CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-981

CHEMISTRY REVIEW(S)

NDA 20-981
Review #1

Oral Hycamtin Capsules
(topotecan hydrochloride capsules)

SmithKline Beecham Corporation
d/b/a GlaxoSmithKline

Brian Rogers
Pre-Marketing Assessment and Manufacturing Science
Division III
Office of New Drug Quality Assessment

Division of Drug Oncology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 20-981

2. REVIEW #1

3. REVIEW DATE: September 28, 2007

4. REVIEWER: Brian Rogers

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	April 11, 2007
Amendment	July 11, 2007
Amendment	September 24, 2007
Amendment	October 4, 2007
Amendment	October 5, 2007

7. NAME AND ADDRESS OF APPLICANT:

Name:	SmithKline Beecham Corporation d/b/a GlaxoSmithKline
Address:	One Franklin Plaza P.O. Box 7929 Philadelphia, PA 19101
Representative:	N/A
Telephone:	888-825-5249

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Oral Hycamtin® Capsules
b) Non-Proprietary Name (USAN): topotecan hydrochloride capsules
c) Code Name/# SKF-104864A
d) Chem. Type/Submission Priority:

- Chem. Type: 3
- Submission Priority: P

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

10. PHARMACOLOGICAL CATEGORY: topoisomerase I inhibitor

11. DOSAGE FORM: Gelatin Capsule

12. STRENGTH/POTENCY: 0.25-mg and 1-mg capsules

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

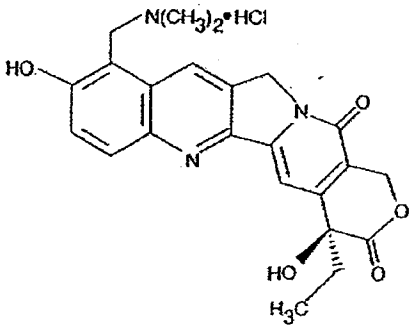
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

Chemistry Review Data Sheet



(*S*)-10-[(dimethylamino)methyl]-4-ethy1-4,9-dihydroxy-1*H*-pyrano[3',4'.6,7]indolizino [1,2-*b*]quinoline-3,14-(4*H*,12*H*)-dione monohydrochloride.
$C_{23}H_{23}N_3O_5$•HCl
MW = 457.9
CAS # [123948-87-8]

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
	4			4	N/A		
	4			4	N/A		
	4			4	N/A		
	3			4	N/A		
	3			4	N/A		
	3			4	N/A		
	3			4	N/A		

b(4)

[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)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
N20-671	SmithKline Beecham Corp.	Hycamtin Injection Solution	AP	5/28/96	Referenced for information on the drug substance.
N20-671/ SCM-013	SmithKline Beecham Corp.	Hycamtin Injection Solution	AP	8/5/03	Referenced for proposed manufacturing method for drug substance.
I42,993	SmithKline Beecham Corp.	Hycamtin Capsules	Active		Referenced for impurity qualification via stability studies on clinical batches.

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	32,693	SmithKline Beecham	Hycamtin (topotecan HCl) solution for injection.

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				No consult submitted
EES			Acceptable 10/10/07	Puerto Rico site inspection request cancelled as not critical
Pharm/Tox			Completed/10/5/07 W. McGuinn	Qualification of related impurities requested. Summary provided 10/9/07
Biopharm				No consult submitted
LNC				No consult submitted. Conventional dosage form.
Methods Validation				No post-approval verification will be requested owing to previous experience with methods.
OSE/DMETs			Completed/JPark	Filed 10/5/07
EA				Categorical exclusion requested and granted
Microbiology				No consult submitted - Oral dosage form

The Chemistry Review for NDA 20-981

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

All CMC review issues have been resolved adequately. The Office of Compliance provided acceptable cGMP recommendation on October 10, 2007. The NDA is recommended for approval from a CMC perspective. Two comments listed at the end of the review need to be included in the action letter.

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

None at this time.

II. Summary of Chemistry Assessments

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

Drug Substance

All information for the drug substance is incorporated by cross-reference to approved NDA 20-671 for Hycamtin® (topotecan hydrochloride) for Injection. Reference is made to NDA 20-671 and all amendments, supplements, and annual reports thereto for chemistry, manufacturing, and control information (CMC) for topotecan hydrochloride.

Topotecan is a semi-synthetic drug substance. The starting material, [redacted] camptothecin, is obtained from [redacted] suppliers. The [redacted] camptothecin [redacted] An alternate source of [redacted] camptothecin is [redacted] The material is [redacted] A uniform specification exists for acceptance of [redacted] which may be manufactured by Smith Kline Beecham (SB) or purchased from [redacted]. b(4)

Drug Product

Oral Hycamtin (topotecan) are provided in two strengths, 0.25 mg and 1 mg, for oral administration. Capsules contain topotecan hydrochloride with label claims expressed as topotecan free base. Both strengths are Size– preprinted hard gelatin capsules; the 0.25 mg capsules are white to yellowish white, and the 1 mg capsules are pink. Capsules are preprinted with 'HYCAMTIN' and the strength, '0.25 mg' or '1 mg'. b(4)

Capsules are packaged into [redacted] bottles with [redacted] b(4)

The other components of topotecan 0.25 mg and 1 mg capsules are Hydrogenated Vegetable Oil, and Glyceryl Monostearate NF. The total fill weight is — mg. The preprinted hard gelatin capsule, Size —is sealed with —— NF. The capsules contain gelatin, TiO_2 and red iron oxide. Black Ink is used for printing the strength and identity on each capsule shell. b(4)

b(4)

The inspection of the testing and manufacturing sites is not completed as of the date of this review. The —— site has not been inspected and thus no overall recommendation from the OC has been provided.

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

Topotecan 0.25 mg and 1 mg capsules are an oral formulation for therapeutic use in treatment of reoccurring SCLC.

C. Basis for Approvability or Not-Approval Recommendation

CMC deficiencies have been sent to the applicant on 9/20/07 and 10/2/07, and were replied to in the 9/24/07, 10/4/07 and 10/5/07 amendments, respectively.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CMC Reviewer Name/Date: Brian Rogers/9/28/07
CMC BC Name/Date
ProjectManager Name/Date

C. CC Block

85 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Brian Rogers
10/10/2007 06:05:42 PM
CHEMIST

Ravi Harapanhalli
10/10/2007 06:10:43 PM
CHEMIST
Ap recommendation. Two comments at the end of the review need to be included in the action letter.