DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

SEP 13 2013

Peter J. Pitts
President
Center for Medicine in the Public Interest
757 Third Ave. 20th Floor
New York, NY 10017

RE: FDA-2013-P-0693

Dear Mr. Pitts:

This letter responds to your citizen petition received on June 7, 2013, and submitted on behalf of the Center for Medicine in the Public Interest (Petition). You request that the United States Food and Drug Administration (FDA or the Agency) refrain from approving any New Drug Application (NDA) or Supplemental NDA (sNDA) for a ready-to-dilute liquid formulation of Treanda (bendamustine hydrochloride (HCl)) until:

- the applicant demonstrates that the ready-to-dilute liquid formulation of Treanda does not have degradation products above the acceptable limits set by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), with appropriate qualification studies and appropriate justification for the presence of impurities that are not present in the approved lyophilized formulation of Treanda;
- the applicant demonstrates the safety of the excipients used to formulate the ready-to-dilute liquid formulation of Treanda as compared to those used in the approved lyophilized formulation of Treanda, particularly with respect to excipients (especially dimethylacetamide (DMA)) that are present in quantities that exceed published acceptance levels; and
- the applicant demonstrates that significant dosing errors will not occur with the ready-to-dilute liquid formulation due to different dilution requirements than the lyophilized product.[1]

FDA has considered the information submitted in the Petition and other relevant data. Based on our review of this information, and for the reasons described below, your Petition is denied.

[1] Petition at 3.

I. BACKGROUND

On March 20, 2008, FDA approved NDA 22-249 for Treanda (bendamustine hydrochloride) for Injection, for intravenous infusion. The original indication, the treatment of patients with chronic lymphocytic leukemia (CLL), was expanded on October 31, 2008, to include treatment of Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen (NDA 22-303).

Treanda was originally formulated as a lyophilized powder that is reconstituted using sterile water for injection, as defined by the United States Pharmacopeoia (USP), to yield a clear, colorless-to-pale-yellow solution. The reconstituted solution is then further diluted into a 500 milliliter (mL) infusion bag of either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, within 30 minutes of reconstitution. The resulting admixture is a clear and colorless-to-slightly-yellow solution and is stable for 24 hours when refrigerated (2-8°C or 36-47°F) or for 3 hours when stored at room temperature (15-30°C or 59-86°F) and room light.

Today, FDA is approving a supplement to the Treanda NDA for a ready-to-dilute liquid formulation, Treanda (bendamustine HCl) Injection. The ready-to-dilute liquid formulation is packaged in a single-use vial of 90 milligrams (mg)/mL solution. The required dose is aseptically withdrawn from the single-use vial and immediately transferred to a 500 mL infusion bag of either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP. The resulting admixture is a clear and colorless-to-slightly-yellow solution and is stable for 24 hours when refrigerated or for 2 hours when stored at room temperature and room light.

II. DISCUSSION

A. Degradation Products and Related Toxicity

The Petition expresses concerns that the ready-to-dilute liquid formulation of Treanda uses a 66% (v/v) N,N-dimethylacetamide (DMA) and 34% (v/v) propylene glycol (PG) vehicle[2] to create the stable liquid version of the product and that after 12 months of refrigerated storage degradants from PG not present in the lyophilized product and exceeding ICH limits develop in the liquid.[3] You then claim that, since bendamustine is a known genotoxin and these PG-ester impurities are structurally similar to the parent molecule, it is probable that these impurities may exhibit additional genotoxic activity that could be harmful to patients.[4] For these reasons, you request that FDA require qualification of all bendamustine-related impurities and other impurities present in the ready-to-dilute liquid formulation in accordance with current guidelines and that FDA refrain from approving any application for a ready-to-dilute liquid formulation of Treanda until studies are completed to demonstrate that any benefits associated with its

[2] Petition at 3.
[3] Petition at 4.
[4] Id.

use warrant exposure to degradation products that are not present in the lyophilized form.[5]

PG-esters (PGEs) of bendamustine hydrochloride are present in the ready-to-dilute liquid formulation of Treanda. PGEs are formed in the drug product due to esterification of bendamustine with PG during manufacturing of the drug product and upon storage. These degradants do not exist in the lyophilized formulation of Treanda as that formulation does not contain PG.

Cephalon, Inc., a wholly-owned subsidiary of Teva Pharmaceutical Industries Ltd. (Cephalon), the manufacturer of Treanda, submitted information to the sNDA regarding the presence of impurities in the ready-to-dilute liquid formulation of Treanda. The PGEs were qualified with data from an animal toxicology study and an acceptable specification was set. The animal toxicology study demonstrated that PGEs did not increase bendamustine-related toxicities. Similarly, other degradation products present in the ready-to-dilute liquid formulation of Treanda have been appropriately qualified. Therefore, there is no need for FDA to require further studies of these degradation products as the Petition requests.

Contrary to the claims in the Petition, FDA does not believe that excessive levels of PG degradants form when the ready-to-dilute liquid formulation of Treanda is stored under the labeled conditions – twelve months of refrigerated storage. The sNDA included stability data, which FDA carefully reviewed. FDA has concluded that accelerated and long-term primary stability data support this approved shelf-life in accordance with ICH Q1A(R2) and ICH Q1E.

The Petition also expresses concerns regarding the genotoxicity of PGEs. Genotoxicity can be an indicator as to whether a drug has a potential to be carcinogenic; however, because bendamustine HCl is itself a known carcinogen (as are many chemotherapy agents) and is also genotoxic, the presence of small amounts of potentially genotoxic degradation products does not alter the safety profile of the ready-to-dilute liquid formulation of Treanda or increase the "genotoxic burden to the patient" as the Petition suggests.

B. DMA

The Petition claims that a patient undergoing treatment with the ready-to-dilute liquid formulation of Treanda would receive a DMA dose of 1.43 mL, equivalent to 1.34 grams (g), and at the maximum dosage would receive 2.47 g of DMA, which would be 122 and 225 times the permissible daily exposure set by the USP and ICH (10.9 mg/day), respectively.[6] The Petition also claims that the pharmacology review in the summary basis of approval for Busulfex (busulfan) Injection, another approved parenteral product that uses DMA as an excipient, states that "the use of DMA in other drug products should

[5] Id.
[6] Petition at 4-5.

be carefully evaluated."[7] Finally, you are concerned that the DMA in the ready-to-dilute liquid formulation of Treanda may extract potentially toxic leachable materials from the vial stopper.[8] For these reasons, you request that FDA refrain from approving a ready-to-dilute liquid formulation of Treanda until a comprehensive toxicological assessment of DMA has been undertaken and FDA has assessed the extent of the risk of DMA exposure as compared to the perceived benefit of the ready-to-dilute liquid formulation.

The Petition cites ICH Q3C(R5) and USP-NF General Chapter <467>, which set out acceptable levels for residual solvents, which are described as "organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products," and which "are not completely removed by practical manufacturing techniques."[9] In the manufacture of the ready-to-dilute liquid formulation of Treanda, DMA and PG are considered excipients, which are defined by the USP as "components of a finished drug product other than the active pharmaceutical ingredient (API) [that] are added during formulation for a specific purpose."[10]

Because the limits set by ICH Q3C(R5) relate to limits for residual solvents, they do not apply to DMA and PG when they are used as excipients. Therefore, the sections of the ICH and USP referenced in the Petition are not applicable to the ready-to-dilute liquid formulation of Treanda.

Bendamustine HCl is susceptible to hydrolysis and undergoes rapid degradation in the presence of water. DMA is non-aqueous and therefore does not facilitate degradation of bendamustine HCl. In addition, an animal toxicology study submitted by Cephalon supports the conclusion that use of 66% (v/v) DMA in the ready-to-dilute liquid formulation of Treanda does not pose a safety concern. Accordingly, DMA is an acceptable excipient for the ready-to-dilute liquid formulation of Treanda.

The Petition, as noted above, includes certain statements regarding Busulfex,[11] another parenteral product approved by FDA that is formulated with DMA. Based on calculations using the highest dose of 120 mg/m^2/day for Treanda[12] administered over 30 minutes and an 0.8 mg/kg/dose for Busulfex (Busulfex is administered every 6 hours for 4 days for a total of 16 doses), the amount of DMA each patient will receive from the ready-to-dilute liquid formulation of Treanda is significantly less than the amount patients receive when treated with Busulfex. For these doses, the ready-to-dilute liquid formulation of Treanda would deliver up to 3 g of DMA to patients; whereas, Busulfex would deliver 40 g of DMA during each cycle. We do not anticipate the amount of DMA

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[7] Petition at 5.
[8] Id.
[9] ICH Q3C Guideline, p. 1.
[10] USP Guideline for Submitting Requests for Revision to USP-NF V3.1 April 2007.
[11] Each vial of BUSULFEX contains 60 mg (6 mg/mL) of busulfan, the active ingredient. Busulfan is dissolved in DMA, 33% vol/vol, and Polyethylene Glycol 400, 67% vol/vol.
[12] The prescribed dose, schedule, and administration time of Treanda varies by indication. Patients with CLL are to receive Treanda at 100 mg/m^2 over 30 minutes on Days 1 and 2 of up to six 28-day cycles; patients with NHL are to receive Treanda at 120 mg/m^2 over 60 minutes on Days 1 and 2 of up to eight 21-day cycles.

in the highest dose of Treanda administered over 30 or 60 minutes to cause overt toxicities. Furthermore, the amount of DMA in the ready-to-dilute liquid formulation of Treanda is significantly less than that given to patients being treated with Busulfex, and the level of DMA in Busulfex has not caused an increased toxicological risk to patients.

Finally, the issue of leachables was adequately addressed by the data provided in the sNDA for the ready-to-dilute liquid formulation and is not a concern. The sNDA included detailed extractable/leachable studies on the glass vial and rubber stoppers (with FluroTec coating). A batch of bendamustine HCl solution stored under the labeled refrigerated conditions in the inverted position for 42 months was tested for the selected leachables and FDA determined that the levels of leachables were acceptable.

C. Dosing Errors

You claim that an increase in concentration of bendamustine HCl in the ready-to-dilute liquid formulation compared to the lyophilized formulation may lead to dosing errors if one formulation is mistakenly used in place of the other. You state that an overdose would likely produce very severe adverse events. Because of this, you request that FDA refrain from approving any NDA or sNDA for a liquid Treanda product until the Agency reviews appropriate data from a failure mode and effects analysis (FMEA) and ensures that appropriate steps are taken to mitigate the risk of unintentional overdose or other medication errors due to differences between the ready-to-dilute liquid and lyophilized formulations of Treanda.[13]

There is always a risk of errors in dosing resulting from one formulation mistakenly being used in place of another. These concerns are not unique to Treanda. Applicants can address product selection errors in a variety of ways depending on the circumstances surrounding the drug at issue. Product selection errors may, in many instances, be addressed by labeling changes.

In this case, FDA does not believe an FMEA is necessary and believes that the risk of product selection errors can be sufficiently mitigated by product labeling. The following changes were made to the packaging of the ready-to-dilute liquid formulation of Treanda to mitigate the risk of selection errors:

- Different color schemes are used to distinguish the labels and labeling of the ready-to-dilute liquid formulation from the lyophilized formulation.
- The label for the ready-to-dilute liquid formulation expresses the statement of strength in terms of total drug content per total volume [i.e. 180 mg/2mL (90 mg/mL) and 45 mg/0.5 mL) respectively], whereas the label for the lyophilized formulation expresses the strength in terms of total drug content per vial (i.e. 100 mg/vial).

[13] Petition at 6.

- A bolded statement "New Concentration and Storage Information" appears in a colored banner on the top of the carton labeling for the ready-to-dilute liquid formulation.
- A prominent statement "Refrigerate" appears in the upper part of the carton labeling for the ready-to-dilute liquid formulation.
- The applicant changed the vial size and volume to be extracted from the vial for the ready-to-dilute liquid formulation.
- In addition, Cephalon has agreed to implement an education program for healthcare practitioners to decrease the risk of medication errors.

FDA believes these changes are appropriate and sufficient to reduce the risk of medication errors due to selection confusion between the ready-to-dilute liquid and lyophilized formulations of Treanda.

III. CONCLUSION

We have reviewed the information submitted in the Petition as it relates to the sNDA for the ready-to-dilute liquid formulation of Treanda. After careful evaluation, FDA determined that the issues raised in your Petition do not pose a safety concern for the ready-to-dilute liquid formulation of Treanda. For the reasons described above, the Petition is denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research