CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-249

OFFICE DIRECTOR MEMO

March 18, 2008

NDA#: 22-249
Applicant Name: Cephalon, Inc.
PDUFA Goal Date: March 20, 2008
Proprietary Name/USAN Name: TREANDA/BENDAMUSTINE HCl
Action/Recommended Action for NME: Approval

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.

Clinical:

The safety and efficacy of bendamustine were evaluated in a randomized, controlled, European multi-center trial comparing bendamustine to chlorambucil as first-line treatment for CLL patients. The trial was conducted in 301 patients (153 on bendamustine and 148 on chlorambucil) 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. Patients were randomized to receive either bendamustine, 100 mg/m^2 intravenously on days 1 and 2 every 28 days, or to receive chlorambucil, 0.8mg/kg/day orally on days 1 and 15 every 28 days. Up to 6 cycles were administered to each patient.

The efficacy analyses were based on National Cancer Institute-Sponsored Working Group criteria. The overall response rate was 59% for bendamustine versus 26% for chlorambucil ($p < 0.0001$) with 8% versus <1% complete responses on the bendamustine and chlorambucil arms, respectively. The median progression-free survival was 18 months for bendamustine versus 6 months for chlorambucil (hazard ratio 0.27, 95% CI 0.17, 0.43; $p < 0.0001$). Survival data are not mature.

Patients treated with bendamustine had a higher incidence of adverse reactions (89%) than those treated with chlorambucil (79%). The most common adverse reactions (frequency ≥15%) were neutropenia, pyrexia, thrombocytopenia, nausea, anemia, leucopenia, and vomiting. Neutropenic fever was more common in the bendamustine group compared the chlorambucil group. Red blood cell transfusions were administered to 20% of the bendamustine-treated patients compared to 6% of those receiving chlorambucil.The most frequent adverse reactions leading to study withdrawal for patients receiving bendamustine were hypersensitivity and pyrexia. The number of deaths during the treatment period was similar in both the treatment arms.

The Division Director (see Dr. Robert Justice's review) and clinical review team agreed that the application with the above indication be approved. The clinical review recommended that "the applicant should continue to follow subjects of the study 02CLLIII for survival outcomes." The Cross-Discipline Team Leader Review recommended that "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."

The Pharmacology/Toxicology review stated that the non-clinical studies submitted to this NDA provide sufficient information to support the use of Treanda for patients with CLL and that no additional non-clinical studies are required. The Clinical Pharmacology/Biopharmaceutics review considered the NDA to be deficient from a clinical pharmacology perspective due to the lack of data available regarding the 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. To address these problems, the following phase 4 commitments were requested. The sponsor is requested to submit the completed report and data sets for the mass-balance evaluation. Results from this report may indicate a need for a dedicated renal and/or hepatic organ impairment study. The sponsor is also requested to investigate the potential for bendamustine to affect QT intervals, the influence of CYP1A2 inducers and inhibitors on bendamustine *in vivo* pharmacokinetics, and if bendamustine is an inhibitor or substrate of p-glycoprotein. There were no outstanding issues in the clinical microbiology review.

This application was not presented at the Oncologic Drugs Advisory Committee. The endpoints (response rate and PFS) had been used previously in drug approvals. The observed improvements in these endpoints provide internal consistency of a therapeutic effect and are statistically robust. The safety profile is consistent with other drugs used for the treatment of CLL.

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MEDICAL OFFICER