

Efficacy Results:

Out of the 100 patients in the primary population, 97% patients were patients who were refractory to rituximab, defined as patients who relapsed within 6 months of either the first (monotherapy) or last dose (maintenance regimen or combination therapy) of rituximab; 99% patients received previous chemotherapy; 91% patients received previous alkylator therapy; 13% patients were refractory to rituximab monotherapy and combination therapy, 58% to rituximab monotherapy, and 26% to rituximab chemotherapy combination. This was a fairly heavily treated population.

Per applicant, treatment was planned for a minimum of 6 cycles. If patients were still receiving clinical benefit, treatment could be continued for a maximum of 8 cycles. Of the 100 patients treated with bendamustine, 60 (60%) patients received treatment for 6 or more cycles. Patients were discontinued from study drug treatment because they had either received maximum benefit from treatment (52%), had adverse events (28%), had disease progression (11%), refused further treatment (2%), or for other reasons (4%). By the data cut-off date, 97 (97%) patients had end-of-treatment evaluations and 3 (3%) patients had completed study drug treatment but did not have an end-of treatment evaluation.

Efficacy Summary

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

Thirteen patients had a CR according to the modified IWG criteria. It is conceivable that if an 'adequate' biopsy sample size (defined in the IWG-CR as at least 2 cm.) was required at baseline, the percentage of patients in CR may have been lower. This is because a repeat biopsy at best response after treatment was required only for patients who had a negative bone marrow biopsy at baseline. However, the ORR of 74% is not expected to have been affected. In addition, as part of the SPA agreement, FDA had encouraged but not required a bone marrow biopsy at baseline. This objective response rate of 74% combined with a median duration of response of 9.2 months has been taken as evidence of clinical benefit in a rituximab-refractory population.

The response rate above was downgraded from an ORR of 75% that was submitted by the applicant. One patient had the CR downgraded to CRu by the IRC and another achieved PR after the date.

Exploratory analysis: ORR and DR in "Need to Treat" Population

Generally the goal of treatment in indolent lymphoma is to maintain the quality of life. Patients are treated only if symptoms are present. This was not an enrollment criterion and was not otherwise prespecified in the protocol. The applicant was requested to provide an exploratory analysis of efficacy of Treanda in patients who had symptoms at baseline that may have required treatment. The applicant provided the information in the table below. Almost 70% patients were identified as having B-symptoms, cytopenias, $ALC > 5.0 \times 10^9/L$, clinical findings of tumor pain, cancer pain, effusion,

ascites, edema, fatigue, malaise, pruritis or weight loss, baseline tumor lesion larger than 7 cm in their greatest dimensions, focal lesions in kidney or liver. The ORR in this patient population was 72% and the median DR was 8.3 months. This exploratory analysis supports the benefit provided by Treanda in refractory patients with NHL.

Exploratory Analysis on Need to Treat Population

Need to Treat Criteria	Percentage of Patients
B-Symptoms	16%
Bulky lymphadenopathy	9%
Other symptoms: edema, pain from bulky tumors, threatened organ function, worsening cytopenias	69%
Ann Arbor Stage III or IV	76%
FLIPI score ≥ 2 in Follicular NHL	71%

From the clinical review by Virginia Kwitkowski, based on the applicant analysis
More than one criterion may have been observed in a patient

The pilot study that was submitted as a supportive study was not found adequate for labeling claims. Due to absence of objective data on progression, it was not clear that the population of patients in that study was the same as in the major study.

Peter Holland PhD, statistical reviewer in his review dated 9/25/2008 (cosigned by Rajeshwari Sridhara PhD and Aloka Chakravarty PhD) states *“The primary study being used to support the proposed indication is study SDX-105-03, a single arm, multi-center study in approximately 100 patients with indolent B-cell NHL who are refractory to rituximab. A Phase II study (SDX-105-01) with a similar design is being used to support this NDA. Both trials enrolled patients in the US and Canada.”*

“The sponsor is claiming that the effectiveness of bendamustine in the proposed indication has been demonstrated by these two trials. Because these are single-arm studies, no statistical inferences are being drawn from them in this review. Rather, the emphasis is on the response rate and duration of responses.”

“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.”

Ms. Kwitkowski recommends approval of this NDA in her clinical review, signed 10/22/2008. She states that *“this recommendation is based upon demonstration of a clinically meaningful overall response rate of adequate duration in a refractory population in a single-arm study. The co-primary endpoints (ORR and DR) for the study were based upon an independent, central review.”*

8. Safety

The safety database was adequate. No new findings were reported from the two studies using single agent Treanda. However information on Toxic Epidermal Necrolysis (TEN) was added in the Warning and Precautions section of the label. This adverse reaction was observed in a combination study with rituximab. TEN has been observed with rituximab and relationship with Treanda can not be ascertained.

The safety data described below reflect exposure to Treanda in 176 patients treated in two single-arm studies of patients with indolent B-cell NHL. 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/m² intravenously on Days 1 and 2 for up to 8 21-day cycles.

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. The major toxicity for Treanda is hematological. Most common hematologic abnormalities (frequency ≥15%) are lymphopenia, anemia, leukopenia, thrombocytopenia, and neutropenia. Please see table below for grade 3 or 4 hematological adverse reactions.

Clinically important chemistry laboratory values that were new or worsened from baseline and occurred in >1% of patients at grade 3 or 4, were hyperglycemia (3%), elevated creatinine (2%), hyponatremia (2%), and hypocalcemia (2%).

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 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. 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. Anaphylaxis has been reported post marketing.

Differences in hematological toxicities (Cross-Study Comparison)

Hematology variable	Grade 3/4 hematological toxicities %	
	NHL Study	CLL Study
Lymphocytes Decreased	94	47
Neutrophils Decreased	61	43
Leukocytes Decreased	55	28
Platelets Decreased	25	11
Hemoglobin Decreased	11	13

As expected due to the dosage difference, the rate of adverse reactions is higher in the NHL study than in the CLL study, although caution is advised in drawing conclusions from cross-comparisons. Ms Kwitkowski notes in the clinical review that the population in the NHL study had been previously treated and this may also be a contributing factor. Overall, 68 (68%) patients had dose reductions or dose delays in the major NHL study, most commonly due to neutropenia and thrombocytopenia. Adverse reactions caused deaths in three patients within 30 days of drug administration. These were pulmonary alveolar hemorrhage concurrent with grade 3 thrombocytopenia, neutropenic sepsis and CMV pneumonia.

According to the clinical reviewer Virginia Kwitkowski, RN, ACNP-BC,
“The extent and duration of exposures to bendamustine during the Second study and the Primary study are adequate for the assessment of safety for the intended use in a population with limited available therapies and a life-threatening condition” and “The safety review of the two phase 2 trials with single-agent bendamustine indicates that adverse events associated with bendamustine are typical of

those seen with other cytotoxic chemotherapies. The main areas of concern with regard to the safety of bendamustine include hematologic toxicity, infections, and gastrointestinal toxicity. No significant cardiac toxicity signals were detected during this review.”

Difference in approved dosage and infusion duration for CLL and NHL indications:

The dose and infusion duration approved for the CLL study is different for that used in the NHL study. See table below

Dose and infusion durations in the CLL and NHL studies

Study	Dose	Infusion duration	Cycles
CLL	100 mg/m ²	30 minutes	up to 6 cycles
NHL	120 mg/m ²	60 minutes	up to 8 cycles

The difference is not a safety issue. Some patients may be administered Treanda in a lower dose and infusion duration due to the health-care provider being used to the currently approved CLL dose and infusion duration. In order to alert health-care providers, these differences will be alluded to in the ACSO Burst and email to ONS (Oncology Nursing Society). In addition, the applicant plans a letter to the health care providers notifying them of this difference in dosage and infusion time.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held.

10. Pediatrics

The applicant requested a pediatric waiver. Indolent lymphoma is rare in the pediatric population. A pediatric waiver is appropriate for this indication.

11. Other Relevant Regulatory Issues

DSI Audits:

According to the DSI memo dated 10/3/2008 signed by Robert Young MD, data may be used in assessment of the pending application. In addition, Dr Young notes that “EIR has not been received in DSI for Dr. (b) (6). This preliminary report is based on a written summary provided by the field inspector. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.”

Financial Disclosure:

An investigator from a site for the major study reported receiving \$37,600 speaking honoraria from Cephalon. As stated by Ms Kwitkowski, *the applicant appears to have performed due diligence with regard to providing sufficient data on financial conflicts of interest via financial disclosures. The results for the (b) (6) studies do not appear to be impacted by any significant conflicts. The disclosure from (one investigator) is not likely to impact the results of the study because his site only enrolled (c) patients. If that site were excluded from the analysis, no impact upon the study findings would result.*^b

12. Labeling

Some major issues identified during labeling are as follows:

Indication:

The applicant proposed the following indication:

Indolent B-cell non-Hodgkin's lymphoma (NHL) (b) (4) have progressed during or (b) (4) treatment with rituximab or a rituximab-containing regimen

This indication was changed to reflect the population enrolled in the major study more accurately and is as follows:

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

Studies used to support Efficacy

Although the applicant proposed using two studies to support the efficacy results, only one of them is being used to support the efficacy claim. The second study did not capture the objective data on progression for enrollment in to the study. It can not be ascertained that the population of the pilot study is the same as the one for which Treanda is being approved.

Mechanism of Action:

Because of conflicting published reports, some information was not accepted by pharmacology review team.

Other:

Some changes have been proposed based on AERS and accepted by OSE for Carton and container. There have also been changes to the CMC section and clinical Pharmacology sections (for PK/PD).

Discussions regarding minor labeling issues are ongoing and have not been finalized at this time.

13. 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.

CDTL Review
NDA 22303; Treanda® for NHL

Recommendation for other Postmarketing Study Commitments

There are no new PMCs, voluntary or required.

Amna Ibrahim, MD
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/s/

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