# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**22-203**

# SUMMARY REVIEW

# Summary Review for Regulatory Action

| | |
|---|---|
| **Date** | October 31, 2008 |
| **From** | Robert L. Justice, M.D., M.S. |
| **Subject** | Division Director Summary Review |
| **NDA/BLA #**<br>**Supplement #** | 22-303 |
| **Applicant Name** | Cephalon |
| **Date of Submission** | December 31, 2007 |
| **PDUFA Goal Date** | October 31, 2008 |
| **Proprietary Name /**<br>**Established (USAN) Name** | Treanda Injection/<br>Bendamustine hydrochloride |
| **Dosage Forms / Strength** | Single-use vial containing 100 mg of bendamustine HCl as lyophilized powder |
| **Proposed Indication(s)** | 1. TREANDA for Injection is indicated for the treatment of patients with indolent B-cell non-Hodgkin's lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen |
| **Action/Recommended Action for NME:** | *Approval* |

| **Material Reviewed/Consulted**<br>OND Action Package, including: | |
|---|---|
| Medical Officer Review | X |
| Statistical Review | X |
| Pharmacology Toxicology Review | X |
| CMC Review/OBP Review | X |
| Microbiology Review | |
| Clinical Pharmacology Review | X |
| DDMAC | X |
| DSI | X |
| CDTL Review | X |
| OSE/DMETS | |
| OSE/DDRE | |
| OSE/DSRCS | |
| Other | |

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

# Signatory Authority Review

## 1. Introduction

This review will summarize the safety and efficacy data supporting the approval of a new indication for TREANDA and each discipline's recommendation regarding approval.

## 2. Background

TREANDA NDA 22-249 was approved on 3/20/08 for the indication of treatment of patients with chronic lymphocytic leukemia. This efficacy supplement "for the treatment of patients with indolent B-cell non-Hodgkin's lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen" was submitted on 12/28/07 prior to the approval of 22-249 and thus has a different NDA number.

## 3. CMC/Device

The CMC review of 10/14/08 stated that "Based on the review of additional compatibility data and the previous review of CMC information under NDA 22-249, this application is recommended for approval action for chemistry, manufacturing, and controls under section 505 of the Act. The review of 10/30/08 stated that "The immediate container (vial) and carton labels submitted in e-mail amendment of 29-Oct-2008 (and attached to this memorandum) are acceptable from a CMC point of view." The review of 10/31/08 concluded that the claim for Categorical Exclusion for submission of an Environmental Assessment is adequately justified.

*Comment: I concur with the conclusions reached by the chemistry reviewer. There are no outstanding CMC issues.*

## 4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Review and Evaluation of 10/22/08 made the following recommendations:

**Recommendations**

A. Recommendation on approvability: The non-clinical studies submitted to cross reference NDA 22-249 provide sufficient information to support the use of Treanda ® (bendamustine hydrochloride) for the treatment of patients with indolent B-cell non-Hodgkin's lymphoma (NHL) who have progressed during or following treatment with rituximab or a rituximab-containing regimen.

B. Recommendation for nonclinical studies: No additional non-clinical studies are required.

C. Recommendations on labeling: Recommendations to the sponsor's proposed labeling are given below.

*Comment: I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.*

## 5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review of 10/27/08 provided the following summary.

> The only new clinical pharmacology information submitted in the current submission is the exposure-response analysis conducted for the Phase 3 Study SDX-105-03. No exposure measures were found to be significant predictors of responder status, duration of response, or progression-free survival within the studied exposure range. Among the safety endpoints evaluated in the PK/PD analyses, nausea was the only safety endpoint that was found to be statistically significantly related to bendamustine exposure.

The review stated that "The NDA is considered acceptable from a clinical pharmacology perspective."

*Comment: I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.*

## 6. Clinical Microbiology

Not applicable to this supplement.

## 7. Clinical/Statistical-Efficacy

A description of the study design and the efficacy results used to support approval are provided in the following excerpt from section 14.2 of the agreed-upon package insert.

> The efficacy of TREANDA was evaluated in a single arm study of 100 patients with indolent B-cell NHL that had progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. Patients were included if they relapsed within 6 months of either the first dose (monotherapy) or last dose (maintenance regimen or combination therapy) of rituximab. All patients received TREANDA intravenously at a dose of 120 mg/m$^2$, on Days 1 and 2 of a 21-day treatment cycle. Patients were treated for up to 8 cycles.
>
> The median age was 60 years, 65% were male, and 95% had a baseline WHO performance status of 0 or 1. Major tumor subtypes were follicular lymphoma (62%), diffuse small lymphocytic lymphoma (21%), and marginal zone lymphoma (16%). Ninety-nine percent of patients had received previous chemotherapy, 91% of patients had received previous alkylator therapy, and 97% of patients had relapsed within 6 months of either the first dose (monotherapy) or last dose (maintenance regimen or combination therapy) of rituximab.

Efficacy was based on the assessments by a blinded independent review committee (IRC) and included overall response rate (complete response + complete response unconfirmed + partial response) and duration of response (DR) as summarized in Table 6.

**Table 6: Efficacy Data for NHL***

| | **TREANDA (N=100)** |
|---|---|
| **Response Rate (%)** | |
| Overall response rate (CR+CRu+PR) | 74 |
| (95% CI) | (64.3, 82.3) |
| Complete response (CR) | 13 |
| Complete response unconfirmed (CRu) | 4 |
| Partial response (PR) | 57 |
| **Duration of Response (DR)** | |
| Median, months (95% CI) | 9.2 months (7.1, 10.8) |

CI = confidence interval

*IRC assessment was based on modified International Working Group response criteria (IWG-RC) [2]. Modifications to IWG-RC specified that a persistently positive bone marrow in patients who met all other criteria for CR would be scored as PR. Bone marrow sample lengths were not required to be ≥20 mm.

Clinical Review

The Clinical Review of 10/28/08 made the following Recommendation/Risk Benefit Analysis.

### 1.1 Recommendation on Regulatory Action

Cephalon has submitted New Drug Application # 22,303 for the following proposed indication:

*TREANDA is indicated for treatment of patients with indolent B-cell non-Hodgkin's lymphoma (NHL) who have progressed during or following treatment with rituximab or a rituximab-containing regimen*

The clinical team recommends approval of this NDA. The basis of this recommendation are the results of a single-arm study using single-agent bendamustine in 100 patients with rituximab-refractory indolent Non-Hodgkin's lymphoma that was submitted in support of the efficacy and safety of bendamustine in this population. Study SDX105-03(hereafter referred to as the *primary study*) met its dual primary endpoints of Objective Response Rate and Duration of Response. The study was well-conducted in a North American population making the results easily extrapolated to the U.S. population. The results of the primary study indicate that bendamustine is effective in inducing sustainable, objective tumor response in 74% of patients in this treatment-refractory population.

The primary study treated 100 patients with indolent B-cell lymphoma with bendamustine at a dose of 120 mg/m$^2$ IV over 60 minutes on days 1 & 2 every 21 days for up to 6-8 cycles. The Overall Response Rate (ORR) was 74% in the Intent To Treat (ITT) population with Complete Response (CR) and Complete Response unconfirmed (CRu) rates of 13% and 4% respectively. The median duration of response in this study was 40.3 weeks (9.2 months). Three patients among these 100 did not meet the protocol definition for rituximab-refractory disease. However, the efficacy data for all 100 patients will be presented because the overall response rate is minimally changed when these non-refractory patients are removed.

The safety population for this review is comprised of 176 patients who received single-agent bendamustine in two studies at 120 mg/m2 IV Days 1 & 2 of every 21 day cycle for up to 9 cycles. The safety profile of bendamustine in this combined study population appears unchanged from the previous safety review during the CLL application review.

Based upon the review of the submitted studies, the proposed indication is altered slightly as follows to more clearly identify the population studied:

*Indolent B-cell non-Hodgkin's lymphoma (NHL) which has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.*

### 1.2 Risk Benefit Analysis

Based upon my review of the clinical data submitted in support of this application, the benefits of the treatment of indolent NHL with bendamustine outweigh the risks. Reduction in tumor size

of adequate duration and magnitude is believed to represent a surrogate for clinical benefit in single-arm trials of indolent NHL. Objective responses (Complete Response, Complete Response unconfirmed, and Partial Response) in the primary study were observed in 74% of patients with a median duration of response being 9.2 months.

The safety assessment of bendamustine was initially made during the review of NDA 22-249 by the comparison of adverse reactions experienced by patients with newly diagnosed CLL treated with bendamustine versus chlorambucil. The safety assessment in the single-arm studies for this application did not reveal any unexpected toxicities of bendamustine that would hinder approval of this agent in this even more heavily pre-treated and treatment-refractory population. Both single-arm studies had similar adverse reaction profiles.

Up front treatment of patients with indolent lymphoma typically involves the use of rituximab in combination with chemotherapy. Indolent lymphoma remains incurable and refractoriness to rituximab often occurs. Agents that are in the armamentarium for the treatment of rituximab-refractory patients include both FDA-approved agents for this specific population, and FDA-approved agents that are used off-label by oncologists. FDA-approved agents include Bexxar and Zevalin; two radioimmunotherapies that are underutilized by oncologists due to the difficulty of administration and the persistent hematologic toxicities observed with the use of these agents. Single-agents used off-label include chlorambucil, cyclophosphamide, fludarabine, pentostatin, and cladribine with varying efficacy and similar hematologic toxicity profiles.

No new post-marketing risk management activities or post-marketing study commitments were recommended.

Statistical Review and Evaluation

The Statistical Review and Evaluation of 9/25/08 made the following conclusions and recommendations.

Based on this reviewer's analysis of the assessments made by the independent review committee (IRC) in study SDX-105-03, 74 out of 100 patients (74%) achieved a best response of PR, CRu, or CR (95% CI: 64.3%, 82.3%). These results differ slightly from those of the sponsor due to a correction to the status of Patient 24093 whose best response was changed from a PR to a SD since the PR response occurred 2 days after the data cut-off date of July 15, 2007. The recalculated median duration of response (DR) is 40 weeks (95% CI: 30.3, 46.9). These results are consistent with those based on investigator assessments and with those from the subset of patients in study SDX-105-01 who had indolent NHL. Subgroup analyses mostly revealed consistent results between subgroups based on demographic and baseline characteristics, although effectiveness was somewhat diminished among patients who were refractory to prior alkylator therapies and prior chemotherapies.

Whether the effectiveness is adequate for approval of bendamustine for the proposed indication will be determined by clinical judgment and an assessment of the product's overall risk/benefit profile.

Cross-Discipline Team Leader Review

The CDTL Review of 10/28/08 made the following recommendations/risk benefit assessment.

Recommended Regulatory Action

All disciplines recommend the approval of Treanda treatment of patients with indolent B-cell non-Hodgkin's lymphoma (NHL) that have progressed on or within 6 months of treatment with rituximab or a rituximab-containing regimen

Risk Benefit Assessment

The recommendation is based on a clinically relevant response rate and magnitude of duration of response in the indicated population. The general toxicity profile is common to chemotherapy agents. The risk-benefit ratio is acceptable for the indicated patient population.

Recommendation for Postmarketing Risk Management Activities

No postmarketing risk management activities are required.

Recommendation for other Postmarketing Study Commitments

There are no new PMCs, voluntary or required.

# 8. Safety

The following excerpt from section 6.2 of the package insert describes the safety information regarding the use of this dose and schedule of bendamustine in non-Hodgkin's lymphoma.

> The data described below reflect exposure to TREANDA in 176 patients with indolent B-cell NHL treated in two single-arm studies. The population was 31-84 years of age, 60% male, and 40% female. The race distribution was 89% White, 7% Black, 3% Hispanic, 1% other, and <1% Asian. These patients received TREANDA at a dose of 120 mg/m$^2$ intravenously on Days 1 and 2 for up to 8 21-day cycles.
>
> The adverse reactions occurring in at least 5% of the NHL patients, regardless of severity, are shown in Table 3. The most common non-hematologic adverse reactions (≥30%) were nausea (75%), fatigue (57%), vomiting (40%), diarrhea (37%) and pyrexia (34%). The most common non-hematologic Grade 3 or 4 adverse reactions (≥5%) were fatigue (11%), febrile neutropenia (6%), and pneumonia, hypokalemia and dehydration, each reported in 5% of patients.

**Table 3: Non-Hematologic Adverse Reactions Occurring in at Least 5% of NHL Patients Treated with TREANDA by System Organ Class and Preferred Term (N=176)**

| System organ class<br>Preferred term | Number (%) of patients* | |
|---|---|---|
| | All Grades | Grade 3/4 |
| **Total number of patients with at least 1 adverse reaction** | 176 (100) | 94 (53) |
| **Cardiac disorders** | | |
| Tachycardia | 13 (7) | 0 |
| **Gastrointestinal disorders** | | |
| Nausea | 132 (75) | 7 (4) |
| Vomiting | 71 (40) | 5 (3) |
| Diarrhea | 65 (37) | 6 (3) |
| Constipation | 51 (29) | 1 (<1) |
| Stomatitis | 27 (15) | 1 (<1) |
| Abdominal pain | 22 (13) | 2 (1) |
| Dyspepsia | 20 (11) | 0 |
| Gastroesophageal reflux disease | 18 (10) | 0 |
| Dry mouth | 15 (9) | 1 (<1) |
| Abdominal pain upper | 8 (5) | 0 |
| Abdominal distension | 8 (5) | 0 |
| **General disorders and administration site conditions** | | |
| Fatigue | 101 (57) | 19 (11) |
| Pyrexia | 59 (34) | 3 (2) |
| Chills | 24 (14) | 0 |
| Edema peripheral | 23 (13) | 1 (<1) |
| Asthenia | 19 (11) | 4 (2) |
| Chest pain | 11 (6) | 1 (<1) |
| Infusion site pain | 11 (6) | 0 |
| Pain | 10 (6) | 0 |
| Catheter site pain | 8 (5) | 0 |
| **Infections and infestations** | | |
| Herpes zoster | 18 (10) | 5 (3) |
| Upper respiratory tract infection | 18 (10) | 0 |
| Urinary tract infection | 17 (10) | 4 (2) |
| Sinusitis | 15 (9) | 0 |
| Pneumonia | 14 (8) | 9 (5) |
| Febrile Neutropenia | 11 (6) | 11 (6) |
| Oral Candidiasis | 11 (6) | 2 (1) |

| | | |
|---|---|---|
| Nasopharyngitis | 11 (6) | 0 |
| **Investigations** | | |
| Weight decreased | 31 (18) | 3 (2) |
| **Metabolism and nutrition disorders** | | |
| Anorexia | 40 (23) | 3 (2) |
| Dehydration | 24 (14) | 8 (5) |
| Decreased appetite | 22 (13) | 1 (<1) |
| Hypokalemia | 15 (9) | 9 (5) |
| **Musculoskeletal and connective tissue disorders** | | |
| Back pain | 25 (14) | 5 (3) |
| Arthralgia | 11 (6) | 0 |
| Pain in extremity | 8 (5) | 2 (1) |
| Bone pain | 8 (5) | 0 |
| **Nervous system disorders** | | |
| Headache | 36 (21) | 0 |
| Dizziness | 25 (14) | 0 |
| Dysgeusia | 13 (7) | 0 |
| **Psychiatric disorders** | | |
| Insomnia | 23 (13) | 0 |
| Anxiety | 14 (8) | 1 (<1) |
| Depression | 10 (6) | 0 |
| **Respiratory, thoracic and mediastinal disorders** | | |
| Cough | 38 (22) | 1 (<1) |
| Dyspnea | 28 (16) | 3 (2) |
| Pharyngolaryngeal pain | 14 (8) | 1 (<1) |
| Wheezing | 8 (5) | 0 |
| Nasal congestion | 8 (5) | 0 |
| **Skin and subcutaneous tissue disorders** | | |
| Rash | 28 (16) | 1 (<1) |
| Pruritus | 11 (6) | 0 |
| Dry skin | 9 (5) | 0 |
| Night sweats | 9 (5) | 0 |
| Hyperhidrosis | 8 (5) | 0 |
| **Vascular disorders** | | |
| Hypotension | 10 (6) | 2 (1) |

*Patients may have reported more than 1 adverse reaction.

**NOTE:** Patients counted only once in each preferred term category and once in each system organ class category.

Hematologic toxicities, based on laboratory values and CTC grade, in NHL patients treated in both single arm studies combined are described in Table 4. Clinically

important chemistry laboratory values that were new or worsened from baseline and occurred in >1% of patients at Grade 3 or 4, in NHL patients treated in both single arm studies combined were hyperglycemia (3%), elevated creatinine (2%), hyponatremia (2%), and hypocalcemia (2%).

**Table 4: Incidence of Hematology Laboratory Abnormalities in Patients Who Received TREANDA in the NHL Studies**

| Hematology variable | Percent of patients | |
|---|---|---|
| | All Grades | Grades 3/4 |
| Lymphocytes Decreased | 99 | 94 |
| Leukocytes Decreased | 94 | 56 |
| Hemoglobin Decreased | 88 | 11 |
| Neutrophils Decreased | 86 | 60 |
| Platelets Decreased | 86 | 25 |

In both studies, serious adverse reactions, regardless of causality, were reported in 37% of patients receiving TREANDA. The most common serious adverse reactions occurring in ≥5% of patients were febrile neutropenia and pneumonia. Other important serious adverse reactions reported in clinical trials and/or post-marketing experience were acute renal failure, cardiac failure, hypersensitivity, skin reactions, pulmonary fibrosis, and myelodysplastic syndrome.

Serious drug-related adverse reactions reported in clinical trials included myelosuppression, infection, pneumonia, tumor lysis syndrome and infusion reactions *[see Warnings and Precautions (5)]*. Adverse reactions occurring less frequently but possibly related to TREANDA treatment were hemolysis, dysgeusia/taste disorder, atypical pneumonia, sepsis, herpes zoster, erythema, dermatitis, and skin necrosis.

Section 5.1 of the Warnings and Precautions section notes the following.

Patients treated with TREANDA are likely to experience myelosupppression. In the two NHL studies, 98% of patients had Grade 3-4 myelosuppression (see Table 4). Three patients (2%) died from myelosuppression-related adverse reactions; one each from neutropenic sepsis, diffuse alveolar hemorrhage with Grade 3 thrombocytopenia, and pneumonia from an opportunistic infection (CMV).

## 9. Advisory Committee Meeting

This application was not taken to an advisory committee meeting because the basis for approval of this application is similar to that for the approvals of Zevalin and Bexxar in the same indication.

## 10. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

## 11. Labeling

Agreement has been reached on the package insert and container and carton labels. There are no unresolved labeling issues.

## 12. Decision/Action/Risk Benefit Assessment

I concur with the recommendations of all reviewers regarding approval of this application. While myelosuppression and other toxicities are significant with the NHL dose and schedule, including a 2% incidence of death due to complications of myelosuppression, the response rate and duration of response in this previously treated population is clinically important. I agree that there is no need for additional post-marketing risk management activities or post-marketing study commitments.

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/s/
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Robert Justice
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MEDICAL OFFICER