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

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-055

2. REVIEW # 1

3. REVIEW DATE: 25-Feb-2007

4. REVIEWER: Dorota Matecka

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	12-Jun-2006

6. SUBMISSION(S) BEING REVIEWED:

Previous Documents	Document Date
Original	12-Jun-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	GlaxoSmithKline
Address:	One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19101-7929
Representative:	Deborah E. Zuber, R. Ph., CMC Global Regulatory Affairs
Telephone:	(610) 917-6884

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

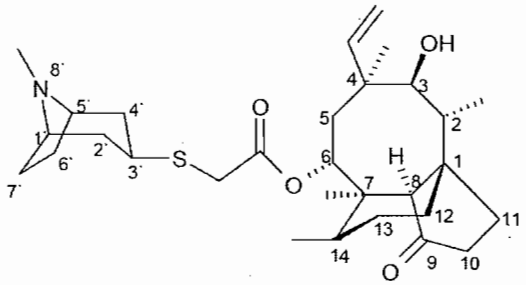
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

Molecular weight: 517.78

Molecular formula: $C_{30}H_{47}NO_4S$

Chemical structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]	[redacted]	3	Adequate	4/30/99	N/A
	III			4			N/A
	III			4			N/A
	III			3	Adequate	10/20/04	N/A
	III			4			N/A

[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
[redacted]		GSK's IND for retapamulin ointment, 1%
		GSK's NDA for retapamulin ointment, 1%

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	ACCETPABLE ([redacted]	17-Aug-2006	Shawnte Adams
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	N/A	N/A	N/A
DMETS	ACCEPTABLE ([redacted], proprietary name: Altabax)	2-Aug-2006	Todd Bridges
EA	N/A (request for a categorical exclusion)	N/A	N/A
Microbiology	ACCEPTABLE [redacted]	14-Jun-2006	Anastasia Lolas

The Chemistry Review for NDA [redacted]

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 [redacted]. 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

[redacted]

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 [redacted]. The drug substance is suspended in white petrolatum, USP, which is the only excipient used in the Altabax formulation. 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 ([redacted] 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 [redacted] 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 [redacted] tubes [redacted] (5, 10, and 15 gram fill [redacted]).

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 [redacted].

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: [redacted] tubes (5 g, 10 g, and 15 g fill) [redacted]. 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 [redacted].

III. Administrative

A. Reviewer's Signature

DFS

B. Endorsement Block

ChemistName/Date:

ChemistryTeamLeaderName/Date:
ProjectManagerName/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 GRP LTD
Org Code	: 520		1 FRANKLIN PLAZA
Priority	: 1S		PHILADELPHIA, PA 19101
Stamp Date	: 29-NOV-2005	Brand Name :	SB-275833 (RETAPAMULIN)
PDUFA Date	: 29-SEP-2006	Estab. Name:	
Action Goal	:	Generic Name:	RETAPAMULIN
District Goal:	31-JUL-2006	Dosage Form:	(OINTMENT)
		Strength :	1%

FDA Contacts:	R. HUMMEL	Project Manager (HFD-800)	301-796-1981
	R. MADURAWE	Review Chemist	301-796-1408
	R. MADURAWE	Team Leader	301-796-1408

Overall Recommendation: ACCEPTABLE on 17-AUG-2006by S. ADAMS (HFD-322) 301-827-9051

Establishment : CFN : 9610421 FEI : 3002807078

GLAXO WELLCOME LTD

DL128DT

BARNARD CASTLE, , UK

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Profile : OIN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-DEC-05

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9610414 FEI :

GLAXO WELLCOME OPERATIONS UK

DA1 5AH

[redacted]

Appears This Way
On Original

CHEMISTRY REVIEW

Chemistry Assessment Section

DARTFORD, KENT, UK

DMF No: AADA:

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

Profile : CPN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-DEC-05
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CPN : 9610412 FEI :
GLAXOSMITHKLINE
WORTHING, WEST SUSSEX, UK

DMF No: AADA:

[redacted]

Appears This Way
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ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Responsibilities: INTERMEDIATE MANUFACTURER
INTERMEDIATE RELEASE TESTER
INTERMEDIATE STABILITY TESTER

Profile : CFN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-DEC-05
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :
GLAXOSMITHKLINE
11 RIMINI MEWS
MISSISSAUGA, ONTARIO, CA
DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile : OIN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 17-AUG-06
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9615283 FEI : 3002807086
GLAXOSMITHKLINE INC
7333 MISSISSAUGA NORTH ROAD
MISSISSAUGA, , CA
DMF No: [redacted] AADA:

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

Profile : OIN OAI Status: NONE

[redacted]

Appears This Way
On Original

Last Milestone:		OC RECOMMENDATION
Milestone Date:		15-AUG-06
Decision	:	ACCEPTABLE
Reason	:	DISTRICT RECOMMENDATION