

**Studies reviewed within this submission:**

None submitted

**Studies reviewed under NDA 22-249:**

#### **4.2.1 Pharmacology**

##### **4.2.1.1 Primary Pharmacodynamics**

- 4.2.1.1.1 Effect of Bendamustine on Different Human Tumour Cell Lines *In vitro*. Study 0640.00.C7.04.
- 4.2.1.1.5 Cell Cycle Alterations by Bendamustine in Comparison with Other Cytotoxic Agents. Study 0640.00.C7.01.
- 4.2.1.1.6 The Efficacy of Bendamustine is Slightly Decreased by P-glycoprotein and MXR/BCRP Resistance Mechanisms. Study 0640.00.C7.02
- 4.2.1.1.9 Bendamustine Hydrochloride and the Antitumor Drug Screen Program of the National Cancer Institutes (NCI). Study F-DE-NCI-2004.
- 4.2.1.1.7 Analysis of the Cytotoxic Potential of Bendamustine Hydrochloride on Human Lymphocytes as Compared to its Degradation and By-Products. Study 744303.
- 4.2.1.1.8 Analysis of the Cytotoxic Potential of Bendamustine Hydrochloride on Tumor Cell Lines as Compared to its Degradation Products. Study 754900.
- 4.2.1.1.10 Analysis of the Cytotoxic Potential of Bendamustine Hydrochloride on Tumor Cell Lines as Compared to its Metabolite N-Desmethyl Bendamustine. Study 789401
- 4.2.1.1.11 Analysis of the Cytotoxic Potential of Bendamustine Hydrochloride on Tumor cell Lines as Compared to its Metabolite N-Desmethyl Bendamustine. Study 789403.
- 4.2.1.1.2 Effect of Bendamustine Hydrochloride By-Products and Beta-OH-Bendamustine on Tumour Cell Growth. Study 0640.01.C07.06.
- 4.2.1.1.3 Efficacy of Bendamustine Hydrochloride on the Human Mammary Carcinoma MDA-MB 231 in the NMRI nu/nu Mouse after Intravenous Treatment. Study 0640.00.C8.02.
- 4.2.1.1.4 Efficacy of Bendamustine Hydrochloride on the Human Lung Carcinoma LX-1 in the NMRI nu/nu Mouse after Intravenous Treatment. Study 0640.00.C08.01.
- 4.2.1.1.13 Efficacy Dose Response for SDX-105 in a Xenograft Model of SUDHL-1 in SCID Mice. Study T109.
- 4.2.1.1.14 Efficacy of SDX-105 and Rituxan in a Xenograft Model of Daudi in SCID Mice. Study T116.
- 4.2.1.1.15 Efficacy of SDX-105 and Rituxan in a Xenograft Model of Daudi in SCID Mice. Study T124.
- 4.2.1.1.16 Dose Response of SDX-105 and SDX-101 in a Xenograft Model of Daudi in SCID Mice. Study T110.

#### **4.2.1.2 Secondary Pharmacodynamics**

- 4.2.1.2.1 Effect of Bendamustine Hydrochloride on Different Non-Malignant Cells of Mice and Humans in Comparison to Other Well-Known Cytostatic Drugs. Study 0640.01.C07.07.
- 4.2.1.2.2 Determination of the Cytotoxic Potential of SDX-105 in Cultured Human Hepatocytes after *In vitro* Exposure. Study DM-2005-002.
- 4.2.1.1.12 Cytotoxicity Assay *In vitro* with BALB/C3T3 Cells: Neutral Red (NR) Test with Bendamustine Hydrochloride at Simultaneous Irradiation with Artificial Sunlight. Study 789402.

#### **4.2.1.3 Safety Pharmacology**

- 4.2.1.3.1 Evaluation of Effect on Urine Output, Urinary Electrolyte Balance and Glomerular Filtration Rate in the Rat with a Saline Overload Following Two Successive 30-Minute Intravenous Infusions. Study 20010337 PGR.
- 4.2.1.3.2 Evaluation of Effect on Cardiac Action Potential in Isolated Canine Purkinje Fibers. Study 20010339 PECM.
- 4.2.1.3.3 Bendamustine Hydrochloride: Effects on HERG-1 Tail Currents Recorded from Stably Transfected HEK 293 Cells. Study 853896.

#### **4.2.1.4 Pharmacodynamic Drug Interactions. N/A**

#### **4.2.2 Pharmacokinetics**

##### **4.2.2.1 Analytical Methods and Validation Reports**

- 4.2.2.1.1 Validation of a High Performance Liquid Chromatographic Method for the Measurement of Bendamustine and Two Major Metabolites in Dog Plasma and Urine. Study KLG-09.
- 4.2.2.1.2 Validation Report: Determination of Bendamustine M3 Metabolite, and M4 Metabolite in K2EDTA rat plasma. Study DP-2007-030.

##### **4.2.2.2 Absorption**

- 4.2.2.2.1 Studies on the Pharmacokinetics of Bendamustine [<sup>14</sup>C] in the Rat. Study DM-2006-012.

##### **4.2.2.3 Distribution**

- 4.2.2.3.1 Disposition of <sup>14</sup>C-Bendamustine in Mice and Rats. Study DM-2007-001.
- 4.2.2.3.2 The Tissue Distribution of Total Radioactivity in the Rat Following Intravenous Administration of [<sup>14</sup>C]-CEP-18083. Study DM-2005-006.

4.2.2.3.3 The Tissue Distribution of Total Radioactivity in the Pigmented Rat Following Intravenous Administration of [<sup>14</sup>C]-CEP-18083.HCl (Quantitative Whole Body Autoradiography). Study Am 02 DM-2005-007.

4.2.2.3.4 Excretion and Distribution Studies of <sup>14</sup>C-Bendamustin in the Dog. Study KLG-05.

#### 4.2.2.4 Metabolism

4.2.2.4.1 *In vitro* Evaluation of CEP-18083 (Bendamustine) as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes. Study DM-2005-004.

4.2.2.4.2 *In vitro* Metabolism studies of <sup>14</sup>C-Bendamustin. Study 99-37-KLG-01.

4.2.2.4.4 *In vitro* Plasma Protein Binding Studies of Bendamustine. Study KLG-06.

4.2.2.4.3 Metabolic Profile of [<sup>14</sup>C]-CEP-18083 (Bendamustine) in Rat Urine and Bile: Preliminary Structural Identification of Metabolites. Study DM-2006-002.

#### 4.2.2.5 Excretion

4.2.2.5.1 The Disposition of [<sup>14</sup>C]-CEP-18083 in the Rat Following Intravenous Administration. Study Am 01 DM-2005-005.pdf

4.2.2.6 Pharmacokinetic Drug Interactions: N/A

4.2.2.7 Other Pharmacokinetic Studies: N/A

#### 4.2.3 Toxicology

##### 4.2.3.1 Single Dose Toxicity Studies

4.2.3.1.1 Bendamustine Single-Dose Toxicity Study in Mice and Rats. Haertl 1989.

##### 4.2.3.2 Repeat Dose Toxicity Studies

4.2.3.2.1 5-Day Intermittent Intravenous Infusion Dose Range Finding Toxicity Study with CEP-18083 (Bendamustine) in Rats with a 16-Day Recovery Period. Study DS-2006-011.

4.2.3.2.2 15-Week Intermittent Intravenous Infusion Toxicity and Toxicokinetic Study with CEO-18083 (Bendamustine) in Rats with a 4-Week Recovery Period. Study DS-2006-010.

4.2.3.2.5 Bendamustine One-Month Oral Toxicity Study in Rats. Horn et al 1984.

4.2.3.2.6 Bendamustine 3-Months Oral Toxicity Study in Rats. Janowski 1985

4.2.3.2.3 Bendamustine Hydrochloride Maximum Tolerated Dose and Five Day Repeated Dose Study in Dogs by Intravenous Infusion. Study 0640.98.C2.01.

4.2.3.2.4 Bendamustine Hydrochloride Toxicity to Dogs by Daily Intravenous Infusion Over a Minimum of Three 4-Day Cycles Each Followed by a Period Without Treatment of up to 31 Days. Study 0640.98.C2.02.

#### **4.2.3.3 Genotoxicity Studies**

4.2.3.3.1 Bendamustine Hydrochloride Bacterial Mutation Assay. Study 0640.00.C4.01.

4.2.3.3.2 Bendamustine Hydrochloride *In vitro* Mammalian Chromosome Aberration Test in Human Lymphocytes. Study 0640.00.C4.02.

4.2.3.3.3 CEP-18083: Rat Bone Marrow Erythrocyte Micronucleus Test. Study DS-2007-001.

4.2.3.3.4 Chromosome Aberration Test in Human Lymphocytes *In vitro* with Hydroxy-Bendamustine (HP1). Study 831200.

**4.2.3.4 Carcinogenicity:** N/A

**4.2.3.5 Reproductive and Developmental Toxicity:** N/A

#### **4.2.3.6 Local Tolerance**

4.2.3.6.1 Perivenous and Intra-Arterial Tolerance Study in the Rabbit. Study 0640.00.C14.01.

#### **4.2.3.7 Other Toxicity Studies:**

4.2.3.1.2 Estimate the LD<sub>50</sub> Value of Dihydroxy Bendamustine Ethyl Ester (HBI) in Female BDF-1 Mice. Study PT-VIV-108.

### **4.3 Literature References**

#### **Carcinogenicity:**

Oncogenicity of  $\gamma$ -[1-methyl-5-bis-( $\beta$ -chloroethyl)-amino-benzimidazolyl-(2)]-butyric acid hydrochloride in mice. Guttner, Bruns, and Junstand, Arch Geschwulstforsch 43/1: 16-21, 1974.

#### **Reproductive and Developmental Toxicity:**

##### **Embryofetal Development**

On the embryotoxic and teratogenic action of the nitrogen mustard derivatives IMET 3393 and IMET 3106 in mice. Heinecke & Klaus, Zbl Pharm 10(10):1067-76, 1971.

The Effect of Nitrogen Mustard Compounds on the Formation of Accessory Ribs in the Fetuses of Mice. Heinecke & Klaus, Arzneimittelforschung 22(1):122-5, 1972.

On the Effect of the "Cytostasan" Mustard Derivative on Murine Pregnancy and Embryonic Development. Wendler, Pabst, and Bertolini, Anat Anz.Bd 139: 100-114, 1976.

### Labeling Review

The sponsor has proposed to keep the same Pharmacology/Toxicology (P/T) labeling for TREANDA (NDA 22-303) for NHL and CLL indications as approved by the FDA for TREANDA (NDA 22-249) for CLL indication except for the Mechanism of Action section under CLINICAL PHARMACOLOGY. Their proposal to utilize the same language is acceptable. Our recommendation for the Mechanism of Action section follows the sponsor's proposed language, and previously approved language by the FDA.

## 12 CLINICAL PHARMACOLOGY

The sponsor proposed

### 12.1 Mechanism of Action

Bendamustine is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring. Mechlorethamine and its derivatives form electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties, resulting in interstrand DNA crosslinks<sup>(b) (4)</sup> [REDACTED] The bifunctional covalent linkage can lead to cell death via several pathways.<sup>(b) (4)</sup> [REDACTED]

[REDACTED] Bendamustine is active against both quiescent and dividing cells

The exact mechanism of action of bendamustine remains unknown.

### FDA Approved for NDA 22-249.

#### 12.1 Mechanism of Action

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 is active against both quiescent and dividing cells.

FDA Recommends for NDA 22-303

**12.1 Mechanism of Action**

Bendamustine is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring. Mechlorethamine and its derivatives form electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties, resulting in interstrand DNA crosslinks. The bifunctional covalent linkage can lead to cell death via several pathways. Bendamustine is active against both quiescent and dividing cells.

The exact mechanism of action of bendamustine remains unknown.

Rationale

Deleted extra words for clarity and discourage promotional statements like (b) (4)



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/s/  
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