APOTEX
Innovating for patient affordability

December 13, 2022

VIA ELECTRONIC SUBMISSION

Division of Dockets
Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

RE: Request to Assign a Therapeutic Equivalence Evaluation Code to Apotex's Bendamustine Hydrochloride Injection, 100 mg/4 mL (25 mg/mL), NDA No. 215033

CITIZEN PETITION

The undersigned submits this Citizen Petition on behalf of Apotex Inc. ("Apotex") to the U.S. Food and Drug Administration ("FDA") and in accordance with 21 C.F.R. §§ 10.25(a) and 10.30,[1] and pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the "FD&C Act"). For the reasons discussed below, Apotex respectfully requests that FDA assign a Therapeutic Equivalence Evaluation Code ("TE Code") for Apotex's Bendamustine Hydrochloride Injection, 100 mg/4 mL (25 mg/mL), New Drug Application ("NDA") No. 215033 ("Apotex's NDA") in relation to its reference listed drug ("RLD"), Eagle Pharmaceuticals Incorporation's ("Eagle's") Belrapzo® (Bendamustine Hydrochloride Injection, 100 mg/4 mL (25 mg/mL)) ("Eagle's NDA"). FDA approved Apotex's NDA on December 7, 2022, which was submitted to the Agency pursuant to FD&C Act § 505(b)(2) (a "505(b)(2) NDA"). Eagle's NDA, also submitted as a 505(b)(2) NDA, was approved under NDA No. 205580 on May 15, 2018.

I. ACTION REQUESTED

Apotex requests that FDA assign in the Agency's Orange Book a TE Code of "AP" to Apotex's NDA. As demonstrated below, Apotex's NDA meets the requirements for a TE

[1] The Preface to FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book") states that "[a] person seeking to have a therapeutic equivalence rating for a drug product approved in a 505(b)(2) application may petition the Agency through the citizen petition procedure (see 21 CFR 10.25(a) and 21 CFR 10.30)." Orange Book Preface (42nd ed., 2022), at xxiv.

Code with respect to Eagle's NDA, since the drug products are pharmaceutical equivalents that have been demonstrated to be bioequivalent through a biowaiver.

In addition, Apotex requests a TE Code so Apotex will, among other things, be exempt from, or can otherwise obtain a refund of, any Prescription Drug User Fee Act annual "program fee" FDA may assess with respect to NDA 215033 for Fiscal Year 2023 and thereafter.[2]

II. STATEMENT OF GROUNDS

A. Factual and Regulatory Background

The Orange Book Preface explains that there are "two basic categories into which multisource drugs have been placed": (1) "A-rated" drug products (i.e., "Drug products that FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products"; and (2) "B-rated" drug products (i.e., "Drug products that FDA at this time, considers not to be therapeutically equivalent to other pharmaceutically equivalent products").[3]

An FDA regulation defines the term "therapeutic equivalents" to mean "approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling."[3] FDA further explains in the Orange Book Preface that:

> FDA classifies as therapeutically equivalent those drug products that meet the following general criteria:
>
> (1) they are approved as safe and effective;
>
> (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the identical active drug ingredient in the identical dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity;

[2] Under the FD&C Act, a prescription drug product is not assessed a program fee under FD&C Act § 736(a)(2)(B)(ii) if such product qualifies for an exception under FD&C Act § 736(a)(2)(B) (i.e., if such product is "the same product as another product" approved under an NDA or Abbreviated NDA and that is listed in the Prescription Drug Product List section of the Orange Book).

[3] 21 C.F.R. § 314.3(b). Another FDA regulation defines the term "pharmaceutical equivalents" to mean: "drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates." 21 C.F.R. § 314.3(b).

(3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard;

(4) they are adequately labeled; and

(5) they are manufactured in compliance with Current Good Manufacturing Practice regulations.[4]

For non-Drug Efficacy Study Implementation Drug products, an "A" TE Code falls under the policy:

(1) for those active ingredients or dosage forms for which no *in vivo* bioequivalence issue is known or suspected, the information necessary to show bioequivalence between pharmaceutically equivalent products is presumed and considered self-evident based on other data in the application for some dosage forms (e.g., solutions) or satisfied by a showing that an acceptable i*n vitro* dissolution standard is met. A therapeutically equivalent rating is assigned such products so long as they are manufactured in accordance with Current Good Manufacturing Practice regulations and meet the other requirements of their approved applications (these are designated **AA**, **AN**, **AO**, **AP**, or **AT**, depending on the dosage form, as described below);[5]

The Orange Book Preface also defines and explains FDA's policies for various "A" sub-codes. In particular, the TE Code "AP" is defined as "Injectable aqueous solutions and, in certain instances, intravenous non-aqueous solutions."[6]

FDA has approved at least two NDAs for pharmaceutically-equivalent versions of Bendamustine Hydrochloride Injection, 100 mg/4 mL (25 mg/mL): (1) Apotex's NDA; and (2) Eagle's NDA. Both NDAs are listed in Drugs@FDA-Approved Drugs with the Active Ingredient "BENDAMUSTINE HYDROCHLORIDE", the Strength "100MG/4ML (25 MG/ML)", the Dosage Form/Route "SOLUTION; IV (INFUSION)", and the Marketing Status as "Prescription."

[4] Orange Book Preface (42nd ed., 2022), at vii (reformatted).

[5] Orange Book Preface at xiii-xiv.

[6] Orange Book Preface at xvi.

As highlighted below, Apotex's NDA product includes the addition of ethanol, the elimination of propylene glycol, and has a small difference in concentration of PEG 400 compared to Eagle's NDA product.

Product	**Listed Drug** **BELRAPZO™ (bendamustine HCl injection) 25 mg/mL (100 mg/4 mL)**		**Apotex Approved Product** **Bendamustine HCl Injection 25 mg/mL (100 mg/4 mL)**	
Dosage Form	**Sterile solution**		**Sterile solution**	
Vial Composition (before dilution)	**Ingredient**	**Amount/vial**	**Ingredient**	**Amount/vial**
	Bendamustine HCl	100 mg	Bendamustine HCl, USP	100 mg
	Propylene Glycol, USP	0.4 mL	Absolute Ethanol (100%), USP	152 mg
	Monothioglycerol, NF	20 mg	Monothioglycerol, USP-NF	20 mg
	Polyethylene Glycol 400 (PEG 400), NF	QS to 4 mL (~3.6 mL)	Polyethylene Glycol 400 (PEG 400), NF	QS to 4 mL (~3.7 mL)
	Sodium hydroxide, NF*	-	Sodium Hydroxide, NF	0.32 mg
Reconstitution	No reconstitution is needed (A ready to dilute solution of 25 mg/mL)		No reconstitution is needed (A ready to dilute solution of 25 mg/mL)	
Example 1: After dilution of single vial (containing 100 mg bendamustine HCl) – final drug concentration of 0.2 mg/mL in the infusion bag				
Total Volume	**504 mL (4 mL concentrate + 500 mL admixture)**		**504 mL (4 mL concentrate + 500 mL admixture)**	
Individual Ingredient Amount and Concentration	**Ingredient**	**Listed Drug**	**Ingredient**	**Apotex Product**
	Bendamustine HCl	100 mg (0.1984 mg/mL)	Bendamustine HCl	100 mg (0.1984 mg/mL)
	Propylene Glycol, USP	0.4 mL (0.0008 mL/mL)	Absolute Ethanol (100%)	152 mg (0.3016 mg/mL)
	Monothioglycerol, NF	20 mg (0.0396 mg/mL)	Monothioglycerol, NF	20 mg (0.0397 mg/mL)
	Polyethylene Glycol 400 (PEG 400), NF	~3.6 mL (0.0071 mL/mL)	Polyethylene Glycol 400 (PEG 400), NF	~3.7 mL (0.0073 mL/mL)
	Sodium hydroxide, NF*		Sodium hydroxide, NF	0.32 mg (0.0006 mg/mL)

Product	**Listed Drug** **BELRAPZO™ (bendamustine HCl injection) 25 mg/mL (100 mg/4 mL)**		**Apotex Approved Product** **Bendamustine HCl Injection 25 mg/mL (100 mg/4 mL)**	
Example 2: After dilution for a maximum recommended dose (120 mg/m^2 dose for NHL) prepared for an oversized patient with 2.7 m^2 body surface area requiring 324 mg of bendamustine HCl – final drug concentration of 0.6 mg/mL in the infusion bag				
Total Volume	**512.96 mL (12.96 mL concentrate + 500 mL admixture)**		**512.96 mL (12.96 mL concentrate + 500 mL admixture)**	
Individual Ingredient Amount and Concentration	**Ingredient**	**Listed Drug**	**Ingredient**	**Apotex Product**
	Bendamustine HCl	324 mg (0.6316 mg/mL)	Bendamustine HCl	324 mg (0.6316 mg/mL)
	Propylene Glycol, USP	1.296 mL (0.0025 mL/mL)	Absolute Ethanol (100%)	492.480 mg (0.9601 mg/mL)
	Monothioglycerol, NF	64.8 mg (0.1263 mg/mL)	Monothioglycerol, NF	64.8 mg (0.1263 mg/mL)
	Polyethylene Glycol 400 (PEG 400), NF	~11.664 mL (0.0227 mL/mL)	Polyethylene Glycol 400 (PEG 400), NF	~12.001 mL (0.0234 mL/mL)
	Sodium hydroxide, NF*	-	Sodium hydroxide, NF	1.0368 mg 0.0020 mg/mL)

Note: * - Quantity of sodium hydroxide not disclosed in BELRAPZO™ label

In Apotex's NDA, FDA granted Apotex's Biowaiver Scientific Bridge between the two products, demonstrating that these differences would "not have any significant impact on the disposition kinetics of bendamustine and thus the efficacy, safety and tolerability of intravenously-administered bendamustine hydrochloride would remain unaltered." In summary, Apotex demonstrated with its own data and supportive literature and NDAs that, among other things: 1) Apotex's NDA product and Belrapzo have identical bendamustine hydrochloride concentration before and after dilution with 500 mL admixture 2) Apotex's NDA product has the same recommended dosages, mode of administration, drug concentration at the time of administration, volume of infusion solution and administration time as Belrapzo; 3) comparative physicochemical data shows that the pH and osmolality of the infusion solution, using the 0.9% Sodium Chloride Injection USP and 2.5% Dextrose+0.45% Sodium chloride Injection as the diluent, for Apotex's NDA product are similar to those of Belrapzo at both concentrations 0.2mg/mL and 0.7mg/mL; and 4) the formulation differences between Apotex's NDA product and Belrapzo will not impact the PK, efficacy, and safety/tolerability of intravenously-administered bendamustine hydrochloride.

Apotex's 505(b)(2) NDA Product, Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL), therefore, should be determined by FDA to be bioequivalent to, and that is otherwise the same as Eagle's Belrapzo (Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL)), and be assigned an "AP" TE Code.

B. Request for TE Code Assignment for Apotex's Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL) Drug Product

Apotex's NDA Product, Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL), meets all applicable requirements for a TE Code with respect to its RLD, Eagle's Belrapzo (Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL)).

First, both Apotex's NDA product and Eagle's NDA product are pharmaceutical equivalents in that both drug products contain identical amounts of the identical active drug ingredient and are in identical dosage forms for the same route of administration and are both "ready to dilute" IV formulations with the same Preparation for Intravenous Administration requirements, e,g., "Aseptically withdraw the volume needed for the required dose (based on 25 mg/mL concentration) as per Table A below and immediately transfer to a 500 mL infusion bag of 0.9% Sodium Chloride Injection, USP (normal saline)" [or as an alternative, 2.5% Dextrose/0.45% Sodium Chloride Injection USP].

Second, both Apotex's NDA product and Eagle's NDA product are equivalent to one another and are "expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." 21 C.F.R. § 314.3(b).

In addition, Apotex's NDA product is manufactured in compliance with current Good Manufacturing Practice ("cGMP") regulations, and the drug products are adequately labeled. As such, Apotex's NDA product, Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL), and Eagle's Belrapzo (Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL)) should be identified in the Orange Book with an "AP" TE Code.

III. ENVIRONMENTAL IMPACT

Petitioner claims a categorical exclusion under 21 C.F.R. § 25.31.

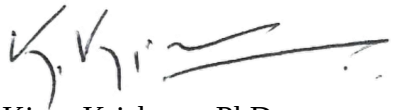
IV. ECONOMIC IMPACT STATEMENT

Petitioner will, upon request by the Commissioner, submit economic impact information, in accordance with 21 C.F.R. § 10.30(b).

V. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner that are unfavorable to the Petition.

Sincerely,



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