

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203585Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be reviewed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: NDA 203585 Omacetaxine mepesuccinate for injection, for subcutaneous injection

PMR Description: Continue follow-up of patients (on treatment and in protocol defined post-treatment follow-up) and submit a final analysis report of CGX-635-CML-300 with 24 months of minimum follow-up data for each patient. If 24 months of follow-up is not possible for certain patients, justification should be provided.

PMR Schedule Milestones:	Final Protocol Submission:	<u>n/a</u>
	Study / Trial Completion:	<u>03/2012</u>
	Final Report Submission:	<u>04/2013</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The goal is to obtain and review additional follow-up data (efficacy/safety) to provide 24 months of follow-up data for conversion to regular approval. 24 months follow-up data is necessary to assess the results for conversion from an accelerated to regular approval. The submission on which accelerated approval was based provided 19.5 and 11.5 months of follow up data for the CML-CP and CML-AP populations, respectively.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The submission did not contain the requisite 24 months of follow-up data required for regular approval in this indication.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Additional follow-up data (efficacy/safety) of existing trials (which constituted one analysis for this NDA submission) is needed to confirm and verify the clinical benefit of omacetaxine in patients with CML who have received at least two prior TKIs.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
24 months follow-up data is needed for regular approval
 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
 - Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Reviewer, DO YOU WANT TO REQUEST THE SPONSOR TO:

Submit a labeling supplement for this PMR trial with the final clinical study report and with complete raw datasets. Yes

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: NDA 203585 / Omacetaxine mepesuccinate

PMR Description: Conduct a Phase 1/2 single arm clinical trial to investigate the pharmacokinetics, safety, and preliminary efficacy of omacetaxine following fixed dose administration in patients with chronic phase (CP) of chronic myeloid leukemia (CML) or acute phase (AP) of chronic myeloid leukemia (CML) who have failed TKI therapy. In Cycle 1, evaluate the PK and safety of omacetaxine following fixed dose administration. Continue treatment if tolerated using a fixed dose as long as patients are clinically benefiting from therapy.

Include in the action letter, but not in the PMR text itself:
Sponsor should submit labeling to incorporate the results.

PMR Schedule Milestones:	Preliminary Protocol Submission	<u>12/2012</u>
	Final Protocol Submission:	<u>03/2013</u>
	Trial Completion:	<u>02/2016</u>
	Final Report Submission:	<u>06/2016</u>
	Other: _____	<u>MM/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.
 - Unmet need
 - Life-threatening condition
 - Long-term data needed
 - Only feasible to conduct post-approval
 - Prior clinical experience indicates safety
 - Small subpopulation affected
 - Theoretical concern
 - Other
2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Objective: To find a better dosing regimen by evaluating the effects of demographic covariates such as gender, age, and body surface area on exposure and efficacy following a fixed dosing regimen

Why: The recommended dose of 1.25 mg/m², a body surface area-based dosing regimen was determined by the sponsor based on literature prior to the pivotal clinical trials. The results from the pivotal trials indicated a potential issue of insufficient dosing for patients with lower body surface area. The FDA reviewer's analysis supports the notion that a fixed dosing regimen would prevent insufficient exposure in patients with low body surface area thereby potentially improving safety by increasing efficacy. Failure in efficacy in patients with a life-threatening disease is considered a safety failure to prevent disease-related death or disease progression, thus the results from the PMR are expected to enhance efficacy and safety.

Plan: Conduct a clinical trial in the target population with a fixed dosing regimen. Depending on the results obtained from the study, the recommended dose in the labeling will be changed accordingly.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

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Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The clinical trial will be conducted in the target patient population with a fixed dosing regimen, evaluating PK, safety and efficacy. In this case, a reduction in efficacy represents a safety problem since deaths may be increased as a result. Blood samples for pharmacokinetics analysis will be collected. Safety, major cytogenetic response for chronic phase CML patients and major hematologic response for accelerated phase CML patients will be measured. The results will be analyzed for subgroups by gender, age, body surface area and the subgroup analysis results will be compared to data obtained from the pivotal trials that used the body surface area-based dosing regimen.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
data suggest that an alternative dosing regimen may be superior to the current one.
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 Are the objectives clear from the description of the PMR/PMC?
 Has the applicant adequately justified the choice of schedule milestone dates?

- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

RCK _____
(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: NDA 203585/ Omacetaxine mepesuccinate

PMR Description: Conduct a mass balance trial in humans to determine the disposition and elimination pathways as well as to characterize the major metabolites of omacetaxine following subcutaneous injection. Depending on the results, hepatic and/or renal impairment trials may be required.

PMR/PMC Schedule Milestones:	Preliminary Protocol Submission	<u>07/2012</u>
	Final Protocol Submission:	<u>10/2012</u>
	Study/Trial Completion:	<u>06/2015</u>
	Final Report Submission:	<u>12/2015</u>
	Other: _____	<u>MM/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

There are currently no approved treatment options for CML patients who have failed 2 TKIs.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The major elimination route of omacetaxine is unknown. This information is essential for identifying potential risk of increased exposure to omacetaxine and related toxicity secondary to organ impairment and the need to for additional dedicated organ impairment trials to optimize the dose.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
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- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An open-label study to investigate the pharmacokinetics (absorption, distribution, metabolism, and excretion) of omacetaxine mepesuccinate and metabolites (i.e., 4'-DMHHT and cephalotaxine), following subcutaneous administration of [¹⁴C]omacetaxine mepesuccinate in patients with relapsed and/or refractory hematologic malignancies or advanced solid tumors

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

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 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
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- Meta-analysis or pooled analysis of previous studies/clinical trials
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 - Other (provide explanation)
-

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-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

RCK
(signature line for BLAs)

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

/s/

THERESA A CARIOTI
10/25/2012

ROBERT C KANE
10/26/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: September 26, 2012

To: Theresa Ferrara, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Gina McKnight-Smith, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)

CC: Karen Rulli, Professional Review Team II Leader, DPDP
Nisha Patel, Regulatory Review Officer, DPDP
Kathleen Davis, Regulatory Review Officer, DPDP

Subject: Comments on draft labeling (Package Insert) for Synribo™
(omacetaxine mepesuccinate) for Injection, for subcutaneous
injection
NDA 203585

In response to your consult dated May 24, 2012, we have reviewed the draft Package Insert (PI) for Synribo and offer the following comments. DPDP has made these comments using the PI version dated September 23, 2012.

Section	Statement from draft	Comment
Highlights, Indications and Usage	SYNRIBO is indicated for the treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more kinase inhibitors (TKI).	Please add language regarding the limitations of this indication (i.e., accelerated approval). Proposed language might include the following: “This indication is based on response rate. Clinical benefit such as improvement in progression-free survival or overall survival has not been demonstrated”
Highlights, Warnings and Precautions	(b) (4)	

Section	Statement from draft	Comment
		<p>(b) (4)</p> <p>(b) (4) Please consider including this important risk information in the Highlights section. Sponsors tend to use information from the Highlights section in their promotional materials and may omit material facts from the FPI related to the occurrence and monitoring of myelosuppression.</p>
Highlights, Adverse Reactions	(b) (4)	<p>We note that the most common adverse reactions (b) (4) listed in the Highlights section differs from the most common adverse reactions listed in Table 1 (chronic phase) and Table 2 (accelerated phase) of the FPI. (b) (4)</p> <p>Please revise the Highlights, Adverse Reactions section to ensure consistency with the Adverse Reactions section of the FPI.</p>
Full Prescribing Information: Contents		Please update the headers in the “Contents” section to ensure consistency with the headers in the FPI.
2.3 Dose Adjustments and Modifications	(b) (4)	Please consider clarifying (b) (4) to ensure adequate monitoring of CBCs as referenced in Table 16 of the Clinical Review (page 49). This language also appears in Section 5.1.
5.1 Warning and Precautions, Myelosuppression	(b) (4)	<p>Please consider modifying this language to add context and for consistency with labeling from other competitor products. Proposed wording (consistent with competitor labels) may include:</p> <p>SYNRIBO causes a high incidence of severe (NCI CTC Grade 3 or 4) thrombocytopenia, neutropenia, and anemia in patients with chronic phase and accelerated phase CML.</p> <p>Additionally, the term (b) (4) is a non-specific term and does not provide information about the frequency of thrombocytopenia, neutropenia, or anemia. We recommend quantifying this term and including exactly how many patients experienced these adverse reactions.</p>
5.1 Warnings and Precautions,	(b) (4)	Please note that the Clinical Review of Safety, page 48, denoted N=158 because of exclusion

Section	Statement from draft	Comment
Myelosuppression	(b) (4)	of five patients.
5.2 Warnings and Precautions, Bleeding	(b) (4)	<p>Please consider revising to ensure the citation of Grade 4 thrombocytopenia is not used promotionally to minimize the risk associated with other grades of thrombocytopenia. Any occurrence of thrombocytopenia may increase the risk of bleeding. Proposed wording (consistent with competitor labels) may include:</p> <p>SYNRIBO can cause thrombocytopenia which increases the risk of hemorrhage. Fatalities from cerebral hemorrhage occurred in 2% of patients treated with SYNRIBO in the safety population. Severe, non-fatal, gastrointestinal hemorrhages occurred in (b) (4) patients in the same population. Most bleeding events were associated with severe thrombocytopenia.</p>
6 Adverse Reactions 6.1 Clinical Trials Experience, Chronic Phase CML		Please ensure consistency and accuracy with Section 5.1 based on the Clinical Review of Safety (page 48) showing N=158 total, chronic phase (N=103), and accelerated phase (N=55). Please note that Table 1 also requires revision to reflect accurate N=103.
6.1 Clinical Trials Experience, Chronic Phase CML	(b) (4)	<p>According to page 57 of the MO review, “Progressive Disease” is identified as a “Reason for Discontinuation”, not an “adverse event” leading to discontinuation. We recommend clarifying that “progressive disease” was one of the most common reasons for discontinuation. We also recommend replacing the word (b) (4) with “discontinuation” to avoid confusion.</p> <p>Additionally, is (b) (4) the correct percentage for discontinuation due to disease progression? According to page 56 of the MO review (7.3.3 Dropouts and/or Discontinuations): “The most common reasons for discontinuation were progressive disease (32%) and lack of efficacy (16%), with similar percentage of discontinuations for lack of efficacy among patients with CML-CP (17%) and CML-AP (15%) and more discontinuations due to progressive disease in patients with CML-AP (44% versus 26%) as summarized in Table 26.”</p>
6.1 Clinical Trials Experience, Chronic Phase CML	(b) (4)	Please revise (b) (4) to “emergent” to ensure consistency with of the terminology for treatment emergent adverse events (TEAEs) and Section 6.1 Clinical Trials Experience,

Section	Statement from draft	Comment
	(b) (4)	<p>Accelerated Phase CML).</p> <p>We also recommend deleting the phrase, “. . . (b) (4) as it minimizes the additional risks associated with Synribo.</p> <p>Additionally, please consider adding information related to deaths and most frequently reported adverse events. Based on the MO Review (Pages 53 to 56, 7.3.1 and 7.3.2), the major safety results included deaths (34% in CML-CP and 51% in CML-AP) and nonfatal serious adverse events. Furthermore, Section 7.4.1 (Table 30) describes the most common treatment emergent adverse events in ≥ 10% of patients. The additional context associated with the inclusion of these important SAEs balances the benefits and risks often applied in promotional materials.</p>
6.1 Clinical Trials Experience	Tables 1 and 2	<p>Please note that Tables 1 and 2 in the draft PI are incomplete and inconsistent with Tables 30 and 31 in the MO Review.</p> <p>Table 1 is missing pyrexia, constipation, epistaxis, cough, rash, and insomnia. Table 2 is missing anorexia, peripheral edema, pneumonia, arthralgia, and bronchitis.</p>
6.1 Clinical Trials Experience, Chronic Phase CML 6.1 Clinical Trials Experience, Accelerated Phase CML	<p>Chronic Phase CML Serious adverse events of infections were reported by 8% of patients (emphasis added).</p> <p>Accelerated Phase CML Serious adverse events of infections were reported by 11% of patients (emphasis added).</p>	Please consider changing the preposition “by” to “for” to avoid confusing this with patient self-reporting.
6.1 Clinical Trials Experience, Accelerated Phase CML	(b) (4)	<p>According to page 57 of the MO review, “Progressive Disease” is identified as a “Reason for Discontinuation”, not an “adverse event” leading to discontinuation. We recommend clarifying that “progressive disease” was one of the most common reasons for discontinuation.</p> <p>Additionally, are the percentages accurate for disease progression, leukocytosis, and thrombocytopenia? Are leukocytosis and thrombocytopenia the most frequently occurring adverse reactions leading to withdrawal?</p>
6.1 Clinical Trials Experience,	(b) (4)	We recommend deleting the phrase (b) (4)

Section	Statement from draft	Comment
Accelerated Phase CML	(b) (4)	(b) (4) as it minimizes the additional risks associated with Synribo.
6.1 Clinical Trials Experience, Laboratory Abnormalities in Chronic and Accelerated Phase CML		<p>Please provide a definition of (b) (4) to avoid inappropriate use in promotional materials.</p> <p>The term (b) (4) is a non-specific term and does not provide information about the frequency of hyperuricemia. We recommend quantifying this term and including exactly how many patients experienced this adverse reaction.</p>
6.1 Clinical Trials Experience, Laboratory Abnormalities in Chronic and Accelerated Phase CML		Please consider re-wording this language related to decreased glucose to avoid confusion related to important laboratory abnormalities that may occur from use of SYNRIBO.
6.1 Clinical Trials Experience, Laboratory Abnormalities in Chronic and Accelerated Phase CML		<p>Should Table 3, which is based on the applicant analysis of laboratory abnormalities, be replaced with the FDA analysis of laboratory abnormalities (MO Review, page 72, Table 34)?</p> <p>We note that Page 73 of the MO review states, “There are differences in incidences of laboratory abnormalities between the applicant and FDA analyses, which may be due to the different number of subjects included (as those subjects for whom laboratory information was missing were not included in the total by FDA analysis (n=101 and n=50 in CML-CP and CML-AP respectively), in an effort to minimize underestimation of those abnormalities). Furthermore, the applicant’s proposed rates of adverse events are based on analyses that allowed for attribution of adverse events. The Agency does not allow for attribution when analyzing the safety of an NME evaluated in single arm trials. The FDA analysis of laboratory abnormalities should replace that of the applicant in the label.”</p>
8 Use in Specific Populations, 8.5 Geriatric Use, 8.8 Effect of Gender		We note that page 72 of the MO review states, “As for the differences in subgroups and special populations reported in the label for the efficacy and safety population, it is recommended that a statement be included

Section	Statement from draft	Comment
	(b) (4)	<p>indicating that the numbers of the subgroups (numbers of patients with the corresponding parameters discussed) are too small to make meaningful clinical conclusions and these analyses should be considered exploratory.”</p> <p>However, we recommend deleting these claims from the FPI (b) (4)</p>
12.1 Mechanism of Action	(b) (4)	<p>As noted in the original CR letter for the prior submission (Omapro – NDA 22374), reference to the T315I mutation and SYNRIPO’s activity against it is experimental as there is no CDRH-approved companion diagnostic test to validate the presence of the mutation. The MO Review specifies the mechanism of action of omacetaxine as “reversible inhibition of protein elongation, which selectively impacts short-lived proteins.”</p> <p>We recommend deleting the additional statements (b) (4)</p>
12.3 Pharmacokinetics, Absorption	(b) (4)	<p>Is this statement supported by substantial evidence? The term (b) (4) is promotional in tone and could be used to overstate the efficacy of the drug. Please consider deleting this term and quantifying data if available.</p>
12.3 Pharmacokinetics, Drug Interactions	(b) (4)	<p>Is the first bolded phrase supported by substantial evidence?</p> <p>Please consider quantifying the definition of (b) (4) to avoid inappropriate promotional use.</p>
14.1 Chronic Phase CML	(b) (4)	<p>Please consider defining MCyR as “Major Cytogenetic Response (MCyR) = complete cytogenetic response (0% Ph+ cells) or partial cytogenetic response (>0% to 35% Ph+ cells)” to provide context regarding the primary endpoint. Refer to dasatinib (Sprycel) PI, Tables 6 and 7 for similar language.</p> <p>Please consider including in Table 4 a full breakdown of the 14 responders including</p>

Section	Statement from draft	Comment
		those who were unconfirmed (complete and partial) responders to ensure proper context in the promotional materials. Additionally, defining “unconfirmed” and “confirmed” in the PI will help to ensure the use of appropriate context in promotional materials.
14.2 Accelerated Phase CML	The efficacy endpoint was assessed based on MCyR and MaHR (complete hematologic response [CHR] or no evidence of leukemia [NEL]).	<p>Please consider defining CHR and NEL to provide adequate context regarding the primary endpoint:</p> <p>CHR is defined as</p> <ul style="list-style-type: none"> • ANC $\geq 1.5 \times 10^9/L$ • PLT $\geq 100 \times 10^9/L$ • No blood blasts • Bone marrow blasts < 5% • No extramedullary disease <p>NEL is defined as < 5% bone marrow blasts</p>
General Comment		Please provide consistent use of either omacetaxine or SYNRIPO throughout the label.

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

/s/

GINA P MCKNIGHT-SMITH
09/26/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: September 10, 2012

Reviewer: Sarah K. Vee, PharmD
Division of Medication Error Prevention and Analysis

Acting Team Leader: Yelena Maslov, PharmD
Division of Medication Error Prevention and Analysis

Division Director: Carol A. Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Omacetaxine for injection, 3.5 mg per vial

Application Type/Number: NDA 203585

Applicant/sponsor: Cephalon, Inc.

OSE RCM #: 2012-812

*** This document contains proprietary and confidential information that should not be released to the public.

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1 INTRODUCTION

This review summarizes the safety concerns of DMEPA and resolution regarding the proposed preparation, administration, and disposal of this product.

This review also evaluates the proposed vial label, carton and insert labeling for Omacetaxine, NDA 203585, for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

- Originally, NDA 022374 was submitted by ChemGenex on September 8, 2009 for the proposed indication of treatment of patients with chronic myeloid leukemia (CML) who have failed imatinib and have the T315I mutation.
- ODAC was held on March 22, 2010 to vote on the question below: Should a well characterized in vitro diagnostic to identify patients with the T315I mutation be required and reviewed by the FDA and correlated to clinical trial results prior to approval of omacetaxine for the proposed indication? Yes = 7 No = 1 Abstain = 0
- The Application received a Complete Response (CR) on April 8, 2010 due to clinical, clinical pharmacology, nonclinical, and CMC deficiencies (overfill of 5 mg per vial which was more than twice the usual dose).
- Agreement that a combined data set of a homogeneous patient population with respect to prior approved TKI from studies CML-202 and CML-203 could be the basis of an NDA in a third-line setting.
- NDA 022374 was withdrawn on February 4, 2011.
- NDA 203585 (Cephalon) was submitted on March 30, 2012 and was designated as standard review. Consequently, the Applicant submitted a dispute resolution to change the designation to priority review. Although the official PDUFA date will not change, this application will be reviewed as a priority review with a target date of September 30, 2012.

1.2 PRODUCT INFORMATION

The following product information is provided in the August 14, 2012 revised labeling submission.

- Active Ingredient: Omacetaxine mepesuccinate
- Indication of Use: For the treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKI).
- Route of Administration: subcutaneous injection
- Dosage Form: lyophilized powder for injection
- Strength: 3.5 mg per vial
- Dose and Frequency: Induction: 1.25 mg/m² twice daily for 14 days every 28 days until cytogenetic response followed by Maintenance: 1.25 mg/m² twice daily for 7 days every 28 days.

- How Supplied: 3.5 mg per vial
- Storage: Store at (b) (4); excursions permitted between 15°C and 30°C (59°F and 86°F) until use, keep product in carton to protect from light
- Container and Closure System: 8 mL (b) (4) clear glass vial (b) (4) in individual cartons.
- Settings of Use: (b) (4) the product will be prepared, administered, and disposed by healthcare professionals in accordance with the safe use practices in place regarding chemotherapeutics agents.

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Vial Label submitted [September 6, 2012](#) (Appendix A)
- Carton Labeling submitted [September 6, 2012](#) (Appendix B)
- Insert Labeling submitted August 14, 2012 (no image)

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed this product in OSE Review #2009-2302 and we evaluated the review to identify whether any of our previous recommendations still apply. However, DMEPA's comments were not sent to the Applicant (ChemGenex) because the NDA received a CR. The Applicant for this NDA 203585 is Cephalon. Therefore, the vial label and carton labeling are different than what was originally submitted under NDA 022374 in the previous review.

3 DMEPA REVIEW TIMELINE

Date:	Synopsis:
March 30, 2012	NDA 203585 for Omacetaxine for Injection submitted to the FDA
April 6 -9, 2012	(b) (4)

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

April 11, 2012 DMEPA sent an email to Division of Hematology Products (DHP) PM to inquire about CDRH consult status and to request sample kits of the product.

April 13, 2012 DHP PM sent an Information Request (IR) to the Applicant to request samples of the kit.

April 13, 2012 DMEPA sent an email to OSE PM to inquire if DRISK would be involved regarding possible requirement for a REMS program (b) (4)

April 13, 2012 DMEPA sent an email to DHP PM (b) (4). The IR sent to Applicant on the same day.

April 17, 2012 Samples received.

April 18, 2012 DMEPA sent an email to CMC reviewer to inquire about stability of the solution and size of the diluent vial.

April 27, 2012 DMEPA sent an email to DHP PM (b) (4) (See Appendix D).

May 8, 2012 Received responses to questions 1 and 2 (See Appendix E).

May 10, 2012 Planning and Filing Meeting held and Cephalon presented Omacetaxine to the review team. The Agency informed Cephalon that they will need to conduct a new (b) (4) study due to high dosing error rates in the study results and flawed methodology.

May 11, 2012 Received response to question 3 regarding errors in (b) (4) study (See Appendix F).

May 14, 2012 Meeting with DRISK to discuss possibility of REMS.

May 23, 2012 Internal Meeting and teleconference with the Applicant to discuss errors in (b) (4) study and options to mitigate these errors (See Appendix G).

June 11, 2012 Discussed (b) (4) with Patient Labeling Team.

July 3, 2012 Received (b) (4) study protocol, (b) (4), and associated training materials.

July 9, 2012 DHP Administration Rounds: Updated the Division of Hematology Products regarding outstanding safety concerns (e.g. secondary exposure and waste disposal).

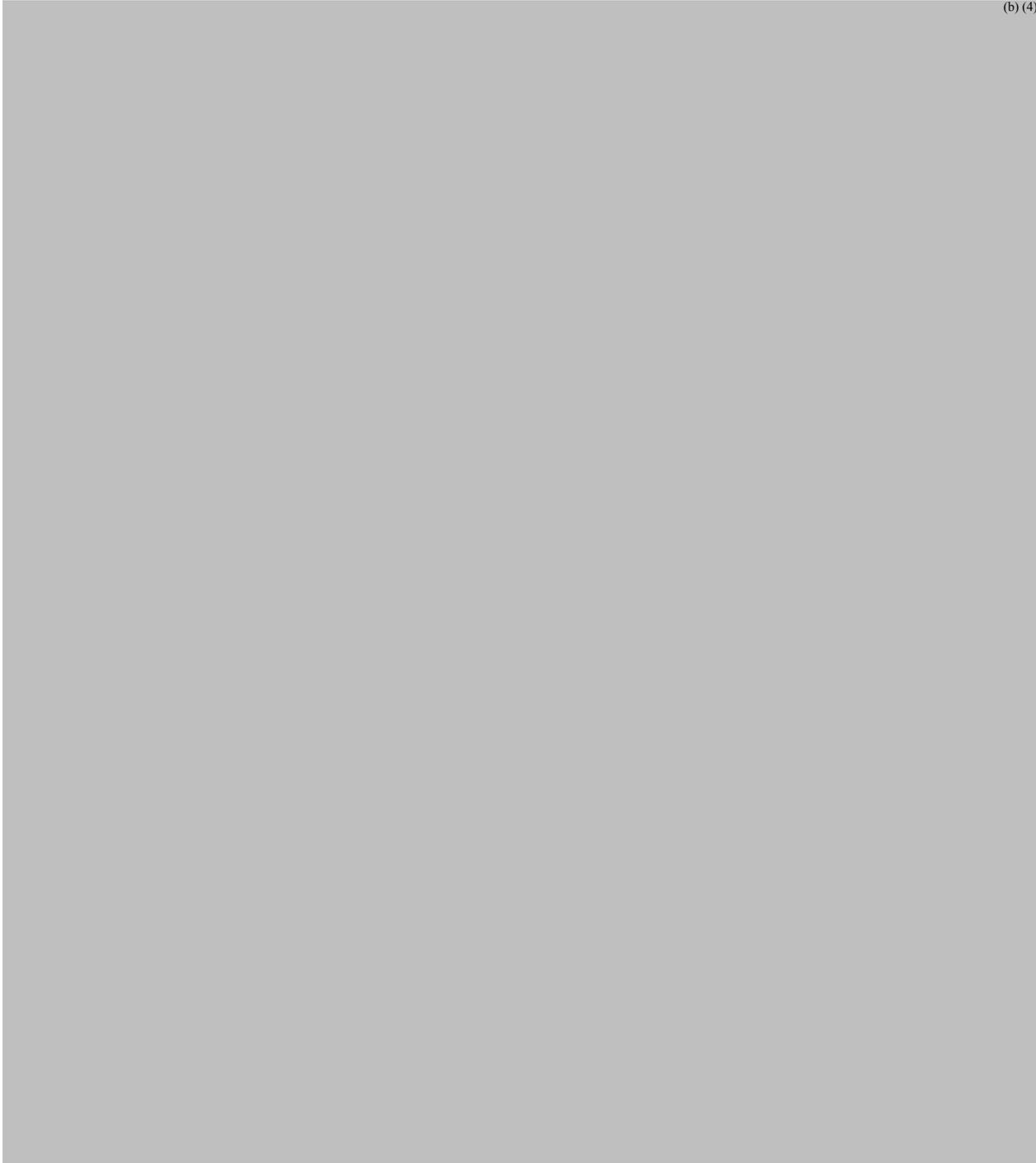
July 12, 2012 Meeting with DHP to discuss outstanding safety concerns and additional study requirement consensus.

July 26, 2012 General Advice Letter sent to the Applicant regarding unresolved safety issues and to discuss options for the Applicant to receive approval of the NDA during this review cycle (See Appendix H).

July 30 & 31, 2012 Internal Meeting with the review team and teleconference with the Applicant to discuss unresolved safety issues and to discuss options for the Applicant to receive approval of the NDA during this review cycle (See Appendix I).

August 14, 2012 Received revised package insert labeling.

4 DISCUSSION



The Applicant submitted a revised labeling to reflect the changes that were discussed during the teleconference (See Appendix I).

5 CONCLUSIONS

This product will be labeled to be used in an in-patient setting, where it will be prepared, administered, and disposed of according to the safe use practices in place regarding chemotherapeutics agents, by a healthcare professional. As such, this addresses our concern [REDACTED]^{(b) (4)}. Additionally, we provide recommendation on the proposed label and labeling to promote the safe use of the product and to clarify information on the label and labeling.

6 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

- A. Vial Label
 - a. Increase the prominence of the established name. Ensure that the prominence of the established name is commensurate with the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing feature in accordance with 21 CFR 201.10(g)(2).
 - b. Minimize the size of the graphic embedded next to the proprietary name. The logo competes with the prominence of the proprietary and established names and product strength. These items should have the most prominence on the labels and labeling.
 - c. Revise the presentation of the proprietary name to appear in title case (i.e. “Synribo”). Words set in upper and lower case form recognizable shapes,

² ASHP (American Society of Health-System Pharmacists) [2006]. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm* 63:1172–1193.

³ http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html#app_vi:2_2 (last accessed July 13, 2012)

⁴ Connor TH, Anderson RW, Sessink PJ et al. Surface contamination with antineoplastic agents in six cancer treatment centers in Canada and the United States. *Am J Health-Syst Pharm*. 1999; 56:1427–32.

making them easier to read than the rectangular shape formed by words set in all capital letters.

- d. Relocate the statement “Single-use vial” to right above or immediately next to the statement “Discard unused portions” to appear as follows:

Single-Use Vial

Discard Unused Portion

Or

Single-Use Vial. Discard Unused Portion.

B. Carton Labeling

- a. See 6.A
- b. Your product is sensitive to light. Thus, add a statement “Protect from light. Keep the vial in the carton until administration”.

C. Package Insert Labeling

- a. Dosage and Administration Section in Highlights of Prescribing information and Full Prescribing Information
 - a. Revise all instances of the symbols ‘<’, ‘>’, ‘≤’, and ‘≥’ to read “less than”, “greater than”, “less than or equal to”, and “greater than or equal to.” The symbols ‘<’ and ‘>’ are dangerous abbreviations that appear on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations because these symbols are often mistaken and used as opposite of intended⁵.
- b. Add the statement “This product should be prepared and administered by healthcare professionals” under section 2.4 Preparation for Subcutaneous Administration and General Use Information.

If you have further questions or need clarifications, please contact Sue Kang, OSE project manager, at 301-796-4216.

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⁵ Institute for Safe Medication Practices, “List of Error-Prone Abbreviations, Symbols, and Dose Designations. www.ismp.org.

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/s/

SARAH K VEE
09/11/2012

YELENA L MASLOV
09/11/2012

CAROL A HOLQUIST
09/11/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: August 24, 2012

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling: [REDACTED] (b) (4)
[REDACTED]

Drug Name (established name): omacetaxine mepesuccinate

Dosage Form and Route: for Injection, for subcutaneous injection

Application Type/Number: NDA 203-585

Applicant: Teva Branded Pharmaceutical Products R&D, Inc. (US Agent for IVAX international GmbH)

1 INTRODUCTION

On March 30, 2012, Cephalon, Inc. submitted for the Agency's review a New Drug Application, NDA 203-585, for omacetaxine mepesuccinate for Injection. The proposed indication for omacetaxine mepesuccinate for Injection is for the treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and /or intolerance to two or more tyrosine kinase inhibitors (TKI). On May 24, 2012, the Division of Hematology Products (DHP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed (b) (4) for omacetaxine mepesuccinate.

On August 21, 2012, FDA was notified that Cephalon, Inc., the original Applicant for NDA 203-585, has been acquired by Teva Pharmaceutical Industries, Ltd. and is now named Teva Branded Pharmaceutical Products R&D, Inc. The new Applicant for this NDA is IVAX international GmbH (IVAX), also owned by Teva Pharmaceuticals Industries, Ltd. (Switzerland). Teva Branded Pharmaceutical Products R&D, Inc. will serve as US Agent on behalf of IVAX.

2 CONCLUSIONS

Following a teleconference between FDA and Teva Pharmaceuticals Ltd. on July 31, 2012, the Applicant revised the labeling to reflect revisions to the preparation and administration of omacetaxine mepesuccinate and submitted revised labeling on August 15, 2012. As a result of the labeling revisions the proposed (b) (4) were removed from labeling for NDA 203-585. Since there is no patient labeling to be reviewed for this NDA, this memo serves to formally close-out DMPP's consult request.

Please notify us if you have any questions.

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/s/

SHARON R MILLS
08/24/2012

BARBARA A FULLER
08/24/2012

LASHAWN M GRIFFITHS
08/24/2012

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Application: 203585

Application Type: New NDA (new molecular entity)

Name of Drug: Omacetaxine mepesuccinate, Lyophilized powder for injection, 3.5 mg/vial

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

Submission Date: March 30, 2012

Receipt Date: March 30, 2012

1.0 Regulatory History and Applicant's Main Proposals

Omacetaxine mepesuccinate is a protein synthesis inhibitor indicated for the treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to prior tyrosine kinase inhibitors, (TKIs including imatinib, dasatinib or nilotinib). The drug product received orphan drug designation for the indication of chronic myelogenous leukemia on March 10, 2006.

Importantly, Omacetaxine was previously submitted as NDA 22374 by ChemGenex. During that review cycle, it was presented to ODAC on March 22, 2010 and received a Complete Response letter on April 8, 2010. Type A meeting was held with ChemGenex on June 30, 2010 to discuss the deficiencies identified in the CR letter. A pre NDA meeting for this application was held on September 13, 2010 with ChemGenex, who was acquired by Cephalon in 2011. NDA 23374 was withdrawn on February 7, 2011.

Cephalon submitted a new drug application as NDA 203585 on March 30, 2012 and it was received the same day. (b) (4)

Although the applicant requested a priority review, it was determined at the filing meeting on May 10, 2012 that the application would be reviewed under a standard, 10 month review clock. The current PDUFA date is **January 30, 2013**.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

Selected Requirements of Prescribing Information (SRPI)

In addition, the following labeling issues were identified:

1. The Package Insert of the labeling should not include a footer with the application number and version date at the bottom of every page of the labeling– please remove the entire footer.
2. The formatting for the section headings within the Full Prescribing Information should have the section identifying numbers presented in bold print and be preceded by the heading or subheading by at least two square em’s (i.e., two squares of the size of the letter “m” in 8 point type).
3. The (b) (4) should start on a new page – please revise accordingly.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by **July 2, 2012**. The resubmitted PI will be used for further labeling review and labeling discussions with the applicant.

Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirements of Prescribing Information (SRPI) version 2 is 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- NO** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

Selected Requirements of Prescribing Information (SRPI)

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *At present, the Highlights section exceeds half page length requirement. The applicant may need to submit a waiver.*

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- NO** 4. White space must be present before each major heading in HL.

Comment: *The applicant should ensure there is adequate white space preceding each major section in the Highlights.*

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **“HIGHLIGHTS OF PRESCRIBING INFORMATION”**.

Selected Requirements of Prescribing Information (SRPI)

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

- YES** 10. Product title in HL must be **bolded**.

Comment: *The proposed proprietary name is still under review.*

Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: *The approval year will be added before any action.*

Boxed Warning

- N/A** 12. All text must be **bolded**.

Comment:

- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A

Selected Requirements of Prescribing Information (SRPI)

19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment: *There is only one contraindicatoin listed - known hypersensitivity to omacetaxine mepesuccinate or mannitol.*

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- "**See 17 for PATIENT COUNSELING INFORMATION**"

If a product **has** FDA-approved patient labeling:

- "**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**"

Selected Requirements of Prescribing Information (SRPI)

- “See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

Selected Requirements of Prescribing Information (SRPI)

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

Selected Requirements of Prescribing Information (SRPI)

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- NO** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”

Selected Requirements of Prescribing Information (SRPI)

- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment: *The applicant needs to add the following statement to the beginning of Section 17, "See FDA-approved patient labeling (Medication Guide and Instructions for Use)".*

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/s/

THERESA A FERRARA
05/30/2012

JANET K JAMISON
05/30/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 203585 BLA#	NDA Supplement #:S- N/A BLA Supplement #	Efficacy Supplement Type SE- N/A
Proprietary Name: TBD Established/Proper Name: Omacetaxine mepesuccinate Dosage Form: Lyophilized powder for injection Strengths: 3.5 mg/vial		
Applicant: Cephalon, Inc. (a wholly owned subsidiary of Teva Pharmaceuticals Ltd) Agent for Applicant (if applicable):		
Date of Application: March 30, 2012 Date of Receipt: March 30, 2012 Date clock started after UN:		
PDUFA Goal Date: January 30, 2013	Action Goal Date (if different):	
Filing Date: May 29, 2012	Date of Filing Meeting: May 10, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1 – New Molecular Entity		
Proposed indication(s)/Proposed change(s) Adult patients with chronic or accelerated phase CML with resistance or intolerance to prior TKI therapy		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the “505(b)(2) Assessment” review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input checked="" type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 62384				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			Proprietary name review is ongoing. Submitted 4.5.12
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			No user fee paid bc orphan designation

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the <i>Orphan Drug Designations and Approvals</i> list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 7 years</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			Requesting 7 yrs of orphan exclusivity
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff :</i></p>		X		

Pediatrics	YES	NO	NA	Comment
<p>PREA</p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		Granted orphan designation for the CML indication
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>			X	

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			X	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		(b) (4) – FDA may determine if REMS will be needed (b) (4)
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	(b) (4)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>			X	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i> <div style="background-color: #cccccc; padding: 2px;">(b) (4)</div> OSE consult: DMEPA & DRISK submitted 5.14.12 QT-IRT consult: submitted 5.15.12 OPDP (DDMAC) consult: submitted 5.24.12 Patient Labeling Team consult: submitted 5.24.12	X			

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		X		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): September 13, 2010 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 10, 2012

BLA/NDA/Supp #: NDA 203585

PROPRIETARY NAME: TBD

ESTABLISHED/PROPER NAME: Omacetaxine mepesuccinate

DOSAGE FORM/STRENGTH: Lyophilized powder for injection; 3.5 mg/vial

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

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Adult patients with chronic or accelerated phase CML with resistance or intolerance to prior TKI therapy, including imatinib, dasatinib or nilotinib

BACKGROUND: Cephalon’s drug product, Omacetaxine mepesuccinate, is a protein synthesis inhibitor for the treatment of adult patients with chronic or accelerated phase CML with resistance or intolerance to prior tyrosine kinase inhibitors, including imatinib, dasatinib or nilotinib. Omacetaxine mepesuccinate was granted orphan designation for the indication of chronic myelogenous leukemia on March 10, 2006.

Of note, omacetaxine was previously submitted as NDA 22374 by ChemGenex. During that review cycle, it was presented to ODAC on March 22, 2010 and received a Complete Response letter on April 8, 2010. Type A meeting was held with ChemGenex on June 30, 2010 to discuss the deficiencies identified in the CR letter.

A pre NDA meeting for this application was held on September 13, 2010 with ChemGenex, who was acquired by Cephalon in 2011. NDA 23374 was withdrawn on February 7, 2011.

Cephalon submitted a new drug application as NDA 203585 on March 30, 2012. Cephalon presented their application during application presentation on Thursday, May 10, 2012.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Theresa Ferrara	Y
	CPMS/TL:	Janet Jamison	N
Cross-Discipline Team Leader (CDTL)	Virginia Kwitkowski		Y
Clinical	Reviewer:	Firoozeh Alvandi	Y
	TL:	Virginia Kwitkowski	Y
Social Scientist Review (for OTC	Reviewer:	N/A	

<i>products)</i>	TL:	N/A	
	Reviewer:	N/A	
OTC Labeling Review (<i>for OTC products)</i>	TL:	N/A	
	Reviewer:	N/A	
Clinical Microbiology (<i>for antimicrobial products)</i>	TL:	N/A	
	Reviewer:	N/A	
Clinical Pharmacology	TL:	Julie Bullock Acting TL Bahru Habtemariam	N Y
	Reviewer:	Joe Grillo	Y
Biostatistics	TL:	Mark Rothmann	Y
	Reviewer:	Chia Wen (Kiki) Ko	Y
Nonclinical (Pharmacology/Toxicology)	TL:	Haleh Saber	Y
	Reviewer:	Stacey Ricci	Y
Statistics (carcinogenicity)	TL:	N/A	
	Reviewer:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements)</i>	TL:	N/A	
	Reviewer:	N/A	
Product Quality (CMC)	TL:	Janice Brown	Y
	Reviewer:	Debasis Ghosh Elsbeth Chikhale	Y Y
Quality Microbiology (<i>for sterile products)</i>	TL:	Bryan Riley	N
	Reviewer:	Erika Pfeiler	Y
CMC Labeling Review	TL:	N/A	
	Reviewer:	N/A	
Facility Review/Inspection	TL:		
	Reviewer:		
OSE/DMEPA (proprietary name)	Reviewer:	Sarah Vee	Y

	TL:	Yelena Maslov	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Anthony Orenca	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers			
Other attendees	Ann Farrell, Acting Director - DHP Robert Kane, Acting Division Director for Safety – DHP Suzanne Robottom – OSE/DRISK Sue Kang - OSE RPM		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: clinical sites audited from previous review under NDA 23374; Applicant received CR letter in April 2010;</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined

<p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<p>Reason: NDA 23374 went to ODAC in March 2010. Applicant followed FDA recommendations outlined in CR letter from April 8b 2010. At filing meeting (May 10, 2012), team determined it is not necessary to go to ODAC for this review cycle.</p>
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments: EA exclusion was requested; however, applicant had to submit additional information and full review of EA is underway</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: facility information was submitted on April 11th and is still pending</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Richard Pazdur, MD, Director, Office of Hematology & Oncology Products</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<p><input type="checkbox"/></p>	<p>Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).</p>
<p><input type="checkbox"/></p>	<p>If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).</p>
<p><input type="checkbox"/></p>	<p>If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.</p>

<input type="checkbox"/>	
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

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

/s/

THERESA A FERRARA
05/25/2012

JANET K JAMISON
05/25/2012