CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-887

CHEMISTRY REVIEW(S)

NDA 21-887

Alli Capsules (OTC Orlistat)

GlaxoSmithKline

Martin Haber
Division of Metabolic and Endocrine Drugs

Consult Review for
Office of Over-the Counter Drugs

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-887

2. REVIEW #1

3. REVIEW DATE: February 23, 2006

4. REVIEWER: Martin Haber, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NA	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Electronic NDA	6/6/05
Amendment	2/6/06

7. NAME & ADDRESS OF APPLICANT:

Name:	GlaxoSmithKline Consumer Healthcare
Address:	1500 Littleton Road, Parsippany, NJ 07054-3884
Representative:	Erin Oliver, Manager, Regulatory Affairs
Telephone:	(973) 889-2516

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: TBD
b) Non-Proprietary Name (USAN): Orlistat
c) Code Name/# (ONDC only): RO-18-0647/008
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: Type 8: Rx to OTC switch and Type 3: new formulation (1/2 Rx dose)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: Weight Loss

11. DOSAGE FORM: Immediate-release Capsules

12. STRENGTH/POTENCY: 60.0 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ___Rx _x__OTC

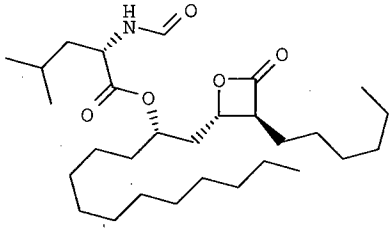
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x___Not a SPOTS product

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

(S)-2-Formylamino-4-methyl-pentanoic acid (S)-1-[[(2S,3S-3hexyl-4-oxo-oxetan-2-yl]methyl]-dodecyl ester
CAS #: 96829-58-2, $C_{29}H_{53}NO_5$, mol. wt. 495.75



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]		3	Adequate	9/27/05	Reviewed by Dr. D. Klein

	III	3	Adequate	1/12/05	Reviewed by Dr. R. Madurawa
		3	Adequate	11/25/02	Reviewed by Dr. J. Boal
		3	Adequate	12/7/05	Reviewed by Dr. R. Frankewich
	III	3	Adequate	10/9/02	Reviewed by Dr. P. Maturu

[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
NDA	20-766	Xenical® (Orlistat) Capsules, 120 mg, approved Rx product (Hoffmann-La Roche)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	2/2/06	S. Ferguson
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	NA		
OPDRA	NA		
EA	NA		
Microbiology	NA		

The Chemistry Review for NDA 21-887

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval.

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

NA

II. Summary of Chemistry Assessments

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

The drug product contains 60 mg of the drug substance, Orlistat, [redacted] opaque [redacted] hard gelatin capsule to which a dark blue gelatin band is applied to provide capsule tamper-evidence. The capsules also contain the following compendial excipients: microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, povidone and talc. The capsule shells contain gelatin, titanium dioxide and FD&C Blue No. 2.

The drug product for this OTC NDA is the same as the immediate-release hard gelatin capsules for the approved Rx NDA 20-766 (Xenical Capsules), except that the strength is exactly one-half, 60 mg, instead of 120 mg, as for the Rx product. The Orlistat OTC 60 mg formulation is compositionally identical to the approved Xenical 120 mg capsule and the same compendial excipients are used. The two products differ in terms of capsule size, fill weight, trade dress and the addition of the tamper-evident gelatin band. Bulk Orlistat 60 mg [redacted] capsules are [redacted] GlaxoSmithKline, Aiken, SC. Capsule banding is performed at GSK Aiden or GSK Zebulon, NC. Capsule manufacturing and testing is very similar to that currently approved for Xenical Capsules.

The drug substance, orlistat, is a synthetic chemical with four chiral centers. It is a crystalline powder with [redacted] very low water solubility. [redacted] accelerated stability studies at elevated temperatures are not informative because of degradation of the drug substance.

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

The drug product immediate-release capsules are taken orally to promote weight loss in overweight adults when used with a reduced calorie, low fat diet. The drug substance is an inhibitor of gastrointestinal lipases. It acts locally in the gastrointestinal tract to inhibit the digestion and subsequently the absorption of dietary fat. Very little drug is systemically absorbed. The recommended dose is 60 mg of Orlistat (one capsule), three times a day, with meals. The proposed expiration dating period is 24 months for capsules stored in [redacted] bottles at controlled room temperature.

C. Basis for Approvability or Not-Approval Recommendation

Chemistry information provided is adequate. The OC overall recommendation for all manufacturing sites by S. Ferguson on 2/2/06 was acceptable. Real time stability data for [redacted] months at room temperature on the three primary stability batches that is adequate to support the proposed expiry of 24 months and adequate qualification data for the GSK-Aiken, SC site was submitted in the 2/06/06 Amendment.

III. Administrative

A. Reviewer's Signature

See DFS

B. Endorsement Block

See DFS

C. CC Block

See DFS

19 Page(s) Withheld

✔ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-\

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/s/

Martin Haber
2/23/2006 02:57:31 PM
CHEMIST

Blair Fraser
2/23/2006 05:07:45 PM
CHEMIST

Alli (60 mg Orlistat, OTC) Capsules
NDA 21-887

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: GlaxoSmithKline Consumer Healthcare

Indication: Used to promote weight loss when taken with food.

Presentation: Immediate-release hard gelatin capsule, packaged in 60, 90, and 120 count [redacted] bottles. There is also a 20 count physician's sample package. The OTC starter kit comes with a plastic carrying case for up to 6 capsules.

EER Status: Acceptable 02-FEB-2006

Consults: EA – Categorical exclusion granted under 21 CFR §25.31(b) for orlistat.
Methods Validation – Revalidation by Agency not requested

Original Submission: 06-JUN-2005
Amendment: 06-FEB-2006 (updated stability data)

Post-Approval Agreements: NA

Drug Substance:

Orlistat is an inhibitor of gastrointestinal lipases which acts locally in the gastrointestinal tract to inhibit digestion of dietary fat. Very little drug is systemically absorbed. Orlistat is a synthetic chemical with four chiral centers. It is a crystalline powder with [redacted] very low water solubility. [redacted] accelerated stability studies at elevated temperatures are not informative because of degradation of the drug substance. The drug substance, orlistat, is identical in all aspects to that described in approved Rx NDA 20-766 for Xenical (Orlistat 120 mg) Capsules, manufactured by Hoffmann La-Roche. Therefore, the chemistry, manufacturing, and controls information contained in NDA 21-887 that pertain to orlistat drug substance is referenced as applicable to NDA 20-766.

Conclusion: Drug substance is acceptable.

Drug Product:

The drug product, Alli (60 mg orlistat) Capsules, contains 60 mg of the drug substance, Orlistat, [redacted] opaque, turquoise, hard gelatin capsule to which a dark blue, gelatin band is applied to provide capsule tamper-evidence. The capsules also contain the following compendial excipients: microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, povidone and talc. The capsule shells contain gelatin, titanium dioxide and FD&C Blue No. 2.

The drug product for this OTC NDA is the same as the immediate-release hard gelatin capsules for the approved Rx NDA 20-766 (Xenical Capsules), except that the strength is exactly one-half, 60 mg, instead of 120 mg, as for the Rx product. The Orlistat OTC 60 mg formulation is compositionally identical to the approved Xenical 120 mg capsule and the same compendial excipients are used. The two products differ in terms of capsule size, fill weight, trade dress and the addition of the tamper-evident gelatin band. The method of manufacture is the same and the processing equipment are similar in design and operating principle to those currently used for commercial production of the approved Rx NDA 20-766 (Xenical Capsules). The proposed storage is at 25°C (controlled room temperature).

Conclusion: Drug product is satisfactory.

Additional Items:

Adequate stability data were provided to support the proposed expiration dating of 24 months for drug product packaged in the proposed bottles and stored at controlled room temperature. The content of impurities increases with time and temperature but remained within acceptance limits at 25°C.

All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.

Overall Conclusion:

From a CMC perspective, the application is recommended for approval.

Blair A. Fraser, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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/s/

Blair Fraser
2/23/2006 05:27:56 PM
CHEMIST