

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203585Orig1s000**

**CHEMISTRY REVIEW(S)**

ONDQA Division Director's Memo  
NDA 203585, SYNRIPO, 3.5 mg/vial  
Date: 05-OCT-2012

## **Introduction**

SYNRIBO (omecetaxine mepesuccinate) is a lyophilized powder for injection, intended for subcutaneous injection following reconstitution with 0.9% Sodium Chloride Injection, USP. Each vial contains 3.5 mg of omezetaxine mepesuccinate and (b) (4) mannitol USP. (b) (4)

The recommended dose of SYNRIPO includes induction and maintenance. Please see the Medical Officer's 02-SEP-2012 review for specific dosing details. The proposed indication is "treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia with resistance and/or intolerance to prior tyrosine kinase inhibitors."

All CMC-related deficiencies have been resolved for this application, and all related reviews are complete. There are no outstanding deficiencies that would preclude a recommendation of approval from a CMC standpoint.

***ONDQA recommends approval of this NDA. There are no pending deficiencies from a CMC standpoint.***

## **Administrative**

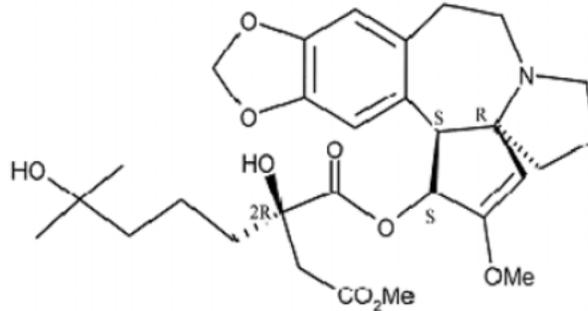
The original submission of this 505(b)(1) NDA was received 30-MAR-2012 from Cephalon, Inc. Ten (10) CMC amendments were also reviewed during the review cycle. All Chemistry, Manufacturing and Controls assessment is captured in the following reviews, respectively: Chemistry Review #1 (07-SEP-2012, Dr. D. Ghosh) and Biopharmaceutics Review #1 (04-SEP-2012, Dr. E. Chikhale).

The NDA is supported by IND 62,384 and three (3) drug master files (DMFs). An overall "acceptable" recommendation was issued in EES (04-SEP-2012), and acceptable container/carton labeling was received on 06-SEP-2012. The Office of Microbiology recommended approval of the NDA (30-AUG-2012, Dr. E. Pfeiler). The application was consulted for an OPS Environmental Assessment review, and received a finding of "no significant impact" on 30-JUL-2012 (see Environmental Assessment review by R. Bloom). The Applicant's proposed trade name (SYNRIBO) was granted by DMEPA in a letter dated 27-SEP-2012.

***This NDA is recommended for approval from a Chemistry, Manufacturing and Controls standpoint. Confirmatory language regarding the expiration dating period is found at the end of this memorandum and should be inserted into the approval letter.***

## Drug Substance (omecetaxine mepesuccinate)

Chemical Name: Cephalotaxine, 4-methyl (2R)-2-hydroxy-2-(4-hydroxy-4-methylpentyl) butanedioate (ester) (MW=545.6 g/mol, C<sub>29</sub>H<sub>39</sub>NO<sub>9</sub>)



Omecectaxine mepesuccinate is a new molecular entity. It exists as a white to off-white crystalline powder at room temperature and contains four chiral centers. Omecectaxine mepesuccinate is manufactured via a semi-synthetic process from a plant-derived material, and the manufacturing process is cross-referenced to a Type 2 DMF (20542). The compound is soluble in acidic pH conditions. Omecectaxine mepesuccinate is relatively stable, and no extraordinary storage precautions are required other than standard protection from moisture and light. The proposed re-test period (b) (4) when stored in the recommended container closure system (protected from light and moisture) at ambient storage conditions was confirmed as acceptable in the CMC review.

## Drug Product (omecetaxine mepesuccinate for injection, 3.5 mg/vial)

Omecectaxine mepesuccinate for injection, 3.5 mg, is supplied as a white to off-white lyophilized powder in 8 mL (b) (4) clear glass single-use vial (b) (4). It is to be reconstituted with 1.0 mL of 0.9% Sodium Chloride Injection, USP, prior to administration by subcutaneous injection. Each vial contains 3.5 mg of omecectaxine mepesuccinate, (b) (4) mannitol USP, (b) (4)

The container closure system is an 8-mL (b) (4) clear glass vial (b) (4). The primary packaging components are compatible with the product, and the adequacy of the materials for the intended use was confirmed during the CMC review (see Chemistry Review #1).

According to the 07-SEP-2012 Chemistry Review, the Applicant's primary stability data package did not adequately support the proposed (b) (4) expiration dating period. The Chemistry Review grants an 18-month expiration dating period for the drug product, when stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C, and protected from light.

*Due to the Agency's disagreement with the proposed expiration dating period, the following confirmatory language is needed in the approval letter:*

*“Based on the provided stability data, an 18-month expiration dating period is granted for the drug product, when stored at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C; and protected from light.”*

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/s/  
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SARAH P MIKSINSKI  
10/05/2012

# **NDA 203585**

**SYNRIBO™**  
**(omacetaxine mepesuccinate) for Injection**  
**3.5 mg/vial**

**IVAX International GmbH, Switzerland**  
**(a wholly owned subsidiary of Teva Pharmaceuticals)**

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

**Review Chemist**

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

**CMC REVIEW OF NDA 203585**  
**For the Division of Drug Oncology Products (HFD-150)**

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CMC Review Data Sheet

# CMC Review Data Sheet

1. NDA 203585
2. REVIEW #: 1
3. REVIEW DATE: 07-Sep-2012
4. REVIEWER: Debasis Ghosh, Ph.D., M. Pharm.
5. PREVIOUS DOCUMENTS:

| <b>Previous Documents</b>  | <b>Document Date</b> |
|--|----------------------|
| Original IND 062384 submission                                   | 13-Apr-2001          |
| CMC review of Original IND 062384 by Li Shan Hsieh               | 07-May-2001          |
| Preliminary Response to meeting (Sep 13, 2010) Request IND 62384 | 10-Sep-2010          |
| EOP2 Meeting IND 62384   | 27-Jun-2007          |
| Pre-NDA Meeting IND 62384  | 04-Nov-2008          |
| NDA 22374 Original Submission                                    | 08-Sep-2009          |
| CMC Review of NDA 22374 by Sue-Ching Lin and Brian Rogers        | 30-Mar-2010          |
| Pre-NDA Type B Meeting (Sep 13, 2010) Minutes IND 62384          | 28-Sep-2010          |

6. SUBMISSION(S) BEING REVIEWED:

| <b>Submission(s)<br/>Reviewed</b> | <b>DARRTS</b> | <b>Description</b>   | <b>Document<br/>Date</b> |
|-----------------------------------|---------------|--|--------------------------|
| NDA 203585 Original               | SD 0000       | eCTD NDA application                                       | 30-Mar-2012              |
| Amendment (SR 0010)               | SD 0005       | Establishment Information                                  | 11-May-2012              |
| Amendment (SR 0012)               | SD 0013       | Response to Information Request                            | 04-Jun-2012              |
| Amendment (SR 0016)               | SD 0017       | Response to Information Request                            | 29-Jun-2012              |
| Amendment (SR 0018)               | SD 0019       | Response to Information Request                            | 09-Jul-2012              |
| Amendment (SR 0023)               | SD 0024       | New Facility Information for Drug<br>Product Manufacturing | 10-Aug-2012              |
| Amendment (SR 0024)               | SD 0025       | Labeling   | 15-Aug-2012              |
| Amendment (SR 0025)               | SD 0026       | Sponsor Name Change  | 21-Aug-2012              |
| Amendment (SR 0026)               | SD 0027       | Response to Information Request                            | 22-Aug-2012              |
| Amendment (SR 0027)               | SD 0028       | Response to Information Request                            | 31-Aug-2012              |
| Amendment (SR 0028)               | SD 0029       | Labeling   | 06-Sep-2012              |

CMC Review Data Sheet

**7. NAME & ADDRESS OF APPLICANT:**

*Submitted in the original application:*

Name: Cephalon, Inc (a wholly owned subsidiary of Teva Pharmaceuticals)  
 Address: 41 Moore Road, P.O. Box 4011, Frazer, PA 19355  
 Representative: Carol Marchione, Sr Director and Group Leader  
 Telephone: (610) 738-6237

*Updated information submitted as an Amendment (SR 0025) on 21-Aug-2012:*

|  |   |
|--|---|
| <p><b>Applicant Name on File:</b><br/>Cephalon Inc.</p>  | <p><b>New Applicant Name and Address:</b><br/>IVAX International GmbH<br/><br/>Alpenstrasse 2<br/>8640 RAPPERSWIL, SWITZERLAND</p>  |
| <p><b>Contact information:</b><br/>Carol Marchione<br/>Senior Director<br/>Head of Global Oncology Regulatory Affairs<br/>Phone: (610) 783-6237<br/>Fax: 610-738-6311<br/>Email: carol.marchione@tevapharm.com</p> | <p><b>US Agent and Contact Information:</b><br/>Teva Branded Pharmaceutical Products R&amp;D, Inc.<br/><br/>Carol Marchione<br/>Senior Director<br/>Head of Global Oncology Regulatory Affairs<br/>Phone: 610-786-7205<br/>Fax: 610-738-6311<br/>Email: carol.marchione@tevapharm.com</p> |

**8. DRUG PRODUCT NAME/CODE/TYPE:**

- a) Proprietary Name: SYNRIBO™ (proposed; under review)
- b) Non-Proprietary Name: omacetaxine mepesuccinate
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 1 (New Molecular Entity)
  - Submission Priority: P (Priority)

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

**10. PHARMACOL. CATEGORY: Anticancer**

**11. DOSAGE FORM: Lyophilized powder for injection**

**12. STRENGTH/POTENCY: 3.5 mg/vial**

## CMC Review Data Sheet

13. ROUTE OF ADMINISTRATION: Subcutaneous injection

14. Rx/OTC DISPENSED:  Rx  OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

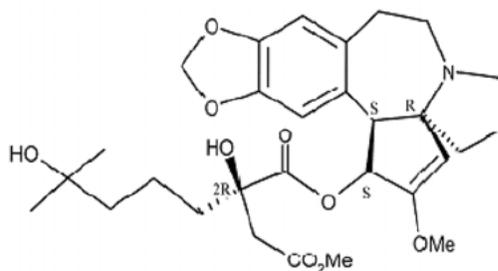
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

**USAN:** Omacetaxine mepesuccinate

**Chemical Name:** Cephalotaxine, 4-methyl (2*R*)-2-hydroxy-2-(4-hydroxy-4-methylpentyl) butanedioate (ester)

**CAS#** 26833-87-4

**Structural Formula:**



**Molecular Formula:** C<sub>29</sub>H<sub>39</sub>NO<sub>9</sub>

**Molecular Weight:** 545.6 g/mol

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF #   | TYPE | HOLDER/ LOA                   | ITEM REFERENCED  | CODE <sup>1</sup> | STATUS <sup>2</sup> | DATE REVIEW COMPLETED           | COMMENTS  |
|---------|------|-------------------------------|--|-------------------|---------------------|---------------------------------|---|
| 20542   | II   | Stragen Pharma<br>15-Oct-2011 | Omacetaxine mepesuccinate (Homoharringtonine) drug substance CMC information | 1                 | Adequate            | 06-Jul-2012                     | The DMF is active. The original DMF was reviewed by Sue Ching Lin on 08-Mar-2010 and the recent updates were reviewed by Debasis Ghosh. The DMF is adequate.  |
| (b) (4) |      |                               |  | 3                 | Adequate            | Micro: 09-Dec-2011              | The DMF is active. It was reviewed by Steven P Donald (b) (4) and found to be adequate.   |
|         |      |                               |  | 4                 | Adequate            | Quality: See P.7 of this review | The DMF was last reviewed by Ravindra K Kasliwal on 11-Jul-2012 and found to be adequate (b) (4). However, the adequacy (b) (4) for omacetaxine mepesuccinate injection was reviewed by Brian Rogers in NDA 22374 on 30-Mar-2010 and found to be adequate. The applicant provided adequate information in the submission which was reviewed by this reviewer to establish adequacy. |
|         |      |                               |  | 3                 | Adequate            | 16-Aug-2010                     | The DMF is active. It was last reviewed by Sheldon B. Markofsky for (b) (4) Glass and found to be adequate. Since then no Amendment is provided in the DMF.   |

CMC Review Data Sheet

<sup>1</sup> 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")

<sup>2</sup> 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      | 62384              | Clinical Studies were conducted under this IND for omacetaxine mepesuccinate for injection which was submitted on 13-Apr-2001   |
| NDA      | 22374              | The applicant proposed 5 mg/vial formulation under this NDA for omacetaxine mepesuccinate for injection which was submitted on 08-Sep-2009. The application was not approved by the Agency. |

CMC Review Data Sheet

18. STATUS:

**ONDQA:**

| <b>CONSULTS/ CMC RELATED REVIEWS</b> | <b>RECOMMENDATION</b>   | <b>DATE</b> | <b>REVIEWER</b>                 |
|--------------------------------------|---|-------------|---------------------------------|
| Biometrics                           | 'no formal statistical conclusions can be made'. See Review in DARRTS | 05-Sep-2012 | Chia-Wen Ko                     |
| EES                                  | 'Overall Acceptable'  | 04-Sep-2012 | D. Smith                        |
| Pharm/Tox                            | 'Recommended for approval'  | 05-Sep-2012 | M. S. Ricci                     |
| Biopharm                             | 'Recommended for approval'  | 04-Sep-2012 | Elsbeth G Chikhale              |
| LNC                                  | N/A   | N/A         | N/A                             |
| Methods Validation                   | "Methods are acceptable for control and regulatory purposes"          | 01-Aug-2012 | Michael Treahy, MVP Coordinator |
| DMEPA*                               | See Reviews in DARRTS   | N/A         | Sarah K Vee                     |
| Environmental Assessment             | A Finding of No Significant Impact (FONSI)                            | 30-Jul-2012 | Raanan A. Bloom                 |
| Microbiology                         | 'Recommended for approval'  | 30-Aug-2012 | Erika A Pfeiler                 |

\*DMEPA: Division of Medication Error Prevention and Analysis

## Executive Summary Section

# The CMC Review for NDA 203-585

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An 'Overall Acceptable' site recommendation from the Office of Compliance has been made. From the CMC perspective, this NDA is recommended for approval pending the 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 active ingredient, omacetaxine, is a new molecular entity provided as a mepesuccinate ester. Omacetaxine is a protein synthesis inhibitor indicated for the treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia (CMC) with resistance and or intolerance to tyrosine kinase inhibitor (TKI). The molecular formula of omacetaxine mepesuccinate is  $C_{29}H_{39}NO_9$  with a molecular weight of 545.6 g/mol. It is a white to off-white crystalline powder and soluble in acidic pH. It contains four chiral centers. It is manufactured by a semi-synthetic process from a plant derived material, Cephalotaxine. Detailed information regarding the drug substance is referenced to DMF 20542. A letter of authorization from the DMF holder Stragen Pharma S.A. to cross-reference this DMF information is provided. This Type II DMF 20542 was reviewed and found to be adequate to support this NDA.

The impurity profile of drug substance and the acceptance criteria is provided in the submission. However, the control strategies to limit the impurities are provided in the DMF 20542. The drug substance specification is adequate to ensure quality of drug substance. It has been noted that the specification at release and stability are identical.

Drug substance stability is referenced to DMF 20542. The drug substance is sensitive to light. Based on the stability data, all stability testing results for the primary registration lots of

## Executive Summary Section

omacetaxine mepesuccinate drug substance remained within the current specification criteria through 36 months storage at both the 5°C and 25°C/60%RH conditions and through 6 months storage at the 40°C/75%RH condition.

**The proposed retest period (b) (4) when stored at 5°C or 25°C/60%RH and protected from light is acceptable.**

**(2) Drug Product**

Omacetaxine mepesuccinate for injection, 3.5 mg, is supplied as a white to off-white lyophilized powder in 8 mL (b) (4) clear glass single-use vial (b) (4). It is to be reconstituted with 1.0 mL of 0.9% Sodium Chloride Injection, USP, prior to administration by subcutaneous injection. Each vial contains 3.5 mg of omacetaxine mepesuccinate, (b) (4) mannitol USP, (b) (4)

The drug product release and stability specifications are same. The acceptance criteria for the quality indicating attributes including impurity profiles are acceptable. The analytical methods are validated by the applicant and assay, impurity and identification methods are also checked by FDA laboratories at St. Louis. See Method validation report in DARRTS. For the adequacy of microbiological attributes, see microbiology review.

The container closure system for omacetaxine mepesuccinate for injection 3.5 mg is a 8 mL molded (b) (4) clear glass vial (b) (4). The primary packaging components are compatible with the product and adequacy of the materials for the intended use is provided.

The applicant provided long-term (25°C/60%RH) and accelerated (40°C/75%RH) stability data for 3.5 mg strength (proposed commercial product) and supportive data from 5 mg strength (used for clinical study). When reporting long-term stability at 25°C/60%RH, the applicant provided 18 months data on one primary batch and 12 months data on two primary batches. Accelerated stability data for 6 months for all three primary batches were provided. For supportive batches (5 mg strength), long-term stability for 48 months for one batch and 24 months for two other batches were provided. All of the stability indicating attributes (listed above) met specification for both accelerated and long-term conditions during the period tested. No significant changes were found in any of the above conditions.

The photostability study was conducted on one batch in accordance with ICHQ1B. The results show that light exposed samples in the immediate container showed a drop in assay value and a

## Executive Summary Section

large increase of impurities including a drop in pH. In addition, the product is found to be degraded in [REDACTED] (b) (4) conditions.

The drug product is to be reconstituted with 0.9% Sodium Chloride for Injection USP before the subcutaneous administration. [REDACTED] (b) (4)

**The proposed shelf-life [REDACTED] (b) (4) is not acceptable. See Sec P.8 for a detailed evaluation.**

**Based on the submission, for omacetaxine mepesuccinate for injection, the shelf-life of 18 months when stored at 20°C to 25°C (68°F to 77°F) excursions permitted to 15°C to 30°C (59°F to 86°F) and protected from light can be granted.**

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

Omacetaxine mepesuccinate for Injection is supplied in a single-use vial containing 3.5 mg omacetaxine mepesuccinate as lyophilized powder. The product must be reconstituted with 1.0 mL of 0.9% Sodium Chloride USP to a clear solution prior to subcutaneous injection by gently swirling the contents for about a minute. After inspecting the solution for particulate matter and discoloration, the required amount (see prescribed dose in the package insert) of reconstituted solution (3.5 mg/mL) should be withdrawn from the vial for subcutaneous administration. After administration, any unused solution should be discarded properly.

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

#### ***Approvability:***

- The sponsor has provided sufficient information on raw material controls, manufacturing process and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.
- An 'Overall Acceptable' site recommendation from the Office of Compliance has been made.

#### ***Non-Approvability:***

- The deficiencies of the label information has not been addressed as of the date of this review.

## Executive Summary Section

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

*(See appended electronic signature page)*

Debasis Ghosh, Ph.D., M. Pharm.  
Reviewer  
Branch II, DNDQA I,  
ONDQA, CDER

**B. Endorsement Block:**

*(See appended electronic signature page)*

Nallaperumal Chidambaram, Ph.D.  
Acting Branch Chief  
Branch II, DNDQA I,  
ONDQA, CDER

**C. CC Block:** entered electronically in DFS

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/s/  
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DEBASIS GHOSH

09/07/2012

Please note that the proposed alternative tradename SYNRIPO is under review by DMEPA, however, CMC has no objection to this tradename.

NALLAPERUM CHIDAMBARAM

09/10/2012

I concur



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

**METHODS VALIDATION REPORT SUMMARY**

**TO:** Debasis Ghosh, CMC Reviewer  
Office of New Drug Quality Assessment (ONDQA)  
E-mail Address: debases.ghosh@fda.hhs.gov  
Phone: (301)-796-4093  
Fax: (301)-796-9745

**FROM:** FDA  
Division of Pharmaceutical Analysis  
Michael Trehy, MVP Coordinator  
Suite 1002  
1114 Market Street  
St. Louis, MO 63101  
Phone: (314) 539-3815

**Through:** Benjamin J. Westenberger, Deputy Director  
Phone: (314) 539-3869

**SUBJECT:** Methods Validation Report Summary

---

Application Number: 203585

Name of Product: Omacetaxine mepesuccinate for injection

Applicant: Cephalon, Inc.

Applicant's Contact Person: Carol S. Marchione

Address: R41 Moores Road, P.O.Box 4011, Frazer, PA 19355

Telephone: (610) 783-6237 Fax: (610) 738-6642

---

Date Methods Validation Consult Request Form Received by DPA: May 18, 2012

Date Methods Validation Package Received by DPA: May 18, 2012

Date Samples Received by DPA: June 29, 2012

Date Analytical Completed by DPA: July 24, 2012

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Laboratory Classification: 1. Methods are acceptable for control and regulatory purposes.   
2. Methods are acceptable with modifications (as stated in accompanying report).   
3. Methods are unacceptable for regulatory purposes.

Comments:  
See attached memo.



Center for Drug Evaluation and Research  
Division of Pharmaceutical Analysis  
St. Louis, MO 63101  
Tel. (314) 539-3897

Date: July 19, 2012  
To: Debasis Ghosh, CMC Reviewer  
Through: B. J. Westenberger, Deputy Director, Division of Pharmaceutical Analysis, (HFD-920)  
From: Wei Ye, Chemist (HFD-920)  
Subject: Method Validation for NDA 203585  
Omacetaxine Mepesuccinate for Injection (35 mg drug product)  
Cephalon, Inc.

The following methods were valuated and are acceptable for quality control and regulatory purposes:

1. Identification By Mass Spectroscopy  
(Cephalon, Inc., 3.2.P.5.2 Analytical Procedures, Page 1)
2. Identification, Assay and Degradation Products by HPLC Liquid Chromatography (HPLC)  
(Cephalon, Inc., 3.2.P.5.2 Analytical Procedures, Page 1-7)

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to this method.

1. Identification, Assay and Degradation Products by HPLC Liquid Chromatography (HPLC)  
(Cephalon, Inc., 3.2.P.5.2 Analytical Procedures, Page 1-7)



## Summary of Results

NDA 203585

- Identification By Mass Spectroscopy  
(Cephalon, Inc., 3.2.P.5.2 Analytical Procedures, Page 1)

Results:

m/z for monoisotopic peak in both sample and reference standard is (b) (4)

**Limit: Spectrum matches the reference standard**

- Identification, Assay and Degradation Products by HPLC Liquid Chromatography (HPLC)  
(Cephalon, Inc., 3.2.P.5.2 Analytical Procedures, Page 1-7)

Assay

|          | Content (%) |
|----------|-------------|
| Sample1  | 98.0        |
| Sample2  | 97.9        |
| Avg.(2): | 98.0        |

**Limit: 90.0%-110.0%**

(b) (4)

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/s/  
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MICHAEL L TREHY  
08/01/2012

BENJAMIN J WESTENBERGER  
08/01/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

**METHODS VALIDATION CONSULT REQUEST FORM**

**TO: FDA**  
**Division of Pharmaceutical Analysis**  
**Attn: Benjamin (Nick) Westenberger**  
**Suite 1002**  
**1114 Market Street**  
**St. Louis, MO 63101**

**FROM:** Debasis Ghosh, CMC Reviewer  
Janice Brown, CMC Lead  
Office of New Drug Quality Assessment (ONDQA)  
E-mail Address: debasis.ghosh@fda.hhs.gov  
Phone: (301)-796-4093

Fax.: (301)-CMC Reviewer's FAX number

**Through:** Sarah Pope Miksinski, Chief Branch 2  
Phone: (301)-796-1436

**and**

Jeannie David, ONDQA Methods Validation Project Manager  
Phone: 301-796-4247

**SUBJECT:** Methods Validation Request

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Application Number: NDA 203585

Name of Product: Omacetaxine mepesuccinate for injection

Applicant: Cephalon, Inc. (a wholly owned subsidiary of Teva Pharmaceuticals Ltd)

Applicant's Contact Person: Carol S. Marchione, Senior Director

Address: R41 Moores Road, P.O. Box 4011, Frazer, PA 19355

Telephone: (610) 738-6237 Fax: (610) 738-6642

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Date NDA Received by CDER: **3/30/12**

Submission Classification/Chemical Class: NME

Date of Amendment(s) containing the MVP: **na**

Special Handling Required: No

DATE of Request: **May 14, 2012**

DEA Class: N/A

Requested Completion Date: **7/3/2012**

**Format of Methods Validation Package (MVP)**

PDUFA User Fee Goal Date: **9/30/2012**

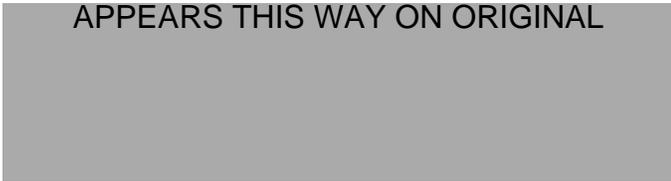
Paper  Electronic  Mixed

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We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

APPEARS THIS WAY ON ORIGINAL



| MVP Reference #  | <b>METHODS VALIDATION REQUEST</b> |                                     |                                    | NDA #<br>203585            |
|--|-----------------------------------|-------------------------------------|------------------------------------|----------------------------|
| ⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT  |                                   |                                     |                                    |                            |
| ITEM   | QUANTITY                          | CONTROL NO. OR OTHER IDENTIFICATION |                                    |                            |
|  |                                   |                                     |                                    |                            |
| ⇒ ITEM 2: Contents of Attached Methods Validation Package  |                                   |                                     |                                    | Volume/Page Number(s)      |
| Statement of Composition of Finished Dosage Form(s)  |                                   |                                     |                                    | 3.2.P.                     |
| Specifications/Methods for New Drug Substance(s)   |                                   |                                     |                                    | 3.2.S.4.1                  |
| Specifications/Methods for Finished Dosage Form(s)   |                                   |                                     |                                    | 3.2.P.5.1.                 |
| Supporting Data for Accuracy, Specificity, etc.  |                                   |                                     |                                    | 3.2.P.5.3                  |
| Applicant's Test Results on NDS and Dosage Forms   |                                   |                                     |                                    |                            |
| Other:   |                                   |                                     |                                    |                            |
| ⇒ ITEM 3: <b>REQUESTED DETERMINATIONS</b><br>Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate. |                                   |                                     |                                    |                            |
| Method ID  | Method Title                      | Volume/Page                         | MV Request Category (see attached) | Comments                   |
| Mass Spec  | Drug Product: Identity            | 3.2.P.5.3                           | 0                                  | Drug Product Identity test |
| HPLC/UV METHOD   | Drug Product: Assay and Impurity  | 3.2.P.5.3                           | 0                                  | Drug Product Potency       |
|  |                                   |                                     |                                    |                            |
|  |                                   |                                     |                                    |                            |
|  |                                   |                                     |                                    |                            |
| Additional Comments:   |                                   |                                     |                                    |                            |

## Methods Validation Request Criteria

| MV Request Category | Description   |
|---------------------|---|
| <b>0</b>            | New Molecular Entity (NME) application, New Dosage Form or New Delivery System  |
| <b>1</b>            | Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)  |
| <b>2</b>            | Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms) |
| <b>3</b>            | Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)   |
| <b>4</b>            | Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)   |
| <b>5</b>            | Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method)   |
| <b>6</b>            | Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)   |
| <b>7</b>            | Methods that are subject to a “for cause” reason  |

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/s/  
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JANICE T BROWN  
05/14/2012

SARAH P MIKSINSKI  
05/16/2012

MICHAEL M FOLKENDT  
05/17/2012

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

|                    |                                    |   |
|--------------------|------------------------------------|---|
| <b>NDA Number:</b> | <b>Supplement Number and Type:</b> | <b>Established/Proper Name:</b>         |
| 203585             |                                    | Omacetaxine mepesuccinate for injection |
| <b>Applicant:</b>  | <b>Letter Date:</b>                | <b>Stamp Date:</b>                      |
| Cephalon, Inc.     | 30-Mar-2012                        | 30-Mar-2012                             |

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

| A. GENERAL |  |     |    |         |
|------------|--|-----|----|---------|
|            | Parameter  | Yes | No | Comment |
| 1.         | Is the CMC section organized adequately?   | X   |    |         |
| 2.         | Is the CMC section indexed and paginated (including all PDF files) adequately?                 | X   |    |         |
| 3.         | Are all the pages in the CMC section legible?  | X   |    |         |
| 4.         | Has all information requested during the IND phase, and at the pre-NDA meetings been included? | X   |    |         |

| B. FACILITIES* |   |     |    |         |
|----------------|---|-----|----|---------|
|                | Parameter   | Yes | No | Comment |
| 5.             | Is a single, comprehensive list of all involved facilities available in one location in the application?  | X   |    |         |
| 6.             | For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b> | X   |    |         |

**PRODUCT QUALITY (Small Molecule)**  
**FILING REVIEW FOR NDA or Supplement (ONDQA)**

|    |  |   |  |  |
|----|--|---|--|--|
| 7. | <p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>   | X |  |  |
| 8. | <p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul> | X |  |  |

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

|     |  |   |  |  |
|-----|--|---|--|--|
| 9.  | <p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul> | X |  |  |
| 10. | Is a statement provided that all facilities are ready for GMP inspection at the time of submission?  | X |  |  |

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

| <b>C. ENVIRONMENTAL ASSESMENT</b> |  |            |           |                |
|-----------------------------------|--|------------|-----------|----------------|
|                                   | <b>Parameter</b>   | <b>Yes</b> | <b>No</b> | <b>Comment</b> |
| 11.                               | Has an environmental assessment report or categorical exclusion been provided? | X          |           |                |

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

| <b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b> |   |            |           |   |
|--|---|------------|-----------|---|
|  | <b>Parameter</b>  | <b>Yes</b> | <b>No</b> | <b>Comment</b>                            |
| 12.  | Does the section contain a description of the DS manufacturing process?                             | X          |           | Cross referenced DMF 20542. LOA provided. |
| 13.  | Does the section contain identification and controls of critical steps and intermediates of the DS? | X          |           | Cross referenced DMF 20542. LOA provided  |
| 14.  | Does the section contain information regarding the characterization of the DS?                      | X          |           | Cross referenced DMF 20542. LOA provided  |
| 15.  | Does the section contain controls for the DS?   | X          |           | Cross referenced DMF 20542. LOA provided  |
| 16.  | Has stability data and analysis been provided for the drug substance?                               | X          |           | Cross referenced DMF 20542. LOA provided  |
| 17.  | Does the application contain Quality by Design (QbD) information regarding the DS?                  |            | X         |   |
| 18.  | Does the application contain Process Analytical Technology (PAT) information regarding the DS?      |            | X         |   |

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

| <b>E. DRUG PRODUCT (DP)</b> |   |            |           |                |
|-----------------------------|---|------------|-----------|----------------|
|                             | <b>Parameter</b>  | <b>Yes</b> | <b>No</b> | <b>Comment</b> |
| 19.                         | Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?  | X          |           |                |
| 20.                         | Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable? | X          |           |                |
| 21.                         | Is there a batch production record and a proposed master batch record?  | X          |           |                |
| 22.                         | Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?   | X          |           |                |
| 23.                         | Have any biowaivers been requested?   |            | X         |                |
|                             | Does the section contain description of to-be-marketed container/closure system and presentations)?   | X          |           |                |
| 24.                         | Does the section contain controls of the final drug product?  | X          |           |                |
| 25.                         | Has stability data and analysis been provided to support the requested expiration date?   | X          |           |                |
| 26.                         | Does the application contain Quality by Design (QbD) information regarding the DP?  |            | X         |                |
| 27.                         | Does the application contain Process Analytical Technology (PAT) information regarding the DP?  |            | X         |                |

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

| <b>F. METHODS VALIDATION (MV)</b> |  |            |           |                |
|-----------------------------------|--|------------|-----------|----------------|
|                                   | <b>Parameter</b>                       | <b>Yes</b> | <b>No</b> | <b>Comment</b> |
| 28.                               | Is there a methods validation package? | X          |           |                |

| <b>G. MICROBIOLOGY</b> |  |            |           |   |
|------------------------|--|------------|-----------|---|
|                        | <b>Parameter</b>   | <b>Yes</b> | <b>No</b> | <b>Comment</b>                          |
| 29.                    | If appropriate, is a separate microbiological section included assuring sterility of the drug product? |            |           | Determined by the Microbiology reviewer |

| <b>H. MASTER FILES (DMF/MAF)</b> |   |            |           |                |
|----------------------------------|---|------------|-----------|----------------|
|                                  | <b>Parameter</b>  | <b>Yes</b> | <b>No</b> | <b>Comment</b> |
| 30.                              | Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete? | X          |           |                |

| <b>I. Labeling</b> |   |            |           |                |
|--------------------|---|------------|-----------|----------------|
|                    | <b>Parameter</b>  | <b>Yes</b> | <b>No</b> | <b>Comment</b> |
| 31.                | Has the draft package insert been provided?                   | X          |           |                |
| 32.                | Have the immediate container and carton labels been provided? | X          |           |                |

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

| <b>J. FILING CONCLUSION</b> |  |            |           |                |
|-----------------------------|--|------------|-----------|----------------|
|                             | <b>Parameter</b>   | <b>Yes</b> | <b>No</b> | <b>Comment</b> |
| 33.                         | <b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>   | X          |           |                |
| 34.                         | If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant. |            |           | NA             |
| 35.                         | Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?   |            | X         |                |

*{See appended electronic signature page}*

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Janice Brown, Branch II/DNDQA1/ONDQA

14-May-2012

*{See appended electronic signature page}*

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Sarah Pope Miksinski, Ph.D. /DNDQA1/ONDQA

14-May-2012

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/s/  
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JANICE T BROWN  
05/14/2012

RICHARD T LOSTRITTO  
05/16/2012

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

**OND Division:** Division of Hematology Products  
**NDA:** 203585 (IND 62384)  
**Applicant:** Cephalon, Inc. (a wholly owned subsidiary of Teva Pharmaceuticals Ltd)  
**Stamp Date:** 30-Mar-2012  
**PDUFA Date:**  
**Proprietary (Brand) Name of Drug Product:** Omasona for Injection (pending)  
**Established Name:** Omacetaxine mepesuccinate for Injection  
**Dosage Form(s):** Lyophilized powder for injection  
**Strength(s):** 3.5 mg/vial  
**Route of Administration:** Subcutaneous injection  
**Proposed Indication(s):** Adult patients with chronic or accelerated phase CML with resistance or intolerance to prior TKI therapy including imatinib (Gleevec), dasatinib (Sprycel) or nilotinib (Tasigna).  
**CMC Lead:** Janice Brown, Branch II/DNDQA1/ONDQA  
**Chief, Branch II:** Sarah Pope Miksinski/DNDQA1/ONDQA  
**Review team recommendation:** CMC reviewer: Debasis Ghosh

|                                   |                                     |  |
|-----------------------------------|-------------------------------------|--|
|                                   | Yes                                 | No   |
| <b>ONDQA Fileability:</b>         | <input checked="" type="checkbox"/> | <input type="checkbox"/> (see information request below) |
| <b>Comments for 74-Day Letter</b> | <input type="checkbox"/>            | <input checked="" type="checkbox"/>                      |

**CONSULTS/ CMC RELATED REVIEWS**

| Consult                | Comment   |
|------------------------|---|
| ONDQA Biopharmaceutics | Elsbeth Chikhale  |
| CDRH                   | Not Applicable  |
| EA                     | EA consult submitted on 25-Apr-2012                           |
| EES                    | Inspection request was submitted on 11-Apr-2012               |
| DMEPA                  | Labeling consult request will be sent as part of DHP request. |
| Methods Validation     | Request forwarded on 06-May-2012                              |
| Microbiology           | Consult requested on 12-Apr-2012                              |
| Pharm-Tox              | Determined by primary reviewer                                |
| Statistics             | Determined by primary reviewer                                |

**Information request to the sponsor:** Your categorical exclusion claim refers only to the exclusion based on the < 1 ppb criteria. There is an additional requirement for an environmental assessment (EA) for drugs derived from plant sources. Submit an EA to your NDA.

Please note that an EA becomes a publicly available document after approval and the information in the body of the EA cannot be confidential. Any material deemed to be confidential needs to be submitted in a confidential appendix to the EA. Additional information on confidential and nonconfidential information can be found in parts IV E. and F. of the EA

GFI

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070561.pdf>).

The applicant adequately responded to the information request by submitting an EA on 25-Apr-2011.

## SUMMARY

Omacetaxine mepesuccinate for Injection is a new molecular entity indicated for the treatment of adult patients with chronic or accelerated phase CML with resistance or intolerance to prior tyrosine kinase inhibitors (TKIs).

Omacetaxine mepesuccinate is a semisynthetic version of a plant alkaloid extracted from *Cephalotaxus fortunei* leaves, a species of evergreen that is indigenous to China. The DS has four asymmetric carbons, and solid state analysis has not shown any polymorphism.

The drug product, omacetaxine mepesuccinate for injection, is supplied as a lyophilized powder that is reconstituted with 1.0 mL 0.9% sodium chloride immediately prior to subcutaneous injection. Each sterile vial contains 3.5 mg of omacetaxine and (b) (4) mannitol. Patients will reconstitute and deliver the appropriate dose of drug at home.

The mechanism of action of omacetaxine is a reversible inhibition of protein synthesis (translation) by blocking peptide bond formation, resulting in a transient inhibition of protein synthesis of selective transcriptional factors and key intracellular signaling proteins. The protein inhibition ultimately leads to induction of apoptosis.

The drug is administered subcutaneously at an initial induction dose of 1.25 mg/m<sup>2</sup> twice daily (2.5 mg/m<sup>2</sup>/day) for 14 consecutive days every 28 days. Patients continue to receive this dose regimen until they show evidence of response, at which time they move to a maintenance dose of 1.25 mg/m<sup>2</sup> twice daily (2.5 mg/m<sup>2</sup>/day) for 7 consecutive days every 28 days. Patients can continue to receive this regimen (b) (4), provided they show a response to therapy and tolerate the treatment.

OMAPRO (omacetaxine mepesuccinate) for Injection, 5 mg was previously submitted under NDA 22-374 by ChemGenex Pharmaceuticals, Inc. and withdrawn on 2/7/2011. Cephalon acquired the U.S. rights and the clinical and CMC development program for omacetaxine mepesuccinate injection following the purchase of ChemGenex Pharmaceuticals in 2011. The CMC review for OMAPRO can be found in DARRTS. On April 8, 2010 the Division issued a Complete Response letter to the applicant citing unresolved clinical, clinical pharmacology, and CMC deficiencies along with manufacturing facility issues. The CMC issues include the following:

1. (b) (4) was originally proposed as a drug product manufacturing site, but the applicant was told to withdraw the site due to inadequate container closure specifications.

2. The strength should be reduced from 5 mg to 3.5 mg of omacetaxine per vial. Each vial contained more than twice the average dose of omacetaxine used in the efficacy and safety studies (CML-202 and CML-203). The overfilled vial size carries significant potential risk for overdose as well as the environmental impact of drug disposal.
3. The manufacturing facility (b) (4) was not ready for an inspection.

During development of the product for this NDA, only one formulation change occurred. The quantity of drug substance was reduced to 3.5 mg of omacetaxine mepesuccinate per vial rather than the 5 mg per vial that was used in the supporting registration studies (studies CGX-635-CML-202 and CGX-635-CML-203).

## DRUG SUBSTANCE

1. The applicant provided a letter of authorization from Stragen Pharma S.A. allowing the agency to review the confidential information in DMF No. 20542. Two DMF amendments were submitted on 1/30/2012 and 3/19/2012 that require a review. The DMF was previously reviewed by Sue Ching Lin and found acceptable on 3/8/2010. Sue Ching's review did not review the two amendments that were submitted after the completion of her review.
2. Cephalotaxine (OP0993) is obtained from *Cephalotaxus fortunei* leaves. Cephalotaxine is combined (b) (4) to yield the drug substance.
3. A list of manufacturer's is appended in attachment 1. The drug substance manufacturing flow diagram and drug substance specification are reproduced in attachments 2 and 3, respectively. Consider revising the specifications to include the addition of a method identification number to avoid confusion with other tests. I found it difficult to request method validation when the method identification stated "HPLC" instead of a unique identifier for each analytical method.
4. Impurities
  - 4.1 The impurity profile of the drug substance is summarized in table 1 below. Two impurities, (b) (4) are controlled directly in the drug substance specification (see attachment 3). (b) (4)  
The remaining impurities are controlled under "Any other unknown impurity" in the drug substance specification. Batch data was provided to support the proposed limits (see last column in table 1).

Table 1: Potential Impurities of Omacetaxine Mepesuccinate

(b) (4)





5. According to the DMF review, a (b) (4) retest date was granted for the drug substance filled in the proposed container/closure system when stored at controlled room temperature. The NDA requests a retest date (b) (4) at 5°C and 25°C/60%RH and 6 months at 40°C/75%RH; however, actual stability data for storage at 5°C was not reviewed. Updated stability data was provided by the applicant to support storage at 5°C.

6. The drug substance is packaged (b) (4)

7. The photostability study showed significant changes in appearance, assay, and impurities for the two drug substance samples exposed to light. Based on these results, omacetaxine mepesuccinate is considered photosensitive and should be protected from light.

**DRUG PRODUCT**

8. Omacetaxine mepesuccinate for injection is supplied as a preservative-free lyophilized powder in a single-use vial. Each vial contains 3.5 mg of active ingredient, mannitol and (b) (4). Prior to administration by subcutaneous injection each vial is reconstituted with 1.0 mL of 0.9% Sodium Chloride Injection, USP. Once reconstituted, the solution is stable for (b) (4) when stored at room temperature (15-30°C / 59-86°F).
9. In the Complete Response letter to NDA 22,374 (dated 8 April 2010), the agency requested that the quantity of drug substance in the vial to be reduced to 3.5 mg of omacetaxine mepesuccinate per vial rather than the 5 mg per vial that was used in the clinical studies. The formulation for omacetaxine mepesuccinate for injection used in the clinical program differs from the commercial formulation in the ratio of (b) (4). The amount of the inactive excipient mannitol was (b) (4). The composition of both the 3.5- and 5-mg formulations is shown in Table 2 below.

Table 2: Composition of Omacetaxine Mepesuccinate for Injection Formulations

| Ingredient                | Amount per vial      |                                 | Function          | Reference to Standard |
|---------------------------|----------------------|---------------------------------|-------------------|-----------------------|
|                           | Clinical formulation | Proposed commercial formulation |                   |                       |
| Omacetaxine mepesuccinate | 5 mg                 | 3.5 mg                          | Active ingredient | In house standard     |
| Mannitol                  | (b) (4)              | (b) (4)                         | (b) (4)           | USP and EP            |
|                           |                      |                                 |                   | NF and EP             |
|                           |                      |                                 |                   | NF and EP             |
|                           |                      |                                 |                   | USP and EP            |
|                           |                      |                                 |                   | USP and EP            |
|                           |                      |                                 |                   | USP and EP            |
|                           |                      |                                 |                   | USP and EP            |
|                           |                      |                                 |                   | NF and EP             |

10. Omacetaxine mepesuccinate for injection is manufactured at (b) (4)

11. The drug product manufacturing flow diagram is reproduced in attachment 4. The omacetaxine mepesuccinate 3.5 mg commercial manufacturing process follows a conventional drug substance (b) (4) process using compendial excipients. The acceptability of the sterile processing will be performed by OPS Microbiology reviewer.

12. The applicant references the impurity information described in the drug substance section. Two impurities (b) (4) were identified and are controlled in the drug product specification (see table 3). Consider revising the drug product specification for “Unspecified Impurities” to “Individual Specified Degradation Products”.

Table 3: Impurities from Degradation Reactions

| Omacetaxine Mepesuccinate Drug Substance | Potential impurities | Control                                     |
|--|----------------------|---|
| omacetaxine mepesuccinate                | (b) (4)              | Controlled under the “Unspecified Impurity” |
| omacetaxine mepesuccinate                | (b) (4)              | Controlled by individual specification      |

13. Drug product is filled into container-closure system listed table 4 below.

Table 4: Description of Packaging Components

| Packaging Component | Description                           | Manufacturer |
|---------------------|---------------------------------------|--------------|
| Vial                | 8 mL (b) (4) clear glass vial (b) (4) | (b) (4)      |

14. The drug product stability specification is appended in attachment 5. Consider revising the specification to include a method identification number.

15. DRUG PRODUCT STABILITY STUDIES

15.1 The applicant submitted 18 months of long term stability data at 25°C/60%RH for one lot (Lot 10G14), 12 months of long term stability data for two lots (lots 10K30 and 10L06) and 6 months of accelerated data for all 3.5 mg primary stability batches

(see table 4). The applicant also provided 48 months for one lot and 24 months for two lots of 5 mg product as supportive data.

Table 4: Stability Data for CEP-41443 for Injection Drug Product

| Drug product lot number | Strength | Use                  | Storage Condition                  |
|-------------------------|----------|----------------------|------------------------------------|
| 10G14                   | 3.5 mg   | Primary stability    | 25°C/60%RH, 40°C/75%RH             |
| 10K30                   | 3.5 mg   | Primary stability    | 25°C/60%RH, 40°C/75%RH             |
| 10L06                   | 3.5 mg   | Primary stability    | 25°C/60%RH, 40°C/75%RH             |
| 06B04                   | 5 mg     | Supportive stability | 25°C/60%RH, 40°C/75%RH             |
| 08K06                   | 5 mg     | Supportive stability | 25°C/60%RH, 30°C/65%RH, 40°C/75%RH |
| 09G22                   | 5 mg     | Supportive stability | 25°C/60%RH, 40°C/75%RH             |

15.2 The applicant has proposed an (b) (4) expiration dating period for omacetaxine mepesuccinate for injection when stored at USP Controlled Room Temperature, 20°C to 25°C (68 – 77°F), with excursions permitted to 15°C to 30°C (59 – 86 °F), and protected from light.

15.3 The stability results for all lots have met all acceptance criteria in the proposed specification when stored under long-term and accelerated storage conditions. The applicant performed a linear regression analysis for Assay and Impurities to support the (b) (4) shelf life; however, results show that these parameters do not significantly change over time. The only parameter that changes over time is (b) (4) and the applicant did not perform any statistical analysis for this metric.

(b) (4)

Table 5 – Stability Parameters

| Test  | Acceptance Criteria | Primary Stability Batches (3.5 mg) |              | Supportive Stability Batches (5 mg) |              |
|-------|---------------------|------------------------------------|--------------|-------------------------------------|--------------|
|       |                     | 25°C/ 60% RH                       | 40°C/ 75% RH | 25°C/ 60% RH                        | 40°C/ 75% RH |
| Assay | (b) (4)             | (b) (4)                            | (b) (4)      | (b) (4)                             | (b) (4)      |

(b) (4)

|          |  |  |  |  |  |         |
|----------|--|--|--|--|--|---------|
| impurity |  |  |  |  |  | (b) (4) |
|----------|--|--|--|--|--|---------|

15.4 **PHOTOSTABILITY** - Omacetaxine mepesuccinate for injection is light sensitive. Unprotected vials exposed to light failed unspecified impurities, total degradation products and pH. The photostability study was repeated with the drug product in the secondary package. Results of the light exposed samples are similar to those of the dark control samples, demonstrating that the secondary package configuration provides adequate protection from light-induced degradation.

Current labeling under section 16.3 Storage includes the following statement: Store at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F – 86°F) [see USP Controlled Room Temperature]. Until use, keep product in carton to protect from light. The proposed labeling is consistent with the results from photostability testing.

15.5 A reconstitution solution stability study was performed on omacetaxine mepesuccinate for injection, 3.5 mg/vial. Twelve month stability samples from lot 10G14 were used in the study. Omacetaxine mepesuccinate for injection, 3.5mg, (Lot 10G14), was reconstituted with 0.9% sodium chloride and tested at 1, 2, 4, 8, 12, and 24 hours when stored at 5°C and 25°C under ambient light for 24 hours. Each reconstituted vial was tested for appearance, pH, percent initial omacetaxine mepesuccinate content and related substances. The results indicate that omacetaxine mepesuccinate is compatible with the 0.9% sodium chloride and the drug product is stable when reconstituted for at least 24 hours at either 5°C or 25°C when tested at 12 months of shelf life. The applicant also has committed to repeat the study at the 24 months test station.

16. Supporting DMFs – Listed below are the referenced DMFs for this NDA.

| <b>DMF</b> | <b>TYPE</b> | <b>HOLDER</b>   | <b>ITEM REFERENCED</b>         |
|------------|-------------|---|--------------------------------|
| (b) (4)    | III         |   | (b) (4)                        |
| 20542      | II          | Stragen Pharma SA<br>Chemin du Pni-Fleuri 3<br>1228 Plan-Les-Ouates / GENEVA<br>Switzerland | Drug Substance<br>Manufacturer |
| (b) (4)    | III         |   | (b) (4)                        |

17. Adventitious Agents – Cephalon, Inc. confirms that no substances of animal origin are used in the manufacture of Omacetaxine mepesuccinate for injection.
18. Environmental Assessment: The applicant has submitted a claim for categorical exclusion under 25.31(b) which states that use of this product will not cause the concentration of the drug substance active moiety to be one part per billion (1 ppb) or greater at the point of entry into the aquatic environment.
19. Establishment Evaluation: A full list of facilities involved in the manufacture, packaging and testing of Omacetaxine mepesuccinate for injection is reproduced in attachment 1.

#### ***CRITICAL ISSUES FOR REVIEW***

1. Overall, this NDA is well written and the conclusions are supported by actual data. Debasis Ghosh (QBD liason) confirmed that there are no QbD aspects to this submission (see attachment 6).
2. The applicant has addressed all the CMC issues that were previously communicated in the Complete Response letter for NDA 22-374.
3. Minor corrections to the drug substance and drug product impurity tests should be considered (see items 3 and 14 for recommendations).
4. Consider granting a 12 month shelf life for the drug product unless the applicant can perform statistical analysis showing that the product can meet the (b) (4) limit at either 18 month (b) (4) (b) (4)
5. Request that the applicant provide a LOA (b) (4)

*Comments for 74-Day Letter:* None.

Attachment 1: Facility information

(b) (4)



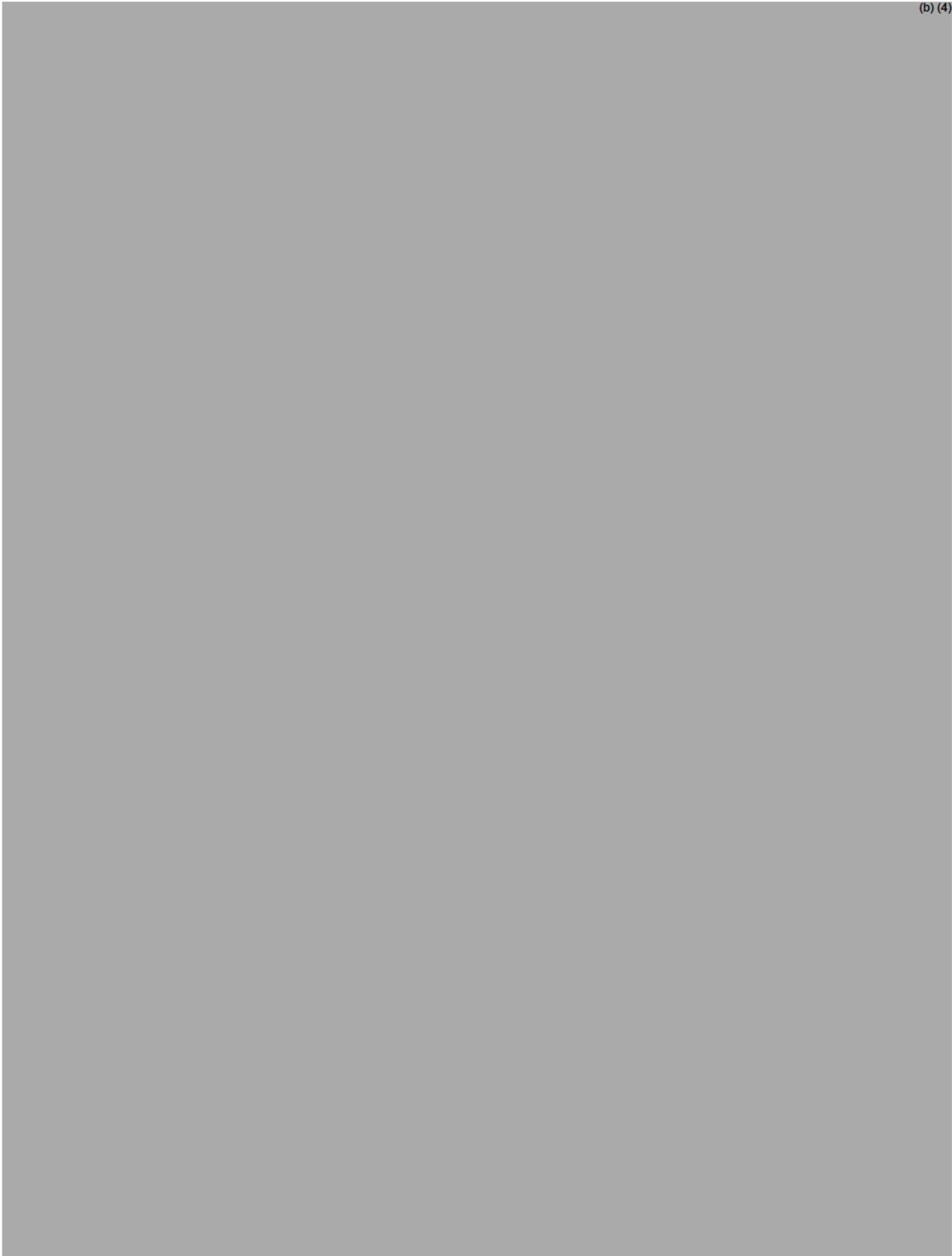
|  |  |                                 |
|--|--|---------------------------------|
| <b>Teva Sellersville</b><br>650 Cathill Road<br>Sellersville, PA 18960 | Facility<br>Establishment<br>Identifier: 2517175 | Labeling<br>Secondary packaging |
|--|--|---------------------------------|

(b) (4)



Attachment 2: Drug Substance Manufacturing Flow diagram (reproduced from DMF review)

(b) (4)



Attachment 3: Drug Substance Specification (reproduced from DMF review)

(b) (4)



Attachment 4: Drug Product Manufacturing Flow Diagram

(b) (4)



Attachment 5: Drug Product Specification

(b) (4)



## Attachment 6: QbD evaluation

**Brown, Janice**

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**From:** Ghosh, Debasis  
**Sent:** Friday, April 13, 2012 9:54 AM  
**To:** Pope Miksinski, Sarah  
**Cc:** Russell, Anne Marie; Brown, Janice  
**Subject:** NDA 203585: QbD Elements

Based on my evaluation, NDA 203585 submission contains no QbD elements. Drug Substance is referenced in the DMF 20542. Drug Product is a lyophilized powder for Injection. Please let me know if you have any questions.

Thanks,  
Debasis

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

JANICE T BROWN  
05/14/2012

RICHARD T LOSTRITTO  
05/16/2012

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

|   |   |
|---|---|
| <b>NDA Number</b>                               | 203-585                                       |
| <b>Submission Date</b>                          | 3/30/12                                       |
| <b>Product name, generic name of the active</b> | Omacetaxine mepesuccinate for Injection       |
| <b>Dosage form and strength</b>                 | Lyophilized powder for Injection– 3.5 mg/vial |
| <b>Route of Administration</b>                  | Subcutaneous Injection                        |
| <b>Applicant</b>                                | Cephalon, Inc.                                |
| <b>Clinical Division</b>                        | Division of Hematology Products               |
| <b>Type of Submission</b>                       | Original NDA – 505(b)(1)                      |
| <b>Biopharmaceutics Reviewer</b>                | Elsbeth Chikhale, Ph.D.                       |
| <b>Biopharmaceutics Supervisory Lead</b>        | Angelica Dorantes, Ph.D.                      |

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

| <b>ONDQA-BIOPHARMACEUTICS</b>                                       |  |            |           |  |
|---|--|------------|-----------|--|
| <b><u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING</b> |  |            |           |  |
|   | <b>Parameter</b>   | <b>Yes</b> | <b>No</b> | <b>Comment</b>   |
| 1.  | Does the application contain dissolution data?                                       |            | x         | NA   |
| 2.  | Is the dissolution test part of the DP specifications?                               |            | x         | NA   |
| 3.  | Does the application contain the dissolution method development report?              |            | x         | NA   |
| 4.  | Is there a validation package for the analytical method and dissolution methodology? |            | x         | NA   |
| 5.  | Does the application include a biowaiver request?                                    |            | x         | The Original NDA did not include a biowaiver request. On 5/10/12 the Applicant was informed that the change in formulation (see table 1 below) requires a biowaiver request or BA/BE data. A response from the Applicant is pending. |
| 6.  | Does the application include an IVIVC model?   |            | x         |  |
| 7.  | Is information such as BCS classification mentioned, and supportive data provided?   |            | x         |  |
| 8.  | Is information on mixing the product with foods or liquids included?                 | x          |           | Drug product should be reconstituted in 0.9% sodium chloride solution (3.2.P.2.6. Compatibility)   |

**PRODUCT QUALITY - BIOPHARMACEUTICS  
FILING REVIEW**

|    |   |   |   |   |
|----|---|---|---|---|
| 9. | Is there any <i>in vivo</i> BA or BE information in the submission? | x | x | BA information provided on the clinical formulation, not the commercial formulation (see table 1 below) |
|----|---|---|---|---|

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

| B. FILING CONCLUSION |   |     |    |  |
|----------------------|---|-----|----|--|
|                      | Parameter   | Yes | No | Comment  |
| 10.                  | <b>IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?</b>  | x   |    | See section 5. Response is pending.  |
| 11.                  | If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant. |     |    |  |
| 12.                  | If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.                 |     |    |  |
| 13.                  | Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?  |     | x  | See section 5. Information request has been sent to the Applicant on 5/10/12. Response is pending. |

**Table 1: Prelyophilization Composition of Omacetaxine Mepesuccinate for Injection Solution**

| Ingredient                | Amount per vial      |                        |
|---------------------------|----------------------|------------------------|
|                           | Clinical formulation | Commercial formulation |
| Omacetaxine mepesuccinate | 5 mg                 | 3.5 mg                 |
| Mannitol                  | (b) (4)              | (b) (4)                |
| (b) (4)                   |                      |                        |

*{See appended electronic signature page}*

Elsbeth Chikhale, Ph.D.  
Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

5/14/12  
Date

*{See appended electronic signature page}*

Tapash Ghosh, Ph.D.  
Acting Biopharmaceutics Lead  
Office of New Drug Quality Assessment

5/14/12  
Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ELSBETH G CHIKHALE  
05/14/2012

TAPASH K GHOSH  
05/14/2012