi-synthetic pleuromutilin (code name SB-275833). This is the first representative of the pleuromutilin class of antibacterial agents developed specifically for use in humans.

Retapamulin is a white to pale yellow, crystalline, anhydrous and non-solvated solid with a melting range of 125 – 127°C. The solubility of retapamulin in water is pH-dependent with higher solubility at a lower pH; retapamulin is also soluble in non-aqueous solvents such as ethanol. Retapamulin drug substance is manufactured __________________________.

and will be used in the commercial drug product.

The drug product, Altabax (retapamulin ointment), is an off-white, smooth ointment for topical use, which contains retapamulin drug substance __________________________. The drug substance is suspended in white petrolatum, USP, which is the only excipient used in the Altabax formulation. The
Executive Summary Section

The proposed commercial formulation is the 1.0% ointment. The formulation, including the grade of white petrolatum, has been constant throughout the development of this product, and the commercial formulation is identical to the non-clinical and clinical formulations.

The drug product specification includes description, SB-275833 assay, minimum fill, and drug-related impurities content. The drug product is not sterile and does not contain any preservative. However, per earlier agreements with the Agency, microbial controls have been established and microbial limits test is included in the drug product specification. The relatively small particle size of SB-275833 is critical to the product quality as it ensures adequate dispersion of the drug substance in the petrolatum and a satisfactory release rate of SB-275833 from the ointment matrix. The morphology of the particles in drug product does not change significantly on stability, and the conversion of __________ in the drug product is not anticipated due to the low solubility of drug substance in white petrolatum. The drug product appears to be stable throughout the expiration dating as indicated by the long term stability data provided in the original submission and updated via subsequent amendments.

The drug product is packaged in __________ tubes __________ (5, 10, and 15 gram fill __________ ).

The current NDA does not include any chemistry, manufacturing and controls information. A statement of categorical exclusion has been submitted in Module 1.3.2 of this application. All other chemistry, manufacturing and controls information for the drug substance and drug product is cross referenced to __________.

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

The proposed indication for Altabax (retapamulin ointment), 1%, is the treatment of primary impetigo. The Dosage and Administration section of the labeling calls for applying a thin layer of Altabax ointment to the affected area twice daily for five (5) days.

The drug product will be available in the following packaging configurations: __________ tubes (5 g, 10 g, and 15 g fill __________ ). The expiration dating for Altabax (retapamulin ointment), 1%, is 24 months with the following storage conditions statement: “Store at 25°C (77°F); with excursions permitted to 15 - 30°C (59 - 86°F)”.

C. Basis for Approvability or Not-Approval Recommendation

Reference to the review of __________.

III. Administrative

A. Reviewer’s Signature

DFS

B. Endorsement Block

ChemistName/Date:
C. CC Block
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
__________________________
Dorota Matecka
2/25/2007 06:09:58 PM
CHEMIST

__________________________
Norman Schmuff
2/26/2007 07:43:37 AM
CHEMIST
IV. Attachment (EER)

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application: [Redacted] Sponsor: GLAXO GEF LTD

Org Code: 520 1 FRANKLIN PLAZA
Priority: 15 PHILADELPHIA, PA 19101

Stamp Date: 29-NOV-2005 Brand Name: SB-275833 (RETAPAMULIN)
POCPA Date: 29-SEP-2006 Etabl. Name:
Action Goal: Generic Name: RETAPAMULIN
District Goal: 31-JUL-2006 Dosage Form: (OINTMENT)

Strength: [Redacted]

FDA Contacts:
R. HERMEL Project Manager (HFD-800) 301-796-1961
R. MADURANEE Review Chemist 301-796-1400
R. MADURANEE Team Leader 301-796-1400

Overall Recommendation: ACCEPTABLE on 17-AUG-2006 by S. ADAMS (HFD-322) 301-627-9051

Establishment: CPN: 9610421 FEI: 3062807078
GLAXO WELLCOME LTD
DL128DT
BARDNA CASTLE, UK

DNF No: [Redacted] AADA:

Responsibilities:
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: OIN OAI Status: NONE

Last Milestone: GC RECOMMENDATION
Milestone Date: 23-DEC-05
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CPN: 9610414 FEI: 3062807078
GLAXO WELLCOME OPERATIONS UK
DAI 5AH
CHEMISTRY REVIEW

Chemistry Assessment Section

DARTFORD, KENT, UK

Responsibilities:
- DRUG SUBSTANCE MANUFACTURER
- DRUG SUBSTANCE RELEASE TESTER
- DRUG SUBSTANCE STABILITY TESTER

Profile: CFN

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-DEC-0x

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment:
- CFN: 9610412
- FEI:
- GLAXOSMITHKLINE
  WORTHING, WEST SUSSEX, UK

Appears This Way
On Original
CHEMISTRY REVIEW

Chemistry Assessment Section

20-AUG-2006

Responsibilities:
INTERMEDIATE MANUFACTURER
INTERMEDIATE RELEASE TESTER
INTERMEDIATE STABILITY TESTER

Profile : CFN
OC RECOMMENDATION

Last Milestone Date: 23-DEC-05
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FRI :
GLAXOSMITHKLINE
11 RIMINI Mews
MISSISSAUGA, ONTARIO, CA

AADA:

Responsibilities:
FINISHED DOSAGE PACKAGER

Profile : OIN
OC RECOMMENDATION

Last Milestone Date: 17-AUG-06
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9615283
GLAXOSMITHKLINE INC
7333 MISSISSAUGA NORTH ROAD
MISSISSAUGA, ONTARIO, CA

AADA:

Responsibilities:
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile : OIN
OC RECOMMENDATION

AADA:

Appears This Way
On Original