CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-249

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	March 19, 2008
From	Robert L. Justice, M.D., M.S.
Subject	Division Director Summary Review
NDA/BLA # Supplement #	22-249
Applicant Name	Cephalon, Inc.
Date of Submission	September 20, 2007
PDUFA Goal Date	March 20, 2008
Proprietary Name / Established (USAN) Name	TREANDA/bendamustine HCl
Dosage Forms / Strength	Single-use vial containing 100 mg of bendamustine HCl as lyophilized powder
Proposed Indication(s)	TREANDA (bendamustine hydrochloride) for Injection is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established.
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Reviews	3/5/08
Statistical Reviews	2/19/08
Pharmacology Toxicology Reviews	2/27/08, 3/11/08
CMC Review/OBP Review	2/27/08, 3/19/08
Microbiology Reviews	12/17/07, 2/6/08
Clinical Pharmacology Reviews	2/19/08, 2/22/08
DDMAC	3/3/08
DSI	2/28/08
CDTL Review	3/5/08
OSE/DMEP	3/6/08
OSE/DDRE	N/A
OSE/DSRCS	N/A
SEALD	2/19/08

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEP=Division of Medication Error Prevention
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

Division Director Summary Review

1. Introduction

This new drug application seeks approval of TREANDA for the following indication:

> TREANDA (bendamustine hydrochloride) for Injection is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established.

The application was submitted on September 20, 2007 and the PDUFA goal date is March 20, 2008. This review will summarize the efficacy and safety data supporting approval, the recommendations of each review discipline, and any outstanding issues.

2. Background

Bendamustine is a bifunctional mechlorethamine derivative. Mechlorethamine and its derivatives dissociate into electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties. The bifunctional covalent linkage can lead to cell death via several pathways. The exact mechanism of action of bendamustine remains unknown.

Bendamustine has been marketed in the German Democratic Republic since 1974, in Germany since 1993, and Bulgaria since 2000. It is authorized for the treatment of **Hodgkin's disease, non-Hodgkin's lymphoma,** chronic lymphocytic leukemia, multiple myeloma, and breast cancer.

An IND was submitted in 2003, an end-of-phase 2 meeting was held on 9/2/04, and pre-NDA meetings were held on 4/12/07 and 4/27/07 (CMC). The issue of the potential acceptability of a single randomized trial to support approval was discussed at the EOP2 meeting.

3. CMC/Device

Chemistry Review

The Chemistry Review of 2/27/08 made the following recommendation regarding approval:

> The application is recommended for an approval action for chemistry, manufacturing and controls under section 505 of the Act, provided trademark and labeling acceptability has been determined by Office of Drug Safety (DMETS) and provided the manufacturing sites are deemed acceptable for cGMP compliance. The product quality microbiology has recommended approval on 06-Feb-2008. The recommendation for Office of Compliance regarding the acceptability of the manufacturing facilities is pending as of the date of this review.

The review listed the following deficiencies:

1. The following agreement should be placed in the action letter.

We remind you of your agreement in an amendment dated 12-Feb-2008 to initiate change controls for all the documents impacted by the revision to the maximum hold time not to exceed [redacted] and to submit appropriate post-approval correspondence reflecting this change.

2. The company should commit to the following phase 4 commitment:

Provide an agreement to study the physico-chemical compatibility of the drug product with commonly used diluents such as [redacted] and submit the data within six months from the date of approval of this NDA.

CMC Branch Chief Memo

The CMC Branch Chief Memo of 3/19/08 made the following overall recommendation:

All pending issues subsequent to completion of the primary CMC review have been resolved satisfactorily. The Office of Compliance made an acceptable cGMP recommendation for the NDA on March 17, 2008. The DDMAC and DMETs reviews on labels and labeling were completed and the combined CMC/DMETs comments on labels and labeling were satisfactorily addressed by the firm. An approval recommendation is made for this NDA. A statement on grantable expiration dating period and reminders on a CMC post-marketing commitment and a CMC agreement, listed at the end of this memo, have been included in the action letter.

Comment: I concur with the conclusions reached by the chemistry reviewer and branch chief regarding the acceptability of the manufacturing of the drug product and drug substance and the recommended phase 4 commitment. Stability testing supports an expiry of 24 months. There are no outstanding CMC issues that would preclude approval.

4. Nonclinical Pharmacology/Toxicology

Pharmacology/Toxicology Review and Evaluation

The Pharmacology/Toxicology Review and Evaluation dated February 27, 2008 made the following recommendations:

A. Recommendation on approvability: The non-clinical studies submitted to this NDA provide sufficient information to support the use of Treanda ® (bendamustine hydrochloride) for the treatment of patients with chronic lymphocytic leukemia (CLL).
B. Recommendation for nonclinical studies: No additional non-clinical studies are required.
C. Recommendations on labeling: A separate review will be conducted.

The pharmacology/toxicology labeling review was completed on March 11, 2008.

Secondary and Tertiary Pharmacology/Toxicology Reviews
The secondary and tertiary reviews concurred that the pharmacology and toxicology data support approval and that there are no outstanding nonclinical issues.

Comment: I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding nonclinical pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology Review
The Clinical Pharmacology Review of February 19, 2008 made the following recommendations:

> The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in the NDA 22-249.
>
> This NDA is considered to be deficient from a clinical pharmacology perspective due to the lack of data available regarding pharmacokinetics at the proposed dose, dose proportionality, human excretion and metabolism, effect on QT prolongation, in-vivo drug-drug interactions, and in-vitro p-glycoprotein screens.
>
> The NDA will be considered acceptable pending the sponsor's agreement to the following Phase 4 commitments:
>
> Phase IV commitments
>
> 1. Submit the completed report and data sets for the mass-balance evaluation. Results from this study may indicate a need for dedicated renal and/or hepatic organ impairment studies.
>
> 2. The potential for bendamustine to affect the QT interval needs to be investigated.
>
> 3. The influence of CYP1A2 inhibitors (fluvoxamine) on bendamustine pharmacokinetics needs to be evaluated in-vivo.
>
> 4. The influence of CYP1A2 inducers (smoking) on bendamustine pharmacokinetics needs to be evaluating in-vivo.
>
> 5. In-vitro p-glycoprotein screens need to be completed to determine if bendamustine is an inhibitor or substrate of p-glycoprotein.
>
> 6. [redacted]

Acting Team Leader Memo
The Acting Team Leader memo of February 22, 2008 concurred with these recommendations.

Clinical Pharmacology NDA Review Amendment
The subsequent Clinical Pharmacology NDA Review Amendment of March 11, 2008 agreed with the sponsor's request to delete the last phase 4 commitment for a [redacted]

Comment: I concur with the recommendations made by the clinical pharmacology/biopharmaceutics reviewers regarding the phase 4 commitments. The applicant has agreed to these commitments. There are no outstanding clinical pharmacology/biopharmaceutics issues that would preclude approval.

6. Clinical Microbiology

The final Product Quality Microbiology Review of February 6, 2008 recommended approval.

Comment: I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

The following brief summary of the clinical trial design and efficacy results is excerpted from the agreed upon labeling.

> The safety and efficacy of TREANDA were evaluated in an open-label, randomized, controlled multicenter trial comparing TREANDA to chlorambucil. The trial was conducted in 301 previously-untreated patients with Binet Stage B or C (Rai Stages I - IV) CLL requiring treatment. Need-to-treat criteria included hematopoietic insufficiency, B-symptoms, rapidly progressive disease or risk of complications from bulky lymphadenopathy. Patients with autoimmune hemolytic anemia or autoimmune thrombocytopenia, Richter's syndrome, or transformation to prolymphocytic leukemia were excluded from the study.
>
> The patient populations in the TREANDA and chlorambucil treatment groups were balanced with regard to the following baseline characteristics: age (median 63 vs. 66 years), gender (63% vs. 61% male), Binet stage (71% vs. 69% Binet B), lymphadenopathy (79% vs. 82%), enlarged spleen (76% vs. 80%), enlarged liver (48% vs. 46%), hypercellular bone marrow (79% vs. 73%), "B" symptoms (51% vs. 53%), lymphocyte count (mean $65.7x10^9$/L vs. $65.1x10^9$/L), and serum lactate dehydrogenase concentration (mean 370.2 vs. 388.4 U/L). Ninety percent of patients in both treatment groups had immuno-phenotypic confirmation of CLL (CD5, CD23 and either CD19 or CD20 or both).

Patients were randomly assigned to receive either TREANDA at 100 mg/m^2, administered intravenously over a period of 30 minutes on Days 1 and 2 or chlorambucil at 0.8 mg/kg (Broca's normal weight) administered orally on Days 1 and 15 of each 28-day cycle. Efficacy endpoints of objective response rate and progression-free survival were calculated using a pre-specified algorithm based on NCI working group criteria for CLL.

The results of this open-label randomized study demonstrate superior efficacy for TREANDA treatment as compared with chlorambucil treatment with a higher rate of overall response and a longer progression-free survival (see Table 3). Survival data are not mature.

Table 3: Efficacy Data

	TREANDA (N=153)	Chlorambucil (N=148)	p-value
Response Rate n (%)			
Overall response rate	90 (59)	38 (26)	<0.0001
(95% CI)	(51.03, 66.62)	(18.64, 32.71)	
Complete response (CR)*	13 (8)	1 (<1)	
Nodular partial response (nPR)**	4 (3)	0	
Partial response (PR)†	73 (48)	37 (25)	
Progression-Free Survival††			
Median, months (95% CI)	18 (11.7, 23.5)	6 (5.6, 8.6)	
Hazard ratio (95% CI)	0.27 (0.17, 0.43)		<0.0001

*CR was defined as peripheral lymphocyte count ≤ 4.0 x 10^9/L, neutrophils ≥ 1.5 x 10^9/L, platelets >100 x 10^9/L, hemoglobin > 110g/L, without transfusions, absence of palpable hepatosplenomegaly, lymph nodes ≤ 1.5 cm, < 30% lymphocytes without nodularity in at least a normocellular bone marrow and absence of "B" symptoms. The clinical and laboratory criteria were required to be maintained for a period of at least 56 days.

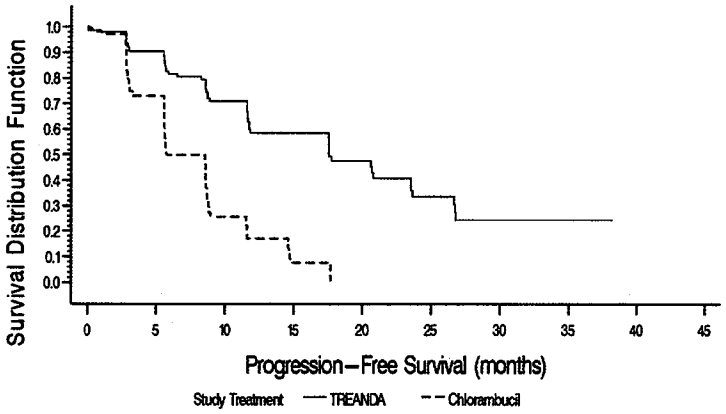
**nPR was defined as described for CR with the exception that the bone marrow biopsy shows persistent nodules.

†PR was defined as ≥50% decrease in peripheral lymphocyte count from the pretreatment baseline value, and either ≥50% reduction in lymphadenopathy, or ≥50% reduction in the size of spleen or liver, as well as one of the following hematologic improvements: neutrophils ≥1.5 x 10^9/L or 50% improvement over baseline, platelets >100 x 10^9/L or 50% improvement over baseline, hemoglobin >110g/L or 50% improvement over baseline without transfusions, for a period of at least 56 days.

††PFS was defined as time from randomization to progression or death from any cause

Kaplan-Meier estimates of progression-free survival comparing TREANDA with chlorambucil are shown in Figure 1.

Figure 1. Progression-Free Survival



Clinical Review
The Clinical Review was completed on March 5, 2008 and made the following recommendation on regulatory action:

> The efficacy and safety reviewers recommend approval of Treanda for the following indication, if the applicant can provide adequate financial disclosure information.
>
> "TREANDA (bendamustine hydrochloride) for Injection is an alkylating agent indicated for the treatment of patients with chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established."

In addition to the phase 4 commitments recommended by Clinical Pharmacology, the Clinical Review recommended that "The applicant should continue to follow subjects of study 02CLLIII for survival outcome."

Clinical Review Addendum
A Clinical Review Addendum was completed on 3/18/08. The addendum reviewed the updated financial disclosure information provided by the applicant, provided an analysis of drug-induced liver injury, and evaluated the data submitted by the applicant to support their labeling recommendations for dose modifications for toxicity.

The applicant was able to obtain financial disclosure information from all but two investigators. One was deceased and the other on an extended vacation. The review reached the following conclusions regarding financial disclosure:

> The available information does not suggest that the study results would be influenced by financial interest since no personal financial interest was reported by any of the investigators. Due to the small number of investigators for whom financial disclosure information is not available and the small number of patients enrolled by these investigators, it is unlikely that the information not available to date would influence FDA's interpretation of the study results.

Cross-Discipline Team Leader Review
The Cross-Discipline Team Leader Review was completed on March 5, 2008. The review recommended the following regulatory action:

> Pending reviews of DMETS and DDMAC, all disciplines recommend approval of Treanda for CLL. A statistically significant improvement in response rate, and progression free survival was observed. The adverse event profile is acceptable.

Statistical Review and Evaluation
The Statistical Review and Evaluation was completed on February 20, 2007 and made the following conclusions and recommendations:

The sponsor submitted this application to evaluate the efficacy of Treanda (Bendamustine) compared with chlorambucil in the initial treatment of patients with chronic lymphocytic leukemia (CLL) in Binet stage B or Binet stage C requiring treatment. The applicant is seeking approval based on the primary efficacy endpoints, overall response rate (ORR) and progression-free survival (PFS). ORR was the proportion of patients in each treatment group with a best response of CR, nPR, or PR. Progression-free survival (PFS) was defined as the time from randomization to progressive disease (PD) or death for any cause, whichever occurred first. The primary analyses were based on the Independent Committee for Response Assessment (ICRA) adjudicated responses and adjudicated event time points. This application was based primarily on data from a Phase III pivotal study (02CLLIII). This was an open-label, randomized, Phase 3 study. Patients were randomly assigned (with stratification by Binet stage and study center) to either the bendamustine or chlorambucil treatment group at a ratio of 1: 1

A total of 302 patients were screened and 301 were randomly assigned to treatment (1 patient was not assigned to a treatment group due to refusal) at 45 centers throughout 8 countries. The sponsor reported that the proportion of patients with ORR was 62% in the bendamustine treatment group compared with 33% in the chlorambucil treatment group ($p<0.0001$) as determined by the Independent Committee for Response Assessment (ICRA). The primary PFS analysis showed that the bendamustine treatment was superior to chlorambucil treatment (median 21 vs. 9 months, hazard ratio (HR) 0.23, $p<0.0001$). Based on the data submitted by the sponsor these results were confirmed by this reviewer and the data support the efficacy claim.

Whether the endpoints and the sizes of the effects on these two endpoints in this phase III study are adequate for approval is a clinical decision.

Statistical Team Leader's Memo

The statistical team leader's memo of 2/25/08 made the following conclusion and recommendation:

This is Team Leader's memo of the New Drug Application (NDA) submission seeking approval for bendamustine (Treanda) as the first line treatment of chronic lymphocytic leukemia (CLL) based on one randomized study comparing to chlorambucil in previously untreated adults with symptomatic Binet stage B or stage C CLL requiring treatment. I concur with the primary reviewer, Dr. Tang's conclusion that the data submitted supports the claim that bendamustine has demonstrated superior overall response rate (ORR) and progression-free survival (PFS) compared to chlorambucil (ORR of 59% vs. 26% and PFS HR = 0.52, p-value < 0.0001). Please refer to the primary review by Dr. Tang for the details of the study and the results.

Progression-free survival was assessed by a panel of three independent expert hematologic oncologists and also objectively calculated using an algorithm based on NCI working group criteria. According to the sponsor, in performing the review the members of the independent panel were allowed to exercise clinical judgment in

determining response and did not include bone marrow evaluations as required by the NCI working group criteria. The FDA reviewers were able to verify the calculated response rates and PFS, but could not verify the same as determined by the independent panel due the subjective nature of the independent evaluation. Therefore, it is recommended that the calculated response rates and PFS estimates be included in the product label.

Comment: There are discrepancies in the response rates in the statistical review and the statistical team leader's memo and in the hazard ratios for PFS in the statistical review, the statistical team leader's memo, and the draft labeling. As noted in the statistical team leader's memo, the calculated response rates and PFS estimates should be included in the package insert. The calculated response rates were 59% for bendamustine and 26% for chlorambucil. The calculated PFS hazard ratios were 0.52 for the unadjusted analysis and 0.27 for the adjusted analysis. Both the statistical reviewer and the statistical team leader confirmed that the hazard ratio for PFS in the package insert should be 0.27 since the adjusted analysis was prespecified.

I concur with the recommendations of the clinical and statistical reviewers. Although only a single randomized trial was submitted, the efficacy results are clinically and statistically robust. There are no efficacy issues that would preclude approval.

8. Safety

The safety profile of bendamustine is summarized in the following excerpts from the agreed upon package insert:

Adverse reactions were reported according to NCI CTC v. 2.0. In the randomized CLL clinical study, hematologic adverse reactions (any grade) in the TREANDA group that occurred with a frequency greater than 15% were neutropenia (28%), thrombocytopenia (23%), anemia (19%), and leukopenia (18%). Non-hematologic adverse reactions (any grade) in the TREANDA group that occurred with a frequency greater than 15% were pyrexia (24%), nausea (20%), and vomiting (16%).

Other adverse reactions seen frequently in one or more studies included asthenia, fatigue, malaise, and weakness; dry mouth; somnolence; cough; constipation; headache; mucosal inflammation and stomatitis.

Worsening hypertension was reported in 4 patients treated with TREANDA in the randomized CLL clinical study and none treated with chlorambucil. Three of these 4 adverse reactions were described as a hypertensive crisis and were managed with oral medications and resolved.

The most frequent adverse reactions leading to study withdrawal for patients receiving TREANDA were hypersensitivity (2%) and pyrexia (1%).

Table 1 contains the treatment emergent adverse reactions, regardless of attribution, that were reported in ≥5% of patients in either treatment group in the randomized CLL clinical study.

Table 1: Adverse Reactions Occurring in Randomized CLL Clinical Study in at Least 5% of Patients

	Number (%) of patients			
	TREANDA (N=153)		Chlorambucil (N=143)	
System organ class Preferred term	All Grades	Grade 3/4	All Grades	Grade 3/4
Total number of patients with at least 1 adverse reaction	**136 (89)**	**88 (58)**	**113 (79)**	**44 (31)**
Blood and lymphatic system disorders				
Neutropenia	43 (28)	36 (24)	20 (14)	13 (9)
Thrombocytopenia	35 (23)	20 (13)	28 (20)	11 (8)
Anemia	29 (19)	4 (3)	16 (11)	0
Leukopenia	28 (18)	23 (15)	4 (3)	2 (1)
Lymphopenia	10 (7)	10 (7)	0	0
Gastrointestinal disorders				
Nausea	31 (20)	1 (<1)	21 (15)	1 (<1)
Vomiting	24 (16)	1 (<1)	9 (6)	0
Diarrhea	14 (9)	2 (1)	5 (3)	0
General disorders and administration site conditions				
Pyrexia	36 (24)	6 (4)	8 (6)	2 (1)
Fatigue	14 (9)	2 (1)	8 (6)	0
Asthenia	13 (8)	0	6 (4)	0
Chills	9 (6)	0	1 (<1)	0
Immune system disorders				
Hypersensitivity	7 (5)	2 (1)	3 (2)	0
Infections and infestations				
Nasopharyngitis	10 (7)	0	12 (8)	0
Infection	9 (6)	3 (2)	1 (<1)	1 (<1)
Herpes simplex	5 (3)	0	7 (5)	0
Investigations				
Weight decreased	11 (7)	0	5 (3)	0
Metabolism and nutrition disorders				
Hyperuricemia	11 (7)	3 (2)	2 (1)	0
Respiratory, thoracic and mediastinal disorders				
Cough	6 (4)	1 (<1)	7 (5)	1 (<1)
Skin and subcutaneous tissue disorders				
Rash	12 (8)	4 (3)	7 (5)	3 (2)
Pruritus	8 (5)	0	2 (1)	0

The Grade 3 and 4 hematology laboratory test values by treatment group in the randomized CLL clinical study are described in Table 2. These findings confirm the myelosuppressive effects seen in patients treated with TREANDA. Red blood cell transfusions were administered to 20% of patients receiving TREANDA compared with 6% of patients receiving chlorambucil.

Table 2—Incidence of Hematology Laboratory Abnormalities in Patients Who Received TREANDA or Chlorambucil in the Randomized CLL Clinical Study				
	TREANDA n=150		Chlorambucil N=141	
Laboratory Abnormality	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**
Hemoglobin Decreased	134 (89)	20 (13)	115 (82)	12 (9)
Platelets Decreased	116 (77)	16 (11)	110 (78)	14 (10)
Leukocytes Decreased	92 (61)	42 (28)	26 (18)	4 (3)
Lymphocytes Decreased	102 (68)	70 (47)	27 (19)	6 (4)
Neutrophils Decreased	113 (75)	65 (43)	86 (61)	30 (21)

In the randomized CLL clinical study, 34% of patients had bilirubin elevations, some without associated significant elevations in AST and ALT. Grade 3 or 4 increased bilirubin occurred in 3% of patients. Increases in AST and ALT of grade 3 or 4 were limited to 1% and 3% of patients, respectively. Patients treated with TREANDA may also have changes in their creatinine levels. If abnormalities are detected, monitoring of these parameters should be continued to ensure that significant deterioration does not occur.

The package insert also includes the following Warnings and Precautions:

- Patients treated with TREANDA are likely to experience myelosuppression. In the randomized CLL clinical study, patients receiving TREANDA experienced Grade 3 or 4 neutropenia (24%), febrile neutropenia (3%), red blood cell transfusions (20%), and **platelet transfusions (<1%)...**
- Infection, including pneumonia and sepsis, has been reported in patients in clinical trials and in post-marketing reports. Infection has been associated with hospitalization, **septic shock and death...**
- Infusion reactions to TREANDA have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred, particularly in the second and subsequent **cycles of therapy...**
- Tumor lysis syndrome associated with TREANDA treatment has been reported in patients in clinical trials and in post-marketing reports. The onset tends to be within the first treatment cycle of TREANDA and, without intervention, may lead to acute renal failure and death. Preventive measures include maintaining adequate volume status, close monitoring of blood chemistry, particularly potassium and uric acid levels, and

the use of allopurinol during the first one to two weeks of TREANDA therapy in patients at high risk...

- A number of skin reactions have been reported in clinical trials and post-marketing safety reports. These events have included rash, toxic skin reactions and bullous exanthema...
- TREANDA can cause fetal harm when administered to a pregnant woman...

Clinical Review Addendum
As noted in section 7 above, the review of drug-induced liver injury identified no cases that met Hy's law. The review also evaluated the applicant's analysis of dose modifications for toxicity that were utilized in the trial and recommended labeling revisions which were accepted by the applicant.

Comment: The size of the safety database is adequate for this indication. The safety data from the clinical trials were supplemented by non-US postmarketing safety data. No REMS are recommended at this time. There are no outstanding safety issues that would preclude approval.

9. Advisory Committee Meeting

This application was not referred to the Oncologic Drugs Advisory Committee because the improvements in response rate and progression-free survival with bendamustine compared to chlorambucil were clinically and statistically robust and the safety profile is comparable to other therapies used for the treatment of CLL.

10. Pediatrics

PREA is not applicable because the applicant has orphan drug exclusivity for the use of bendamustine in CLL.

11. Other Relevant Regulatory Issues

The Clinical Inspection Summary was completed on February 28, 2008 and provided the following overall assessment of findings and recommendations:

> The study data collected by Dr. ~ Dr. ~ Dr. ~ and Dr. ~ appear reliable. The inspection of Cephalon Inc., did not identify any critical issues. Only the sponsor inspection has completed the EIR and provided that to DSI for support of the CIS. The 4 CIs final reports (EIRs) have not been completed to date. While 2 of the 4 clinical investigators inspected were issued Form FDA 483 inspection observations, it does not appear that the compliance deviations would significantly alter overall study outcome.
>
> The 2 CIs that were issued Form FDA 483s appeared to have problems with protocol compliance, appropriate use of the study drug and the timely reporting of serious Adverse Events. The deliberate use of altered dosing levels in certain subjects for both

the study drug and comparator drug at Dr. [redacted] site does not appear to give the study drug a favorable advantage (personal communication with the review division medical officer, Qin Ryan). According to the final establishment inspection report for the sponsor the site deliberately altered drug dosing levels for "safety reasons."

Regarding study sites 01 and 02, the FDA inspectional findings described in this report are not sufficient to make a determination of data reliability associated with those data generated at study sites 01 and 02. The sponsor-described findings of protocol non-compliance and possible human use ethics violations at these foreign sites are very concerning. [redacted]

Observations noted above are based in part on the preliminary communications provided the field investigators. Only the findings at the sponsor, Cephalon Inc., are based on a final EIR. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final remaining EIRs.

Because of the problems identified by both the applicant and DSI with study sites 01 and 02, the applicant conducted a sensitivity analysis excluding patients from these sites. The results of this analysis are discussed in the Clinical Review:

The PFS analysis is still statistically significant after excluding sites 1 and 2. The clinical and statistical reviewers verified applicant's sensitivity analysis and agree that the impact of sites 1 and 2 to the progression free survival is minimal.

DDMAC comments on draft labeling were completed on 3/3/08 and were considered during the labeling discussions.

Comment: There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: OSE/DMEP had no objections to the use of TREANDA as the proprietary name.
- Physician labeling: Agreement has been reached on the physician labeling. The major issues were the appropriate efficacy analysis to include in the label and the inclusion of dose modifications for toxicity. The applicant objected to [redacted] The applicant provided an analysis which supported their proposed dose modifications.
- Carton and immediate container labels: CMC and OSE/DMEP recommendations for changes in the carton and container labels were communicated to and accepted by the applicant. Revised labels were submitted and are acceptable.
- Patient labeling/Medication guide: not applicable.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: approval

- Risk Benefit Assessment: The improvements in response rate and PFS with bendamustine compared to chlorambucil were clinically and statistically robust. The overall response rates were 59% for bendamustine and 29% for chlorambucil ($p<0.001$). The hazard ratio for PFS was 0.27 ($p<0.001$) and the median PFS was 18 months for bendamustine and 6 months for chlorambucil. This was achieved with an acceptable safety profile as noted above.

- Recommendation for Postmarketing Risk Management Activities

  None

- Recommendation for other Postmarketing Study Commitments

  The applicant has agreed to the following postmarketing study commitments:

  1. Cephalon commits to providing an updated study report of Protocol 02CLLIII titled *"Phase III, Open-Label, Randomized, Multicenter Efficacy and Safety Study of Bendamustine Hydrochloride Versus Chlorambucil in Treatment-Naive Patients with (Binet Stage B/C) B-CLL Requiring Therapy"* at data cut off date in May 2008. Response rate, progression-free survival, overall survival and safety updates will be provided in this study report.

     Protocol Submission: N/A
     Study Start: N/A
     Final Report Submission: February, 2009

  2. Cephalon commits to submitting the results and data from the ADME Study 1039 titled "An Open-Label Study to Investigate the Pharmacokinetics (Distribution, Metabolism, and Excretion) of Bendamustine Hydrochloride Following Intravenous Infusion of [^{14}C] Bendamustine Hydrochloride in Patients with Relapsed or Refractory Malignancy (Hematologic or Nonhematologic)". Results from this study may indicate a need for dedicated renal and/or hepatic organ impairment studies.

     Protocol Submission: May, 2008
     Study Start: December, 2008
     Final Report Submission: PK report- December, 2009
     Final report with safety data: March, 2010

  3. Cephalon commits to conducting a study to assess the potential for bendamustine to prolong the QT interval in patients. The QT plan will be submitted prior to initiation for IRT review and concurrence.

Protocol Submission: July, 2008
Study Start: December, 2008
Final Report Submission: June, 2010

4. Since bendamustine is a CYP1A2 substrate *in vitro*, Cephalon agrees to perform an *in vivo* drug interaction study of the ability of fluvoxamine (CYP1A2 inhibitor) to alter the pharmacokinetics of a single dose of bendamustine. The necessity to conduct this study will be predicated upon the results from Study 1039.

   Protocol Submission: March, 2010
   Study Start: September, 2010
   Final Report Submission: PK report - January, 2012
   Final report with safety data: July, 2012

5. Since bendamustine is a CYP1A2 substrate *in vitro*, Cephalon agrees to perform an *in vivo* drug interaction study of the ability of smoking (CYP1A2 inducer) to alter the pharmacokinetics of a single dose of bendamustine. The necessity to conduct this study will be predicated upon the results from Study 1039.

   Protocol Submission: March, 2010
   Study Start: September, 2010
   Final Report Submission: PK report - July, 2012
   Final report with safety data: December, 2012

6. Cephalon commits to conducting *in vitro* screens to determine if bendamustine is a p-glycoprotein substrate or inhibitor.

   Protocol Submission: March, 2008
   Study Start: September, 2007
   Final Report Submission: June, 2008

7. Cephalon commits to assess the physico-chemical compatibility of Treanda with the following diluents as admixtures to reconstituted TREANDA: [redacted] sodium chloride).

   Protocol submission: April 1, 2008
   Study start: May 15, 2008
   Final Report: September 1, 2008

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/s/

Robert Justice
3/19/2008 06:43:22 PM
MEDICAL OFFICER