

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022453Orig1s000

CHEMISTRY REVIEW(S)

NDA 22453

Topotecan Injection

Teva Pharmaceuticals USA

Debasis Ghosh, Ph.D., M. Pharm.

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II**

**CMC REVIEW OF NDA 22453
For the Division of Drug Oncology Products 2 (DOP2)**

Table of Contents

CMC Review Data Sheet	4
The Executive Summary	9
I. Recommendations.....	9
A. Recommendation and Conclusion on Approvability.....	9
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	9
II. Summary of CMC Assessments	9
A. Description of the Drug Product(s) and Drug Substance(s).....	9
B. Description of How the Drug Product is Intended to be Used.....	11
C. Basis for Approvability or Not-Approval Recommendation	11
III. Administrative.....	12
CMC Assessment	13
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	13
S. DRUG SUBSTANCE.....	13
S.1 General Information.....	13
S.1.1 Nomenclature.....	13
S.1.2 Structure.....	14
S.1.3 General Properties.....	15
S.2 Manufacture	15
S.2.1 Manufacturers	15
S.2.2 Description of Manufacturing Process and Process Controls.....	16
S.2.3 Control of Materials.....	16
S.2.4 Controls of Critical Steps and Intermediates.....	16
S.2.5 Process Validation and/or Evaluation	16
S.2.6 Manufacturing Process Development	16
S.3 Characterization	16
S.3.1 Elucidation of Structure and other Characteristics.....	16
S.3.2 Impurities.....	16
S.4 Control of Drug Substance.....	17
S.4.1 Specification	17
S.4.2 Analytical Procedures	20
S.4.3 Validation of Analytical Procedures	22
S.4.4 Batch Analyses	28
S.4.5 Justification of Specification.....	29
S.5 Reference Standards or Materials	30
S.6 Container Closure System.....	30
S.7 Stability	30
P. DRUG PRODUCT	30
P.1 Description and Composition of the Drug Product.....	30
P.2 Pharmaceutical Development.....	31
P.2.1 Components of the Drug Product.....	31

P.2.1.1 Drug Substance.....	31
P.2.1.2 Excipients.....	31
P.2.2 Drug Product.....	31
P.2.2.1 Formulation Development.....	31
P.2.2.2 Overages.....	31
P.2.2.3 Physicochemical and Biological Properties.....	31
P.2.3 Manufacturing Process Development.....	31
P.2.4 Container Closure System.....	33
P.2.5 Microbiological Attributes.....	34
P.2.6 Compatibility.....	34
P.3 Manufacture.....	34
P.3.1 Manufacturers.....	34
P.3.2 Batch Formula.....	34
P.3.3 Description of Manufacturing Process and Process Controls.....	36
P.3.4 Controls of Critical Steps and Intermediates.....	36
P.3.5 Process Validation and/or Evaluation.....	36
P.4 Control of Excipients.....	36
P.4.1 Specifications.....	36
P.4.2 Analytical Procedures.....	42
P.4.3 Validation of Analytical Procedures.....	43
P.4.4 Justification of Specifications.....	43
P.4.5 Excipients of Human or Animal Origin.....	43
P.4.6 Novel Excipients.....	43
P.5 Control of Drug Product.....	43
P.5.1 Specification.....	43
P.5.2 Analytical Procedures.....	46
P.5.3 Validation of Analytical Procedures.....	47
P.5.4 Batch Analyses.....	48
P.5.5 Characterization of Impurities.....	48
P.5.6 Justification of Specification.....	48
P.6 Reference Standards or Materials.....	48
P.7 Container Closure System.....	48
P.8 Stability.....	49
P.8.1 Stability Summary and Conclusion.....	49
P.8.2 Postapproval Stability Protocol and Stability Commitment.....	55
P.8.3 Stability Data.....	58
A. APPENDICES.....	60
A.1 Facilities and Equipment (biotech only).....	60
A.2 Adventitious Agents Safety Evaluation.....	60
A.3 Novel Excipients.....	60
R. REGIONAL INFORMATION.....	60
R1 Executed Batch Records.....	60
R2 Comparability Protocols.....	60
R3 Methods Validation Package.....	60
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1.....	61
A. Labeling & Package Insert.....	61
B. Environmental Assessment Or Claim Of Categorical Exclusion.....	69
C. Establishment Evaluation Report.....	69
III. List Of Deficiencies Communicated.....	69

CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 22453 (RESUBMISSION)
2. REVIEW #: 2
3. REVIEW DATE: 04-Dec-2012
DATE ASSIGNED: 09-Aug-2012
4. REVIEWER: Debasis Ghosh, Ph.D., M. Pharm.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original NDA Submission	17-Dec-2008
CMC Review # 1(Ghosh and Lin)	24-Aug-2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>	<u>Sequence#/SD#</u>
NDA Re-Submission/Amendment	25-Jun-2012	SR0013/SD0014
Amendment	02-Jul-2012	SR0014/SD0015
Amendment	28-Sep-2012	SR0015/SD0016
Amendment	12-Oct-2012	SR0016/SD0017
Amendment	26-Nov-2012	SR0017/SD0018

7. NAME & ADDRESS OF APPLICANT (*last updated 9/28/12*):

Name: Teva Pharmaceuticals USA
Address: 425 Privet Road, Horsham, PA 19044
Representative: Philip Erickson, VP, Regulatory Affairs
Telephone: (215) 591-3141

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

CMC Review Data Sheet

- b) Non-Proprietary Name: Topotecan Injection
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 5 (new formulation)
 - Submission Priority: Class 2 Response Resubmission (6 months)

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

Reference Listed Drug: NDA 20-671, Hycamtin, by GlaxoSmithKline (Hycamtin® is supplied as a sterile, lyophilized powder. Each vial contains topotecan hydrochloride equivalent to 4 mg of topotecan free base.)

10. PHARMACOL. CATEGORY: Anticancer

11. DOSAGE FORM: Injection, Solution

12. STRENGTH/POTENCY: 1 mg/mL (topotecan free base)

13. ROUTE OF ADMINISTRATION: intravenous infusion

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

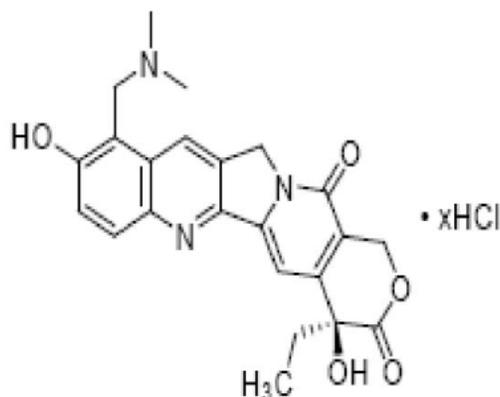
SPOTS product – Form Completed

Not a SPOTS product

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

Chemical Name (Topotecan Free Base): (S)-10-[(Dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione.

CMC Review Data Sheet

Chemical Structure (Topotecan Hydrochloride):

Note: $x = 1.25$

CAS #: 1228035-86-6 (1.25 salt)

Molecular Formula: $C_{23}H_{23}N_3O_5 \cdot x$ HCl ($x = 1.25$)

Molecular Weight: 467.02 g/mol (1.25 salt) 421.45 (free base)

Topotecan Hydrochloride (b)(4) for Teva is manufactured by (b)(4) (see Type II DMF (b)(4)).

Topotecan Hydrochloride ($x=1$) is listed in USP monograph and it is the reference listed drug.

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

MF #	TYPE	HOLDER/LOA	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Topotecan Hydrochloride	1	Adequate	02-Oct-2012	Reviewed by Debasis Ghosh
	III		(b) (4)	4	Adequate	Date of this review	See Section 3.2.P.7
	III			4	Adequate	Date of this review	See Section 3.2.P.7
	III			4	Adequate	Date of this review	See Section 3.2.P.7
	III			3 & 4	Adequate	14-Oct-2008	Reviewed by Donald Klein
	III			4	Adequate	Date of this review	See Section 3.2.P.7

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
IND	(b) (4)	Submitted for pre-NDA meeting
NDA	20-671	Hycamtin for Injection (Reference Listed Drug)
NDA	20-981	Hycamtin Capsules

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	"Overall Acceptable"	31-Aug-2012	R Safaai-Jazi
Pharm/Tox	N/A	N/A	N/A@
Biopharm	Biowaiver is granted	31-Aug-2012	Elsbeth G Chikhale
LNC	N/A	N/A	N.A
Methods Validation	No method validation consult request is needed#	N/A	N/A
DMEPA*	<i>Pending</i>		
Environmental Assessment	FONSI (Finding of no significant impact)@@	19-May-2009	Emily A McVey
Microbiology	"Approve"	24-Oct-2012	Denise A Miller

*DMEPA: Division of Medication Error Prevention and Analysis

@ Based on the information provided in the submission, this reviewer determined that a Pharmacology-Toxicology review is not necessary. A communication has been sent to RPM on 9/26/12 to convey the message to PharmTox Team.

@@ completed in the previous review cycle. The applicant has referenced the same document without any changes to this re-submission

Based on the criteria for requesting methods validation, the product doesn't fit in any of the eight method validation categories (see ONDQA Methods Validation Programs effective 15-Jul-2011, Ver. 1, Document 5105). As described in page 11 of the above document, "examples of analytical methods not requiring FDA lab validation include well established methods such as pH, IR, Karl Fischer, traditional chromatographic methods, loss on drying, heavy metal, Osmolarity, hardness, color, deliverable volume, sterility, pyrogenicity, microbial limits, etc." We believe the test methods provided in this NDA are well established and all non-compendial methods are validated as per ICH/FDA requirements [ICHQ2(R1) Validation of Analytical Procedures: Test and Methods Validation (August 2005) and USFDA Guidance for Industry: Analytical procedures and Methods Validation (August 2000)]. Based on our evaluation of the submitted Analytical Method Validation Reports, no method validation consult request is needed to determine the acceptability and suitability of the proposed analytical procedures.

Executive Summary Section

The CMC Review for NDA 22-453

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An "Overall Acceptable" recommendation from the Office of Compliance has been made. However, labeling issues are still pending as of the date of this review.

From the CMC perspective, this NDA is recommended for approval pending satisfactory resolution of the labeling issues.

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

None

II. Summary of CMC Assessments

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

(1) Drug Substance

The drug substance, topotecan hydrochloride, is a hygroscopic, yellow to orange powder. The drug substance is photo-sensitive. It has a pKa of 6.8 and it is freely soluble in aqueous solution at (b) (4). The drug substance (b) (4). The drug substance manufacturer (b) (4). The ratio of free base and hydrochloride (b) (4) has a melting range of 213-218°C. Topotecan free base has a molecular weight of 421.45. There is only (b) (4) in the molecule (b) (4).

The applicant has referenced DMF (b) (4) for information regarding the control of the materials, description of the controls of the critical steps and intermediates in the manufacturing process, process validation and/or evaluation studies, and description of the manufacturing process development used in the production of the drug substance. The applicant provided a letter of authorization from the vendor. DMF has been reviewed and found to be adequate.

Executive Summary Section

The drug substance has been characterized by using elemental analysis, UV-spectroscopy, Infra-red spectroscopy, mass spectroscopy, and nuclear magnetic resonance.

The drug substance contains two structurally related impurities. In addition, drug substance contains (b) (4). The presence of another organic impurity, (b) (4) have also been reported. However, all of the above impurities comply with the accepted standards or otherwise qualified by toxicological studies.

The Applicant provided independent analytical results to verify and support the quality of the drug substance. All non-compendial analytical procedures have been validated for acceptance. The Applicant provided details of the reference standard including the Certificate of analysis.

The drug substance is packaged into (b) (4) which are then sealed into aluminum foiled bags. It is then placed into HDPE bottles (b) (4) and stored at refrigeration temperature. In this section, the Applicant referenced DMF (b) (4) for additional packaging information. It has been found to be adequate.

The stability program of Topotecan Hydrochloride is designed and conducted by (b) (4) following ICH Q1A. The stability studies include tests at long-term ($5^{\circ} \pm 3^{\circ}\text{C}$) and accelerated ($25^{\circ} \pm 2^{\circ}\text{C}$ at $65 \pm 5\%$ RH) conditions. The frequency of long-term testing is scheduled at 1, 3, 6, 9, 12, 18, 24, 48 and 60 months. The testing frequency of accelerated condition is scheduled at 1, 2, 3, and 6 months. To confirm the continued stability of the drug substance, Teva has assigned a retest date of (b) (4) from the month the lot was initially tested.

Retest date of (b) (4) when stored at long-term ($5^{\circ} \pm 3^{\circ}\text{C}$) condition is acceptable.

(2) Drug Product

The finished drug product is supplied as a single-use vial containing 4 mL of 1 mg/mL solution. Each mL contains topotecan hydrochloride equivalent to 1 mg of topotecan free base, 12 mg of mannitol, USP, 5 mg of tartaric acid, NF. Sodium Hydroxide and hydrochloric acid may be used to adjust the pH (2.0 to 2.5).

Hycamtin® is the reference listed drug marketed by Glaxo Smith Kline as a sterile lyophilized powder. The applicant's drug product is a sterile solution which is identical to the reconstituted Hycamtin®. However, reconstituted solution of Hycamtin® has a pH of 3.0 whereas applicant's product has a pH of 2.2.

Executive Summary Section

The drug product is manufactured by using conventional manufacturing procedure employed for parenteral preparations which include (b) (4)

The applicant performed stability study following ICH Guidelines for the drug product stored up to 6 months at accelerated condition (25°C/60%RH) and up to 36 months at labeled storage condition (2-8°C at ambient humidity). Three drug product Lots were used for the stability studies. Based on stability data, all three lots showed no significant changes of the stability indicating attributes during 36 months period at 5°C/ambient humidity and at 25°C/60%RH.

Based on stability data including statistical analysis, the applicant proposed a shelf-life of 24 months when stored at 5°C ± 3°C at ambient humidity condition and protected from light. The proposed shelf-life can be granted.

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

Topotecan is a topoisomerase inhibitor indicated for small cell lung cancer sensitive disease after failure of first-line chemotherapy. The recommended dose of topotecan is 1.5 mg/m² by intravenous infusion over 30 minutes daily for 5 consecutive days starting on day 1 of 21 day course.

The drug product is supplied in a single-use vial containing 4 mL of 1 mg/mL solution. Each mL contains topotecan hydrochloride equivalent to 1 mg of topotecan base. The drug product is to be diluted with 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP prior to intravenous infusion.

C. Basis for Approvability or Not-Approval Recommendation***Basis for Approval:***

The sponsor referenced drug substance information in Type II DMF (b) (4) and provided sufficient information on drug product to assure identity, strength, purity, and quality of drug product during the expiration dating period. The applicant provided LOA for DMF (b) (4). The DMF is adequate to support this NDA. All drug substance and drug product facilities have received acceptable site recommendations from the Office of Compliance.

Basis for non-approval:

All labeling issues are pending.

Executive Summary Section

III. Administrative**A. Reviewer's Signature:**

(See appended electronic signature page)

Debasis Ghosh, Ph.D., M. Pharm., Branch 2, DNDQA 1, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Nallaperumal Chidambaram, Ph.D. Acting Branch Chief, Branch 2, DNDQA 1,
ONDQA

C. CC Block: entered electronically in DARRTS

59 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

DEBASIS GHOSH
12/04/2012

NALLAPERUM CHIDAMBARAM
12/04/2012
I concur.



CMC Assessment Section

Appendix 1 EES Report (Summary)

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 22453/000 Sponsor: TEVA PHARMS
Org. Code: 107 1090 HORSHAM RD
Priority: 5 NORTH WALES, PA 19454
Stamp Date: 18-DEC-2008 Brand Name: TOPOTECAN HYDROCHLORIDE INJECTION
PDUFA Date: 25-DEC-2012 Estab. Name:
Action Goal: Generic Name: TOPOTECAN HYDROCHLORIDE INJECTION
District Goal: 26-OCT-2012 Product Number; Dosage Form; Ingredient; Strengths
001; INJECTION; TOPOTECAN HYDROCHLORIDE; 1MG/1ML
FDA Contacts: J. MARTIN Project Manager (HFV-530) 3017962072
Z. TANG Review Chemist 3017964956
L. ZHOU Team Leader 3017961781

Overall Recommendation: ACCEPTABLE on 31-AUG-2012 by R. SAFAAI-JAZI () 3017964463
WITHHOLD on 13-OCT-2009 by FERGUSONS

Establishment: CFN: (b) (4) FEI: (b) (4)
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 31-AUG-2012
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION



CMC Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: 2027158 FEI: 2027158
TEVA PARENTERAL MEDICINES INC

DMF No: IRVINE, , UNITED STATES 926181902 AADA:

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

Profile: STERILE-FILLED SMALL VOLUME PARENTERAL OAI Status: NONE
DRUGS

Last Milestone: OC RECOMMENDATION

Milestone Date: 02-AUG-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Memorandum

To: NDA 22-453
CC: Sue-Ching Lin, M.S., R.Ph.; Debasis Ghosh, Ph.D.; Haripada Sarker, Ph.D.
From: Sarah Pope Miksinski, Ph.D.
Date: 10/14/2009
Re: Final CMC recommendation for NDA 22-453

NDA 22-453 (Topotecan Injection) was initially submitted on 17-DEC-2008 and was granted a standard review by the Agency. Chemistry Review #1 (dated 24-AUG-2009) recommended approval of NDA 22-453 pending the receipt of an overall acceptable recommendation from the Office of Compliance.

This memo serves to update that determination. The Office of Compliance issued an overall withhold recommendation for this application on 13-OCT-2009. Accordingly, from a CMC perspective, approval of NDA 22-453 cannot be recommended until any related deficiencies are resolved.

APPEARS THIS WAY ON ORIGINAL

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22453	ORIG-1	TEVA PARENTAL MEDICINE INC	TOPOTECAN HYDROCHLORIDE INJECTION

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

/s/

Sarah Pope Miksinski
10/14/2009



NDA 22-453

Topotecan Injection

Teva Parenteral Medicines, Inc.

**Debasis Ghosh, Ph.D. (Drug Substance Sections)
Sue-Ching Lin, M.S., R.Ph. (Drug Product Sections)**

**Office of New Drug Quality Assessment
Division of Pre-marketing Assessment and Manufacturing Science
Branch V**

**Chemistry, Manufacturing, and Controls (CMC)
Team Review of Original NDA
For the Division of Drug Oncology Products (HFD-150)**

Table of Contents

CMC Review Data Sheet	4
The Executive Summary	8
I. Recommendations.....	8
A. Recommendation and Conclusion on Approvability	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of CMC Assessments	8
A. Description of the Drug Product(s) and Drug Substance(s).....	8
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation	10
III. Administrative.....	10
CMC Assessment.....	11
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	11
S. DRUG SUBSTANCE.....	11
S.1 General Information	11
S.1.1 Nomenclature.....	11
S.1.2 Structure.....	11
S.1.3 General Properties.....	12
S.2 Manufacture	14
S.2.1 Manufacturers	14
S.2.2 Description of Manufacturing Process and Process Controls.....	14
S.2.3 Control of Materials.....	15
S.2.4 Controls of Critical Steps and Intermediates.....	15
S.2.5 Process Validation and/or Evaluation	16
S.2.6 Manufacturing Process Development	16
S.3 Characterization	16
S.3.1 Elucidation of Structure and other Characteristics	16
S.3.2 Impurities.....	16
S.4 Control of Drug Substance.....	19
S.4.1 Specification	19
S.4.2 Analytical Procedures	21
S.4.3 Validation of Analytical Procedures	26
S.4.4 Batch Analyses	36
S.4.5 Justification of Specification.....	38
S.5 Reference Standards or Materials	39
S.6 Container Closure System.....	42
S.7 Stability	42
S.7.1 Stability Summary and Conclusions	42
S.7.2 Postapproval Stability Protocol and Stability Commitment.....	42
S.7.3 Stability Data	42
P. DRUG PRODUCT	43
P.1 Description and Composition of the Drug Product.....	43

P.2	Pharmaceutical Development.....	43
P.2.1	Components of the Drug Product.....	44
P.2.1.1	Drug Substance.....	44
P.2.1.2	Excipients.....	44
P.2.2	Drug Product.....	45
P.2.2.1	Formulation Development.....	45
P.2.2.2	Overages.....	45
P.2.2.3	Physicochemical and Biological Properties.....	45
P.2.3	Manufacturing Process Development.....	46
P.2.4	Container Closure System.....	47
P.2.5	Microbiological Attributes.....	48
P.2.6	Compatibility.....	49
P.3	Manufacture.....	51
P.3.1	Manufacturers.....	51
P.3.2	Batch Formula.....	51
P.3.3	Description of Manufacturing Process and Process Controls.....	52
P.3.4	Controls of Critical Steps and Intermediates.....	55
P.3.5	Process Validation and/or Evaluation.....	57
P.4	Control of Excipients.....	57
P.4.1	Specifications.....	57
P.4.2	Analytical Procedures.....	59
P.4.3	Validation of Analytical Procedures.....	59
P.4.4	Justification of Specifications.....	59
P.4.5	Excipients of Human or Animal Origin.....	59
P.4.6	Novel Excipients.....	60
P.5	Control of Drug Product.....	61
P.5.1	Specification.....	61
P.5.2	Analytical Procedures.....	63
P.5.3	Validation of Analytical Procedures.....	64
P.5.4	Batch Analyses.....	64
P.5.5	Characterization of Impurities.....	66
P.5.6	Justification of Specification.....	67
P.6	Reference Standards or Materials.....	70
P.7	Container Closure System.....	71
P.8	Stability.....	74
P.8.1	Stability Summary and Conclusion.....	74
P.8.2	Postapproval Stability Protocol and Stability Commitment.....	76
P.8.3	Stability Data.....	78
A.	APPENDICES.....	81
A.1	Facilities and Equipment (biotech only).....	81
A.2	Adventitious Agents Safety Evaluation.....	81
A.3	Novel Excipients.....	81
R.	REGIONAL INFORMATION.....	81
R1	Executed Batch Records.....	81
R2	Comparability Protocols.....	81
R3	Methods Validation Package.....	81
II.	Review Of Common Technical Document-Quality (Ctd-Q) Module 1.....	82
A.	Labeling & Package Insert.....	82
B.	Environmental Assessment Or Claim Of Categorical Exclusion.....	92
III.	E-mail Correspondences.....	92
IV.	List Of Deficiencies Communicated and Resolved.....	96

CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 22-453
2. REVIEW #: 1
3. REVIEW DATE: 24-Aug-2009
4. REVIEWER:
Debasis Ghosh, Ph.D. (Drug Substance Sections)
Sue-Ching Lin, M.S., R.Ph. (Drug Product Sections)
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 103,440 submission	N/A*
Pre-NDA meeting	14-Nov-2008

*The sponsor did not submit an original IND. The first submission for this IND was the meeting request for the 11/14/08 pre-NDA meeting

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	DARRTS Supp Document #
Original NDA Submission	17-Dec-2008	1
Amendment (BL) (Revised package insert, container and carton labeling)	08-May-2009	2
Amendment (BI) (Microbiology amendment)	21-May-2009	3
Amendment (BZ) (Microbiology response and revised life cycle format in CTD for labeling)	16-Jun-2009	4
Amendment (Response to 7/10/09 CMC IR)	24-Jul-2009	5
Administrative amendment (Correction to show "replaced files" in e-CTD, no content change.)	05-Aug-2009	6
Amendment (updated stability data)	14-Aug-2009	7
Amendment (revised PI labeling accepting all changes proposed by FDA)	24-Aug-2009	8

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Teva Parenteral Medicines, Inc.
Address: 19 Hughes, Irvine, CA 92618
Representative: Susan O'Brien, Director, Regulatory Affairs
Telephone: 949-455-4724

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
- b) Non-Proprietary Name: topotecan injection
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 5 (new formulation)
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

Reference Listed Drug: NDA 20-671, Hycamtin, by GlaxoSmithKline
(Hycamtin is supplied as a sterile lyophilized powder. Each vial contains topotecan hydrochloride equivalent to 4 mg of topotecan free base.)

10. PHARMACOL. CATEGORY: antineoplastic

11. DOSAGE FORM: injection, solution

12. STRENGTH/POTENCY: 1 mg/mL (The drug product strength is based on the equivalent amount of topotecan free base.)

13. ROUTE OF ADMINISTRATION: intravenous infusion

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

CMC Review Data Sheet

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

Chemical structure	<p>Note: x=1.0-1.5</p>
Molecular formula	C ₂₃ H ₂₃ N ₃ O ₅ · x HCl (x= 1.0-1.5)
Molecular weight	457.91 g/mol
United States Adopted Name (USAN)	topotecan hydrochloride
Chemical name	(S)-10-[(Dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione hydrochloride
Chemical Abstracts Service (CAS) registry number	119413-54-6

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Topotecan hydrochloride	1	Adequate	06-Aug-2009	Reviewed by Debasis Ghosh
	III	(b) (4)		4	N/A	Date of this review	See section 3.2.P.7
	III	(b) (4)		3 & 4	Adequate	14-Oct-2008	Reviewed by Donald Klein
		(b) (4)		4	N/A	Date of this review	See section 3.2.P.7

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)



CMC Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	103,440	Submitted for pre-NDA meeting
NDA	20-671	Hycamtin for Injection (Reference Listed Drug)
NDA	20-981	Hycamtin Capsules

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending	Pending	Pending
Pharm/Tox	(b) (4) are qualified*.	See DARRTS for review*	William D McGuinn
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA**	The applicant does not propose a proprietary name. DMEPA reviewed container carton labeling only.	7/9/09	Carlos M Mena-Grillasca
EA	No significant environmental impact	5/19/09	Raanan Bloom
Microbiology	Approval from microbiology product quality standpoint	7/13/09	Denise Miller

* Dr. McGuinn informed the CMC reviewers in a 3/23/09 e-mail that (b) (4) are qualified. See Dr. McGuinn's e-mail on page 92 of this review, under the heading of "E-mail correspondences." As of the date of this review, the pharm/tox review is not in DARRTS yet.

**DMEPA: Division of Medication Error Prevention and Analysis

The CMC Review for NDA 22-453

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the perspective of chemistry, manufacturing, and controls, this NDA may be approved, pending an "acceptable" overall recommendation from the Office of Compliance.

Based on the provided stability data, a 12-month expiration dating period is granted for the drug product when stored under the proposed refrigerated condition.

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

None

II. Summary of CMC Assessments

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

(1) Drug Substance

The drug substance, topotecan hydrochloride, is a hygroscopic salt. It has a molecular weight of 457.91 g/mol. It is (b) (4) a yellow-orange powder. It is freely soluble in water: (b) (4)
(b) (4) It melts at 213-216°C. Its aqueous solution (1 mg/mL) has a pH of (b) (4)

Detailed information on the drug substance is referenced to DMF (b) (4) which was reviewed on August 6, 2009 and found to be adequate.

The Applicant and the drug substance manufacturer (b) (4) provided independent analytical results to verify and support the quality of the drug substance. All non-compendial analytical procedures have been validated for acceptance. The Applicant provided information on the reference standards including the certificates of analysis.

Executive Summary Section

(2) Drug Product

The finished drug product, topotecan injection, is supplied as a sterile clear light yellow to greenish solution. It is available in one single-dose size: 4 mL fill in a glass vial. Each mL contains topotecan hydrochloride (equivalent to 1 mg of topotecan free base), 12 mg of mannitol, USP, and 5 mg of tartaric acid, NF. Hydrochloric acid and sodium hydroxide may be used to adjust the pH. The solution pH ranges from 2.0 to 2.5.

The referenced listed drug for this NDA is Hycamtin[®] for Injection (NDA 20-671) by GlaxoSmithKline. Hycamtin[®] is supplied as a sterile lyophilized powder. Teva's drug product proposed in this NDA, which is a solution, has identical composition to GlaxoSmithKline's reconstituted Hycamtin[®] with the exception of pH. The pH of Teva's formulation was developed to be 2.2 (2.0-2.5) for finished drug product to ensure physical and chemical stability of the liquid formulation, whereas Hycamtin[®] has a pH of 3.0 (2.5-3.0) upon reconstitution.

The drug product is manufactured by (b) (4)

(b) (4) The drug substance is light sensitive and (b) (4)

procedure such as manufacturing under reduced lighting/yellow light and weighing and dispensing the drug substance inside a safety isolator. Due to the hygroscopic nature of the drug substance, the drug substance container must be opened and closed (b) (4)

The submitted stability data include 12 months of data for the drug product stored under 5°C, 25°C/60% RH, and 30°C/65%RH. The stability study at 40°C/75%RH was discontinued after 3 months due to significant degradation. It is apparent that the rate of degradation accelerates with the increase in storage temperature. Based on the provided stability data, a 12-month expiration dating period is granted for the drug product stored under the proposed refrigerated condition, i.e., store the vials protected from light in the original carton, refrigerated between 2°C and 8°C (36 and 46°F).

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

The drug product, topotecan injection, is indicated for the treatment of (b) (4) carcinoma of small cell lung cancer sensitive disease after failure of first-line chemotherapy. Topotecan injection in combination with cisplatin is indicated for the treatment of stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy.

The drug product is intended for dilution with 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP prior to intravenous infusion.

Executive Summary Section

The recommended dose for the treatment of small cell lung cancer is 1.5 mg/m² by intravenous infusion over 30 minutes daily for 5 consecutive days, starting on day 1 of a 21-day course. The recommended dose for the treatment of cervical cancer is 0.75 mg/m² by intravenous infusion over 30 minutes daily on days 1, 2, and 3; followed by cisplatin 50 mg/m² by intravenous infusion on day 1 repeated every 21 days (a 21-day course).

C. Basis for Approvability or Not-Approval Recommendation

The CMC information of the drug substance was referenced to DMF (b) (4) which was reviewed on August 6, 2009 and found to be adequate.

All the inactive ingredients are USP/NF materials. Adequate data have been provided to ensure the quality of the drug substance and drug product. The microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective.

The applicant does not propose a proprietary name for this drug product. The CMC revisions of the package insert have been incorporated into the revised labeling during the labeling meetings of the NDA. This reviewer had shared the labeling comments regarding container labels and carton labeling with the DMEPA reviewers before the labeling comments were conveyed to the applicant on July 10, 2009. The revised container labels and carton labeling, as amended by the applicant on July 24, 2009, are acceptable.

The inspection for the drug product manufacturing facility is still pending. This NDA is recommended for approval pending an "acceptable" overall recommendation from the Office of Compliance.

III. Administrative**A. Reviewer's Signature:**

(See appended electronic signature page)

Debasis Ghosh, Ph.D., Reviewer, ONDQA
Sue-Ching Lin, M.S., R.Ph., Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Sarah Pope Miksinski, Ph.D., Branch Chief, Branch V, ONDQA

C. CC Block: entered electronically in DARRTS

89 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22453	ORIG 1	TEVA PARENTAL MEDICINE INC	TOPOTECAN HYDROCHLORIDE INJECTION
NDA 22453	ORIG 1	TEVA PARENTAL MEDICINE INC	TOPOTECAN HYDROCHLORIDE INJECTION
NDA 22453	ORIG 1	TEVA PARENTAL MEDICINE INC	TOPOTECAN HYDROCHLORIDE INJECTION
NDA 22453	ORIG 1	TEVA PARENTAL MEDICINE INC	TOPOTECAN HYDROCHLORIDE INJECTION
NDA 22453	ORIG 1	TEVA PARENTAL MEDICINE INC	TOPOTECAN HYDROCHLORIDE INJECTION
NDA 22453	ORIG 1	TEVA PARENTAL MEDICINE INC	TOPOTECAN HYDROCHLORIDE INJECTION
NDA 22453	ORIG 1	TEVA PARENTAL MEDICINE INC	TOPOTECAN HYDROCHLORIDE INJECTION
NDA 22453	ORIG 1	TEVA PARENTAL MEDICINE INC	TOPOTECAN HYDROCHLORIDE INJECTION

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

/s/

SUE CHING LIN

08/27/2009

DEBASIS GHOSH

08/27/2009

Sarah Pope Miksinski

08/28/2009

**Initial Quality Assessment
Branch V
Pre-Marketing Assessment Division III**

OND Division: Division of Drug Oncology Products
NDA: 22-453
Applicant: Teva Parenteral Medicines, Inc.
Letter Date: 17 December, 2008
Stamp Date: 18 December, 2008
PDUFA Goal Date: 18 October, 2009
Trade name: Not proposed
Established Name: Topotecan Hydrochloride Injection
Dosage Form: Injection -- 1 mg base/mL
Route of Administration: IV
Indication: Small cell lung cancer sensitive disease after failure of first-line chemotherapy; Topotecan Hydrochloride Injection in combination with cisplatin is indicated for the treatment of stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy.

Application format Electronic format as an eCTD

Regulatory Filing Related IND For 505 (b) (2)
IND 103,440

Assessed by: Haripada Sarker

Yes No

ONDQA Fileability: x

Comments for 74-Day Letter: x

Summary

The application introduces Topotecan Hydrochloride Injectable solution (1 mg base/mL) by Teva Parenteral Medicines, Inc. Teva utilizes GlaxoSmithKline's Hycamtin® as the previously approved drug under NDA 20-671 and intend to rely on the Agency's previous finding of safety and effectiveness for this drug product. The reference listed drug (RLD), Hycamtin was manufactured as a lyophilized powder and is available in 4 mg single-dose vials. Topotecan Hydrochloride Injection has the same active and inactive ingredients, strength, and route of administration as RLD, however, differ in formulation. A Pre-NDA meeting was held on November 14, 2008 to discuss the regulatory requirements for filing and approval of Topotecan Hydrochloride Injection. Several CMC

questions were discussed along with other issues. The CMC information of the NDA is submitted as per CTDQ format.

Drug Substance (DS)

Teva referred all the CMC information for Topotecan Hydrochloride DS to Type II DMF (b)(4) by (b)(4). Topotecan Hydrochloride is derived from naturally occurring (b)(4).

Applicant provided a summary of DS CMC information in the NDA. The complete manufacturing process is described in Type II DMF (b)(4) for Topotecan Hydrochloride drug substance. DMF (b)(4) is updated, and LOA has been provided. Teva has developed in-house specifications for Topotecan Hydrochloride drug substance in a collaborative effort with DS supplier, (b)(4). Request has been made to office of compliance to provide inspection report for the DS related sites listed in the submission.

DS Critical Issues

- Type II DMF (b)(4) needs to be reviewed, and also to find any change since last review.
- Closer examination of impurities at release and stability of DS is essential to set the retest period.
- Appropriate control on DS starting material is required, since the DS is derived by functional modification of backbone moiety, (b)(4).

Drug Product (DP)

The DP, Topotecan Hydrochloride is an injectable sterile solution manufactured and controlled by Teva Parenteral Medicines, Inc. It is available in one single-dose size: 4 mL fill in a 6-mL glass vial. Each mL of the product solution contains Topotecan Hydrochloride (equivalent to 1 mg Topotecan free base), 12 mg of mannitol, USP, and 5 mg of tartaric acid, NF. The pH of the drug product is adjusted to pH 2.2 (range 2.0 to 2.5) with sodium hydroxide or hydrochloric acid. All the excipients used in drug product manufacture have standard compendial monograph. The DP finished product is diluted with normal saline or 5% dextrose prior to administration.

Several CMC issues were discussed in pre-NDA meeting dated November 14, 2008. Acceptance criterion for (b)(4) in DP specification is proposed to be (b)(4)%; however this compound is not detected in the exhibited stability lots at release (ref. Table 2.3.P.5-3). In the pre-NDA meeting applicant indicated that it would be difficult to obtain API from the RLD supplier. The agency acknowledged and suggested that the sponsor provide any additional information on impurity profiles of drug substance and drug product ICHQ3 guidelines. FDA confirmed that the overall acceptability of the impurity profile of the drug substance is a review issue.

Applicant proposes 24-months shelf-life based on 6 months real time and accelerated stability data on 3 registration batches. Based on best practice, the maximum possible DP shelf-life in this case is (b)(4) provided there is no out of specification results in any of the stability data. Note that (b)(4) (w)(4) expiry is considered a minimum for commercial viability.

DP Critical Issues

- DP shelf-life of 24-months based on 6 months real time and accelerated stability data can't be justified from data provided.
- Make sure that all the pre-NDA CMC commitments are addressed in this NDA submission.
- DP impurity profile should be justified as per ICHQ3B.
- Verify the EES for accuracy.
- There was no M4 (pharm./tox.) section in the electronic submission.

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?		√	Requested 24-months DP shelf-life based on 6 months stability data..
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)	√ √ √ √ √		Microbiology Pharm/Tox Biopharm Statistics (stability) OCP/CDRH/CB ER LNC DMETS/ODS EER

Have all DMF References been identified? Yes (✓) No ()

DMF Number	Holder	Description	LOA Included
(b) (4)	(b) (4)	Topotecan Hydrochloride DS	Yes
		(b) (4)	Yes
		(b) (4)	Yes

Comments and Recommendations

The application is fileable, however, we will have comment regarding proposed shelf-life in 74-Day Letter. Facilities have been entered into EES for inspection. A single reviewer is recommended for this NDA, since the manufacturing process is not particularly complex.

Comment for 74-days letter:

1. Six months of stability data is not adequate (in terms of duration) to support the proposed drug product shelf-life of 24-months. Based on the data provided, the maximum possible shelf-life that may be considered based on this paucity of data is (b) (4) if all of the data (6 months long-term and 6 months accelerated) are acceptable. This is a review issue.
2. It is noted that only labeling text is submitted for the container label and carton labeling. Therefore, submit container label and carton labeling in mock-up format that is proposed for marketed product.

Haripada Sarker
Pharmaceutical Assessment Lead (PAL)

February 17, 2009
Date

Richard T. Lostritto, Ph.D.
Division Director

February 17, 2009
Date

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

/s/

Haripada Sarker
2/17/2009 02:21:11 PM
CHEMIST

Two comments for 74-day letter

Richard Lostritto
2/17/2009 03:31:02 PM
CHEMIST