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Center for Medicine in the Public Interest

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June 6th, 2013

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Citizen Petition Requesting that the Food and Drug Administration Refrain From Approving a New Drug Application or Supplemental New Drug Application for Treanda® Liquid Formulation Until Certain Conditions are Satisfied

Dear Sir or Madam,

The Center for Medicine in the Public Interest respectfully submits this Citizen Petition pursuant to 21 C.F.R. §10.30 to request that the Commissioner of Food and Drugs refrain from approving any new drug application ("NDA"), including any NDA submitted pursuant to section 505(b)(2) of the Food, Drug and Cosmetic Act ("FDCA"), or any supplemental new drug application ("sNDA") for a liquid bendamustine formulation unless and until the conditions specified in this Petition are satisfied. Bendamustine hydrochloride ("HCl") is currently approved only as a lyophilized powder pursuant to NDA# 022249 under the trade name Treanda® for Injection ("Treanda"). It has recently come to our attention that Teva Pharmaceutical Industries Ltd. has submitted, and the U.S. Food and Drug Administration ("FDA") has accepted for review, an sNDA for a liquid Treanda formulation, Treanda LQ[1]. Such a liquid bendamustine formulation is described in US Patent # 8,344,006. As discussed in more detail below, the Center for Medicine in the Public Interest is concerned that a liquid bendamustine formulation such as that described in US Patent # 8,344,006 raises significant safety concerns related, among other things, to the presence of potential degradation products and excipients that are absent from the currently approved Treanda product and the potential for dosing errors due to the high concentration of bendamustine that may be present in the liquid

[1] Teva Pharmaceutical Industries Ltd (TEVA) Q12013 Earnings Call May 2, 2013 8:00 AM ET.

FDA-2013-P-0693

2013-4389

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formulation. We therefore request that, before approving a liquid bendamustine formulation, FDA require data clearly demonstrating the product's safety.

Actions Requested

Treanda® is an alkylating drug that was approved by FDA pursuant to NDA # 022249 on March 20, 2008 for the treatment of chronic lymphocytic leukemia ("CLL") and indolent B-cell non-Hodgkin lymphoma ("NHL") that has progressed during or within six (6) months of treatment with rituximab or a rituximab-containing regimen. Treanda contains bendamustine HCl as its active ingredient, and is supplied as a sterile lyophilized powder in a single-use container of either 25 or 100 mg bendamustine HCl per vial. Prior to injection, Treanda is reconstituted with 5 ml or 20 ml of sterile water (depending on the vial size used), giving a final bendamustine HCl concentration of 5 mg/ml. The reconstituted solution is further diluted into 500 mL of 0.9% Sodium Chloride Injection or, alternatively, 500 mL of 2.5% Dextrose / 0.45% Sodium Chloride Injection.[2]

As a solid dosage form, Treanda is highly stable with a shelf-life of two (2) years.[3] Upon reconstitution of the lyophilized bendamustine HCl powder, the solution must be further diluted into the 500mL admixture within 30 minutes, and this final admixture must then be used within three (3) hours[4] at room temperature (15-30 °C or 59-86 °F) or within 24 hours when refrigerated at 2-8 °C (36-47 °F).[5] As this information demonstrates, aqueous solution preparations of bendamustine HCl degrade in a very short time, presenting a significant technical challenge to the development of a ready-to-use or ready-to-dilute product. As an alternative to an aqueous ready-to-dilute liquid, non-aqueous solvent preparations have been proposed.[6] For example, a bendamustine solution in a combination of 66% dimethylacetamide ("DMA") and 34% propylene glycol ("PG") is described in US Patent # 8,344,006.[7] However, significant amounts of degradants resulting from the PG component develop in such a formulation on storage for 12 months under refrigerated conditions (i.e. prior to dilution into the final admixture).[8] These PG degradation products are not present in the approved lyophilized Treanda product (as this lyophilized product contains no PG), and are well above the acceptable limits established by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH"). The possibility that these degradation products may form in a liquid Treanda formulation must be assessed, along with any associated toxicity concerns, prior to FDA's approval of any liquid formulation to avoid exposing patients to unnecessary risk.

A liquid Treanda formulation also raises safety concerns as a result of the use of organic solvents. The currently-available lyophilized Treanda powder contains mannitol, a common parenteral excipient with acceptable toxicological properties and a well-established safety

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[2] TREANDA® (bendamustine hydrochloride) for Injection. Prescribing Information (August 2012).
[3] U.S. Food & Drug Admin., Center for Drug Evaluation and Research, Treanda NDA 22249 Approval Letter, March 20, 2008.
[4] TREANDA® (bendamustine hydrochloride) for Injection. Prescribing Information (August 2012).
[5] *Id.*
[6] U.S. Patent No. 8,344,006 (filed Jan. 31, 2012).
[7] *Id.*
[8] *Id.*

profile.[9] However, the preparation of a ready-to-dilute liquid bendamustine HCl product with the necessary solubility and chemical stability requires the use of organic solvents that are not needed when the lyophilized powder is administered in an aqueous vehicle. In particular, the liquid formulation of 5 to 120 mg/ml bendamustine described above utilizes a 66% (v/v) DMA and 34% PG vehicle.[10] PG is a recognized excipient in numerous parenteral drug products, and notwithstanding the potential for PG-related degradation products specific to the bendamustine formulation discussed above, PG itself is generally recognized as safe ("GRAS"). In contrast, DMA is a class-2 solvent with known toxicity concerns, and is rarely found in parenteral products.

In addition to containing DMA and PG, a bendamustine concentration of 90 mg/mL has been proposed.[11] This concentration is significantly greater than the 5 mg/mL bendamustine HCl concentration of the reconstituted Treanda lyophilized product.[12] This difference in bendamustine concentration may lead to dosing errors with significant harmful effects.

Accordingly, the Center for Medicine in the Public Interest hereby requests that FDA refrain from approving any NDA or sNDA for a liquid formulation of Treanda until:

- The NDA or sNDA applicant has demonstrated that the product impurity profile does not exhibit degradation products above the acceptable limits defined by the ICH, with appropriate qualification studies and appropriate justification for the presence of impurities that are absent in the lyophilized form.

- The NDA or sNDA applicant has demonstrated the safety of the excipients used to formulate the ready-to-dilute liquid product, as compared to the lyophilized product, particularly with respect to those excipients (including DMA) whose quantities exceed published acceptance levels.

- The NDA or sNDA applicant has demonstrated that, if the bendamustine concentration for further dilution in the liquid Treanda product is sufficiently different from the 5 mg/ml concentration formed upon reconstitution of the lyophilized Treanda product, significant medication dosing errors will not occur as a result of the improper or mistaken utilization of the new, ready-to-dilute product.

Statement of Grounds

I. A non-aqueous liquid formulation of Treanda may form degradation products which may present patients with an increased level of toxicity risk (relative to the available lyophilized product).

[9] Mannitol – *in* FDA 'Database of Select Committee on GRAS Substances (SCOGS) Reviews'. (v. 10/31/2006)
[10] U.S. Patent No. 8,344,006 (filed Jan. 31, 2012).
[11] *Id.*
[12] TREANDA® (bendamustine hydrochloride) for Injection. Prescribing Information (August 2012).

The 90 mg/mL non-aqueous formulation of liquid bendamustine HCl described in US Patent # 8,344,006[13] exhibits bendamustine-propylene glycol ester degradation products following 12 months of storage at 5 °C that are not formed after 24 months of storage of the lyophilized product.[14] These esters are exhibited at a level greater than 1%,[15] exceeding the ICH qualification limit of < 0.2% for any individual impurity, as set forth in ICH guideline Q3B(R2).[16]

Bendamustine is a known genotoxin (mutagenic and clastogenic). It is probable that PG ester-impurities of bendamustine would also exhibit a degree of genotoxic activity, due to their structural similarity to the parent molecule. Therefore, the presence of significant amounts of novel bendamustine-related impurities in any bendamustine liquid product, which are not present in the lyophilized preparation, may result in an increased genotoxic burden to the patient. The Center for Medicine in the Public Interest therefore requests that FDA require any NDA or sNDA for a liquid bendamustine product to include qualification of all bendamustine-related impurities and any other impurities present in the liquid formulation, in accordance with the framework set forth in the current guidelines. In addition, the Center for Medicine in the Public Interest requests that FDA refrain from approving any application for a liquid Treanda product until satisfactory studies are completed to demonstrate that any benefits associated with use of the liquid Treanda formulation warrant exposure to degradation products not present in the currently-available lyophilized form of Treanda.

II. A liquid formulation of Treanda that contains a large quantity of DMA may expose patients to toxicities not applicable to the lyophilized form of the drug.

A liquid Treanda formulation using a 66% (v/v) DMA vehicle contains approximately 0.66 ml of DMA per ml of formulation.[17] The therapy for NHL calls for 120 mg of bendamustine HCl per m^2 of patient body surface area per day for two (2) consecutive days.[18] Therefore, a 1.62 m^2 subject undergoing NHL therapy with a 90 mg/ml bendamustine HCl formulation would require 2.16 ml of the liquid formulation. This results in a DMA dose of 1.43 ml, equivalent to 1.34 g.[19]

DMA is a class-2 solvent.[20] The permissible daily exposure ("PDE") for DMA established by the U.S. Pharmacopeial Convention ("USP") general chapter <467> is 10.9 mg/day.[21] The same PDE is set by ICH guideline Q3C(R5), in which DMA is listed as a class 2 solvent ("solvents to be limited").[22] Incorporating the ICH guideline, FDA's "Guidance for Industry: Q3C — Tables and List" states that "[s]olvents in Class 2... should be limited in

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[13] U.S. Patent No. 8,344,006 (filed Jan. 31, 2012).
[14] *Id.*
[15] *Id.*
[16] *See* ICH, Impurities in New Drug Products (Q3B(R2)) (2006).
[17] U.S. Patent No. 8,344,006 (filed Jan. 31, 2012).
[18] TREANDA® (bendamustine hydrochloride) for Injection. Prescribing Information (August 2012).
[19] The density of DMA is 0.937 g/ml. 0.937 g/ml * 1.43ml = 1.34g.
[20] ICH, Impurities: Guideline for Residual Solvents (Q3C(R5)) (2011), at 13.
[21] USP, United States Pharmacopeia and National Formulary, Chapter <467> – Residual Solvents (2007).
[22] ICH, Impurities: Guideline for Residual Solvents (Q3C(R5)) (2011), at 6.

pharmaceutical products because of their inherent toxicity."[23] However, the DMA dose in the above liquid bendamustine example (1.34g) amounts to *122 times* the permissible daily exposure.[24] Moreover, at the maximum dose of 360 mg bendamustine – which is used when a $3m^2$ patient receives the 120 mg/m^2 bendamustine HCl therapy – 4 ml of the liquid formulation, containing 2.47g of DMA,[25] are required. At this dosage, the patient is exposed to more than *225 times* the permissible daily exposure for DMA.[26]

DMA is rarely found in parenteral products. One exception is busulfan;[27] however, the FDA summary basis of approval for Busulfex® (busulfan) Injection states that the level of DMA was high enough to cause significant toxicities, and warned that "the use of DMA in other drug products should be carefully evaluated."[28] At the labeled dose of 0.8 mg/kg Busulfex every 6 hours for 4 days, the daily (per 24 hours) dose of DMA to a 60 kg subject (with a body surface area of approximately $1.62m^2$) would be approximately 10g. It is unclear if the DMA level in the non-aqueous bendamustine liquid formulation (of up to 2.47g/day) described above would result in significant toxicities, however, given the absence of DMA in the existing lyophilized Treanda product, the potential for toxicity due to DMA requires evaluation.

In addition, as a strong polar aprotic solvent, DMA in a liquid product may extract potentially toxic leachable materials from the vial stopper.[29] In contrast, the risk of exposure to any such leached chemicals associated with use of the lyophilized Treanda product is virtually nonexistent.

In summary, a liquid formulation of Treanda that uses the excipient DMA exposes patients to a potential toxicological risk that is absent from the currently-available lyophilized product. Accordingly, the Center for Medicine in the Public Interest requests that FDA refrain from approving any application for a liquid Treanda product until a comprehensive toxicological assessment of DMA has been undertaken, and the nature and extent of the risk from DMA exposure, relative to any perceived benefit associated with use of the liquid rather than lyophilized Treanda formulation, has been assessed.

III. A liquid formulation of Treanda may contain a much higher bendamustine concentration than that found in the reconstituted lyophilized bendamustine product that may result in potentially-harmful dosing errors.

A liquid Treanda formulation may pose new and significant risks to patients not only due to the presence of organic solvents and degradation products, but also due to any increase in the

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[23] U.S. Food & Drug Admin., Center for Drug Evaluation and Research, Guidance for Industry: Q3C — Tables and List (2012), at 6.

[24] 1.34g / 10.9mg = 122.9.

[25] 360 mg / 90 mg/ml (the concentration of bendamustine HCl in the liquid formulation) = 4 ml of the formulation. 4 ml * 0.66 (the percent of the formulation that is DMA) = 2.64ml. 0.937 g/ml (the density of DMA) * 2.64ml = 2.47g.

[26] 2.47g / 10.9mg = 226.9.

[27] Busulfex® (busulfan) Injection. Prescribing Information (May 2011).

[28] U.S. Food & Drug Admin., Center for Drug Evaluation and Research, Summary Basis of Approval for Busulfex®: NDA 20-954 (1999) Pharmacology Review(s) page 36.

[29] U.S. Food & Drug Admin, Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics (1999).

bendamustine HCl concentration of the liquid Treanda product as compared to the reconstituted lyophilized product. For example, while the concentration of bendamustine HCl in the reconstituted lyophilized Treanda product prior to dilution is 5 mg/ml, the 90 mg/ml bendamustine HCl concentration in the cited liquid formulation is approximately 18 times higher. This difference in product concentrations increases the potential for dosing errors that would result in harmful effects; if the liquid product were mistakenly dispensed in place of the reconstituted lyophilized product, the patient would be subjected to an *18-fold* overdose. An overdose of such magnitude would likely produce very severe adverse events, including possible mortality, as no specific antidote for bendamustine overdose is known.

Accordingly, the Center for Medicine in the Public Interest requests that FDA refrain from approving any NDA or sNDA application for a liquid Treanda product until the Agency reviews appropriate data from failure mode and effects analyses ("FMEA") and ensures that appropriate steps are taken to mitigate the risk of unintentional overdose or other medication errors.[30]

Conclusion

The reformulation of lyophilized Treanda for Injection into a ready-to-dilute liquid form raises several concerns that must be addressed before a new liquid product may safely be approved for marketing. Given the large amount of DMA; the presence of novel bendamustine HCl degradation products; and the high bendamustine HCl concentration that may be present in a proposed liquid formulation, FDA should refrain from approving any NDA or sNDA for a ready-to-dilute liquid Treanda product unless and until the applicant adequately addresses the product's novel risks to patient safety.

Environmental Issues

This petition is categorically exempt from the requirement for an environmental assessment or an environmental impact statement pursuant to 21 C.F.R. § 25.31.

Economic Impact

Information on the economic impact of the petition will be provided upon request.

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[30] These requests are in accordance with FDA's Guidance for Industry: Safety Considerations for Product Design to Minimize Medication Errors December (2012), and Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (2013).

Certifications

Pursuant to 21 C.F.R. § 10.30(b), the undersigned certifies that to the best of its knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully,

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Cc: Richard Pazdur M.D., Director, Office of Hematology and Oncology Products (OHOP)

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