CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208194Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	See electronic signature stamp
From	Janice Brown, M.S.
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 208194
Applicant	Eagle Pharmaceuticals, Inc.
Date of Submission	February 13, 2015 (received February 13, 2013)
PDUFA Goal Date	December 13, 2015
Proprietary Name / Established (USAN) names	BENDEKA (bendamustine hydrochloride)
Dosage forms / Strength	Injection, 100 mg/4 mL (25 mg/mL)
Proposed Indication(s)	For treatment of patients with: • Chronic lymphocytic leukemia (CLL). • Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.
Recommended:	Approval, pending an acceptable recommendation from the Office of Study Integrity and Surveillance (OSIS) of the bioequivalence clinical site inspections

Include the following in the action letter:

A shelf life of 24 months is granted for Bendeka (bendamustine hydrochloride) Injection, when stored in refrigerator at 2 - 8°C (36 - 46°F), protected from light.

1. Introduction

Bendamustine hydrochloride (HCl) is a small molecule, alkylating agent approved for treatment of patients with chronic lymphocytic leukemia (CLL) and indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

The current application for Bendamustine HCl injection is submitted as a 505(b)(2) NDA. The proposed drug product is a ready-to-dilute solution, and does not require reconstitution, as is the case for the listed drug product, Treanda (bendamustine) for injection, which is a lyophilized powder. The proposed drug product is self-preserving and is intended for multiple-uses. (b) (4) the proposed bendamustine HCl injection also must be diluted in 500 mL of 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP prior to intravenous infusion.

2. Background

The subject of the current NDA application is a new formulation for bendamustine HCl. The applicant for this NDA is relying upon information in the public domain (labeling for approved bendamustine HCl product and published studies about bendamustine HCl) to support the safety and efficacy of the proposed product.

(b) (4) New information in NDA 208194 includes a modification of the dose preparation and administration, allowing administration of the product in a smaller volume (50 mL admixture) over a shorter time period (10 minutes), three options for admixtures, drug product stability data to support a 24 month shelf life, a BE study, and a safety and tolerability profile of bendamustine HCl injection when infused over 10 minutes in a 50 mL admixture volume.

Eagle received tentative approval for the companion NDA 205580, bendamustine HCl injection (b) (4) on July 2, 2014 for (b) (4) indolent B-cell NHL only.

3. CMC

Drug Substance: Bendamustine HCl is a (b) (4) nonspecific DNA alkylating agent. It is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring. Mechlorethamine forms electrophilic alkyl groups that form covalent bonds with electron-rich nucleophilic moieties, resulting in interstrand DNA crosslinks. The bifunctional covalent linkage in the DNA leads to cell death.

The chemical name of bendamustine HCl is 1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1 methyl, monohydrochloride. Bendamustine HCl is a (b) (4) powder. (b) (4)

The CMC information for the drug substance was provided in DMF No. (b) (4) from (b) (4) The applicant provided adequate reference to their Type II DMF (b) (4) for information pertaining to the drug substance, bendamustine HCl. Bendamustine HCl is (b) (4) The DMF contains the necessary information related to manufacturing, characterization, physical properties, manufacture, process controls, analytical methods, specification, validation, container closure system, reference standard and stability data for bendamustine HCl. DMF (b) (4) was reviewed and found adequate to support the manufacture of a drug product as a solution dosage form by Joyce Crich, Ph.D. on May 6, 2014. There is no new quality update provided in the DMF since the last review.

Stability data supports a retest period of (b) (4) months for bendamustine HCl drug substance packaged (b) (4)

The NDA included minor drug substance updates and the drug substance reviewer found the information adequate to support the NDA 208194 (refer to the drug substance section of the integrated quality assessment signed by Nina Ni on September 21, 2015).

Drug Product: Bendeka (bendamustine HCl) injection is a ready-to-dilute non-aqueous solution formulation of Bendamustine HCl intended for intravenous administration after further dilution in 50 mL of either 0.9% Sodium Chloride Injection, USP, 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP.

Bendamustine is susceptible to hydrolysis and undergoes rapid degradation (b) (4) Polyethylene glycol 400 (PEG 400) (b) (4) propylene glycol (PG), (b) (4) Monothioglycerol is present at a concentration of 5 mg/mL (b) (4) Sodium hydroxide is used in the formulation to adjust the pH of PEG 400. The excipient levels, in terms of maximum daily dose in the drug product and the admixture are below the levels used in currently approved parenteral drug products.

A shelf life of 24 months is granted for Bendeka (bendamustine HCl) Injection, when stored refrigerated at 2 - 8ºC (36 - 46ºF), protected from light. Storage precautions are required as the

drug product is light sensitive. The primary container must be kept in the secondary packaging in order to protect the drug product from light. Accordingly, the following statement was put on the vial and carton labels: "*Retain in original package until time of use. Protect from light.*"

At the request of the CDTL, the drug product reviewer included the following information on the compatibility of the drug product and admixes in the infusion bags. The drug product review included the following information,

> "However, in the NDA 208194, the applicant did not provide compatibility study in terms of leachable/extractables for the diluted products which contain (b) (4) monothioglycerol, PG, and PEG 400 while prepared and stored in infusion bags. The in-use stability studies provided in the NDA 208194 mainly focused on the stability in terms of assay and degradation products of diluted bendamustine solutions while stored in infusion bags.
>
> Lack of compatibility study is deemed acceptable based on the following risk assessments:
>
> ☐ PG and monothioglycerol are present in the drug product at very low concentrations ((b) (4)%, respectively). (b) (4) PEG 400 is very hydrophilic and is present at no more than (b) (4)% in the admixture solutions. Thus, both formulation and admixtures are considered low risk in terms of extraction power.
>
> ☐ According to USP <88>, extraction in PEG 400 is not required for Class IV plastics. Therefore, the risk associated with presence of PEG 400 for Class IV plastics which is the proposed admixture bags is expected to be low given that USP <88> does not require PEG 400 extraction for Class IV plastics.
>
> ☐ The contact time for admixture solutions in the infusion bags is considered short which is no more than 6 hours at room temperature or no more than 24 hours at refrigerator. The total infusion time is only 10 minutes. Therefore, as a summary, the drug product is considered compatible with the proposed infusion bags as well as all the other commercially available transfer devices, including adaptor, syringe, filter, and tubing."

The CDTL agrees with this risk assessment.

No drug product issues which preclude approval were found and the drug product reviewer found the information adequate to support the approval of NDA 208194 (refer to the drug product section of the integrated quality assessment signed by Nina Ni on September 21, 2015).

Process Review – Drug Product: The manufacturing and packaging process of Bendamustine HCl Injection consists of the following unit operations:

(b) (4)

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