Patent Application

entitled

BENDAMUSTINE PHARMACEUTICAL COMPOSITIONS

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Robert W. Prince

Number of Drawings: 6 (on 6 pages)

Docket No.: 032PRV

FIELD OF THE INVENTION

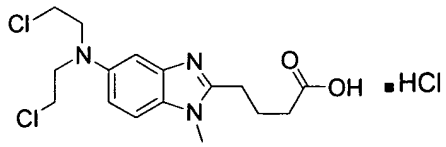
The present invention pertains to the field of pharmaceutical compositions for the treatment of various disease states, especially neoplastic diseases and autoimmune diseases. Particularly, it relates to pharmaceutical formulations comprising nitrogen mustards, particularly the nitrogen mustard bendamustine, e.g., bendamustine HCl.

BACKGROUND OF THE INVENTION

The following description includes information that may be useful in understanding the present invention. It is not an admission that any such information is prior art, or relevant, to the presently claimed inventions, or that any publication specifically or implicitly referenced is prior art.

Because of their high reactivity in aqueous solutions, nitrogen mustards are difficult to formulate as pharmaceuticals and are often supplied for administration in a lyophilized form that requires reconstitution, usually in water, by skilled hospital personal prior to administration. Once in aqueous solution, nitrogen mustards are subject to degradation by hydrolysis, thus, the reconstituted product should be administered to a patient as soon as possible after its reconstitution.

Bendamustine, (4-{5-[Bis(2-chloroethyl)amino]-1-methyl-2-benzimidazolyl} butyric acid, is an atypical structure with a benzimidazole ring, whose structure includes an active nitrogen mustard (see Formula. 1, which shows bendamustine hydrochloride).



Formula I

Bendamustine was initially synthesized in 1963 in the German Democratic Republic (GDR) and was available from 1971 to 1992 in that location under the name Cytostasan®. Since that time, it has been marketed in Germany under the tradename Ribomustin®. It has been widely used in Germany to treat chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, and breast cancer.

Due to its degradation in aqueous solutions (like other nitrogen mustards), bendamustine is supplied as a lyophilized product. The current lyophilized formulation of bendamustine (Ribomustin®) contains bendamustine hydrochloride and mannitol in a sterile lyophilized form as a white powder for intravenous use following reconstitution. The finished lyophilisate is unstable when exposed to light. Therefore, the product is stored in brown or amber-colored glass bottles. The current lyophilized formulation of bendamustine contains degradation products that may occur during manufacturing of the drug substance and/or during the lyophilization process to make the finished drug product.

Currently bendamustine is formulated as a lyophilized powder for injection with 100 mg of drug per 50 mL vial or 25 mg of drug per 20 mL vial. The vials are opened and reconstituted as close to the time of patient administration as possible. The product is reconstituted with 40 mL (for the 100 mg presentation) or 10 mL (for the 25 mg presentation) of Sterile Water for Injection. The reconstituted product is further diluted into 500 mL, q.s., 0.9% Sodium Chloride for Injection. The route of administration is by intravenous infusion over 30 to 60 minutes.

Following reconstitution with 40 mL Sterile Water for Injection, vials of bendamustine are stable for a period of 7 hours under room temperature storage or for 6 days upon storage at 2-8°C. The 500 mL admixture solution must be administered to the patient within 7 hours of vial reconstitution (assuming room temperature storage of the admixture).

The reconstitution of the present bendamustine lyophilized powder is difficult. Reports from the clinic indicate that reconstitution can require at least fifteen minutes and may require as long as thirty minutes. Besides being burdensome and time-consuming for the healthcare professional responsible for reconstituting the product, the lengthy exposure of bendamustine to water during the reconstitution process increases the potential for loss of potency and impurity formation due to the hydrolysis of the product by water.

Thus, a need exists for lyophilized formulations of bendamustine that are easier to reconstitute and which have a better impurity profile than the current lyophilate (lyophilized powder) formulations of bendamustine.

German (GDR) Patent No. 34727 discloses a method of preparing ω-[5-bis-(β-chloroethyl)-amino-benzimidazolyl-(2)]-alkane carboxylic acids substituted in the 1-position.

German (GDR) Patent No. 80967 discloses an injectable preparation of γ-[1-methyl-5-bis-(β-chloroethyl)-amino-benzimaidazolyl-(2)]-butric acid hydrochloride.

German (GDR) Patent No. 159877 discloses a method for preparing 4-[1-methyl-5-bis (2-chloroethyl) amino-benzimidazolyl-2)-butyric acid.

German (GDR) Patent No. 159289 discloses an injectable solution of bendamustine.

Ribomustin® bendamustine Product monograph (updated 1/2002) http://www.ribosepharm.de/pdf/ribomustin_bendamustin/productmonograph.pdf provides information about Ribomustin® including product description.

Ni et al. report that the nitrosourea SarCNU was more stable in pure tertiary butanol than in pure acetic acid, dimethyl sulfoxide, methylhydroxy, water or in TBA/water mixtures (Ni et al. (2001) *Intl. J. Phamaceutics* 226:39-46).

Lyophilized cyclophoshamide is known in the art see e.g., US Patent Nos. 5,418,223; 5,413,995; 5,268,368; 5,227,374; 5,130,305; 4,659,699; 4,537,883; and 5,066,647.

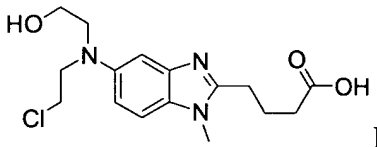
The lyophilized nitrogen mustard Ifosfamide is disclosed in International Publication No. WO 2003/066027; US Pat. Nos. 6,613,927; 5,750,131; 5,972,912; 5,227,373; and 5,204,335.

Teagarden et al. disclose lyophilized formulations of prostaglandin E-1 made by dissolving PGE-1 in a solution of lactose and tertiary butyl alcohol (US Pat. No. 5,770,230).

SUMMARY OF THE INVENTION

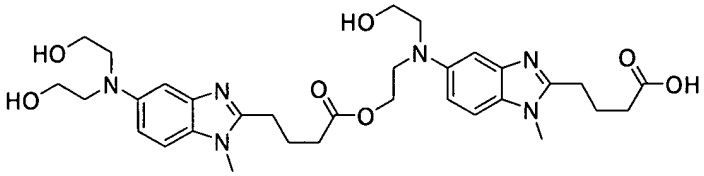
The present invention is directed to stable pharmaceutical compositions of nitrogen mustards, in particular lyophilized bendamustine and its use in treatment of various disease states, especially neoplastic diseases and autoimmune diseases.

An embodiment of the invention is a pharmaceutical composition of bendamustine containing not more than about 0.5% to about 0.9% (area percent of bendamustine) HP1, as shown in Formula II, where the HP1 is the amount of HP1 present at time zero after reconstitution of a lyophilized pharmaceutical composition of bendamustine as described herein.



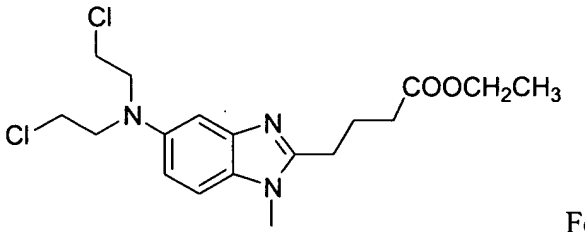
Formula II.

Another embodiment of the invention is a lyophilized preparation of bendamustine containing not more than about 0.1 % to about 0.3 % bendamustine dimer as shown in Formula III at time zero after reconstitution.



Formula III

Yet another embodiment of the invention is a lyophilized preparation of bendamustine containing not more than about 0.5% to about 0.15% bendamustine ethylester, as shown in Formula IV at time zero after reconstitution



Formula IV.

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