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(54) Title: PHARMACEUTICAL COMPOSITION OF BORTEZOMID

(57) Abstract: The present invention relates to a stable ready-to-use injectable pharmaceutical formulation of bortezomib or pharmaceutically acceptable salts thereof. Methods of preparing such formulations are also provided.

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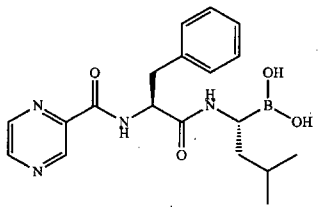
PHARMACEUTICAL COMPOSITION OF BORTEZOMIB

FIELD OF THE INVENTION

The present invention relates to a stable ready-to-use injectable pharmaceutical formulation of bortezomib or pharmaceutically acceptable salts thereof. Methods of preparing such formulations are also provided.

BACKGROUND OF THE INVENTION

Bortezomib [N-(2-pyrazine) carbonyl-L-phenylalanine-L-leucine boronic acid] is an antineoplastic agent. The solubility of bortezomib, as the monomeric boronic acid, in water is 3.3 to 3.8 mg/mL over a pH range of 2 to 6.5. Bortezomib has the following chemical structure.



Commercially, it is available as VELCADE® 3.5 mg sterile lyophilized powder for intravenous infusion in single-dose vials.

Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death.

Many aminoalkylboronic acids (such as bortezomib) undergo a spontaneous 1,3-rearrangement to give the homologous amines, owing to the instability of free α-amino groups. These compounds yield boric acids and alcohols by degradation and undergo oxidative reactions that easily destroy the C—B bond. These alkylboronic acid compounds readily form boroxines (anhydrides) under dehydrating conditions. Both, alkylboronic acid and their boroxines are often air-sensitive. Peroxides or molecular oxygen and its radicals, light, metal ions, and alkaline conditions that normally facilitate oxidation found to be unfavorable to the stability of bortezomib or any other alkyl boronic acid derivative.

US5780454 discloses bortezomib and its pharmaceutically acceptable salts or boronate ester thereof.

US6713446 and US6958319 disclose novel boronate ester compounds. These patents also disclose stable lyophilized compositions comprising boric acid compound and a compound having at least two hydroxyl groups that readily release the boronic acid compound upon dissolutions in aqueous media. However, such reconstituted aqueous solution is stable only for 43 hours when stored at ambient temperature (23^0C). Further, VELCADE® pack insert discloses that such reconstituted aqueous solution should be administered within 8 hours of preparation.

WO2010039762 discloses ready-to-use formulations of bortezomib with a variety of solvents such as WFI, Propylene glycol monocaprylate, dimethylsulfoxide. It also discloses ready-to-use formulation comprising amino acid, vitamin, carboxylic acid, sodium chloride or EDTA in WFI.

IN3324/Del/2012 discloses stable parenteral composition comprising bortezomib with stabilizing agents selected from the group of water soluble polymers and amino acids.

WO2010089768 discloses solution of bortezomib with tromethamine and bulking agent in water; wherein the solution has pH from 6.6 to 7.2.

US8263578, US20110230441, US20120322762 and US20120322763 disclose ready-to-use, storage stable, multi-dose liquid bortezomib formulations comprising substantially non-aqueous solvent system and an aqueous acidic buffer preferably at pH range of 2.7 to 3.3. These prior arts further disclose that the solvent system, the buffer, and the pH are selected such as to be effective to suppress formation of at least one of an amide degradation product, a first carbinolamide degradation product, and a second carbinolamide degradation product when the liquid formulation is stored under storage conditions e.g. storage at 50^0C over 15 days.

Therefore, even though there are many formulations for bortezomib known in the art, all or almost all of them suffer from limited stability when bortezomib is in solution, particularly over extended periods. Thus, there is still a need to provide improved ready-to-use bortezomib formulation with greater stability.

OBJECT OF THE INVENTION

It is therefore an object of the present invention to provide stable ready-to-use injectable pharmaceutical formulation of bortezomib or pharmaceutically acceptable salts thereof.

Another object of the present invention is to provide a stable ready-to-use injectable pharmaceutical formulation comprising bortezomib or pharmaceutically acceptable salts thereof, a substantially non-aqueous solvent system comprising propylene glycol as a predominant component and optionally a buffer.

SUMMARY OF THE INVENTION

In an attempt to develop ready-to-use bortezomib injecatable formulations, the present inventors have surprisingly found that stable ready-to-use bortezomib injectable formulations can be prepared based on substantially non-aqueous solvent system, by maintaining the pH of above 5.

The present specification relates to a stable ready-to-use injectable pharmaceutical formulation of bortezomib or pharmaceutically acceptable salts thereof.

In one aspect, the present specification relates to a stable ready-to-use injectable pharmaceutical formulation comprising bortezomib or pharmaceutically acceptable salts thereof, a substantially non-aqueous solvent system comprising propylene glycol as a predominant component and optionally a buffer.

Various objects, features, aspects and advantages of the inventive subject matter will become more apparent from the following detailed description of preferred embodiments.

DETAILED DESCRIPTION OF THE INVENTION

The present specification relates to a stable ready-to-use injectable pharmaceutical formulation of bortezomib or pharmaceutically acceptable salts thereof.

In one aspect, the present specification relates to a stable ready-to-use injectable pharmaceutical formulation comprising bortezomib or pharmaceutically acceptable salts thereof, a substantially non-aqueous solvent system comprising propylene glycol as a predominant component and optionally a buffer.

The suitable non-aqueous solvent system comprises non-aqueous solvents selected from the group comprising propylene glycol, one or more short chain alcohols (C1-C6) e.g. ethanol, dimethyl acetamide, N-methyl pyrrolidone, dimethyl sulphoxide, glycerol and mixtures thereof. The amount of non-aqueous solvents is at least 60 %w/v, at least 75 %w/v, at least 85 %w/v, at least 95 %w/v, e.g. 90%w/v.

Apart from non-aqueous solvent system the formulations may further comprise water in an amount of equal or less than 25 %w/v, equal or less than 20 %w/v, equal or less than 10 %w/v, equal or less than 5 %w/v, equal or less than 2 %w/v, e.g. 10%w/v.

The buffer, if used in the formulation of present invention is selected from the group comprising of phosphate buffer, benzoate buffer, citrate buffer, tartrate buffer, lactate buffer, succinate buffer, maleate buffer, bicarbonate buffer, TRIS buffer, glycine buffer, histidine buffer and the like.

The formulations of present invention may additionally comprise pH adjusting agents e.g. acids, bases or mixtures thereof. Non-limiting examples of acids include hydrochloric acid, sulfuric acid, and the like. Non-limiting examples of bases include sodium hydroxide, potassium hydroxide, and the like.

The amount of pH adjusting agents and optional buffer employed in the formulations of the present invention is suitable to adjust the pH of the formulation to above 5, e.g. 6, e.g. 6.5, e.g. 7, e.g. 7.5, e.g. 8, e.g. 8.5, e.g. 9.

The pharmaceutical formulations of the present specification may be prepared by suitable conventional process. For example, dissolving bortezomib in substantially non-aqueous solvent either alone or in combination water, and adjusting the pH of the solution above 5 with buffers or pH adjusting agents. The formulation is then filtered through sterile grade filter. Filtered solution then filled in final package

which is clear glass vials with 20mm bromobutyl rubber stoppers. Entire manufacturing process is carried out under continuous nitrogen purging and under sodium vapor lamp.

The following experiments are provided to exemplarily illustrate various aspects of the inventive subject matter presented herein. However, it should be apparent to those skilled in the art that many more modifications besides those already described are possible without departing from the inventive concepts herein.

Example-1a-Composition with Lactate buffer

Sr. No.	Ingredients	% w/v
1	Bortezomib	0.10
2	Propylene glycol	90.00
3	Lactate buffer (0.1 M)	q.s to adjust the pH of 5 and above

Example-1b-Composition with Maleate buffer

Sr. No.	Ingredients	% w/v
1	Bortezomib	0.10
2	Propylene glycol	90.00
3	Maleate buffer (0.1 M)	q.s to adjust the pH of 5 and above

Example-2a-Composition with Water

Sr. No.	Ingredients	% w/v
1	Bortezomib	0.10
2	Propylene glycol	90.00
3	Hydrochloric acid/ Sodium Hydroxide	q.s to adjust the pH of 5 and above
4	Water	9.90

Example-2b-Composition with Ethanol

Sr. No.	Ingredients	% w/v
1	Bortezomib	0.10
2	Propylene glycol	90.00
3	Hydrochloric acid/ Sodium Hydroxide	q.s to adjust the pH of 5 and above
4	Ethanol	9.90

The above test formulations of the present invention were prepared by dissolving bortezomib in substantially non-aqueous solvent either alone or in combination water, and adjusting the pH of the solution above 5 with buffers or pH adjusting agents. The formulation is then filtered through sterile grade filter. Filtered solution then filled in final package which is clear glass vials with 20mm bromobutyl rubber stoppers. Entire manufacturing process is carried out under continuous nitrogen purging and under sodium vapor lamp.

The pharmaceutical formulations of the present specification (Examples 1a, 1b, 2a, 2b) were subjected to accelerated stability studies. Stability data is summarized in Table 1.

Table 1: Accelerated Stability data of Examples 1a, 1b, 2a, 2b (25°C/60%RH)

Stability data	Example 1a		Example 1b		Example 2a		Example 2b	
	Assay (%)	Total Impurity (%)	Assay (%)	Total Impurity (%)	Assay (%)	Total Impurity (%)	Assay (%)	Total Impurity (%)
Initial	99.3	0.049	99.9	0.22	102.4	0.145	99.2	0.069
30 days	100	0.299	101.2	0.693	102.4	0.919	99.6	0.344
90 days	98.2	0.916	97.2	1.572	97.4	1.811	96.9	0.259

Claims:

1) A stable ready-to-use injectable pharmaceutical formulation comprising bortezomib or pharmaceutically acceptable salts thereof, a substantially non-aqueous solvent system comprising propylene glycol as a predominant component and optionally a buffer.

2) The stable ready-to-use liquid pharmaceutical formulation of claim 1, wherein the bortezomib is present at a concentration of between 1 mg/ml and 5 mg/ml.

3) The stable ready-to-use liquid pharmaceutical formulation of claim 1, wherein substantially non-aqueous solvent system comprises from about 1 to about 100 percent by volume of propylene glycol.

4) The stable ready-to-use liquid pharmaceutical formulation of claim 1, wherein the substantially non-aqueous solvent system apart from propylene glycol, may further comprise one or more short chain alcohols (C1-C6).

5) The stable ready-to-use liquid pharmaceutical formulation of claim 4, wherein one or more short chain alcohols (C1-C6) is ethanol.

6) The stable ready-to-use liquid pharmaceutical formulation of claim 1, may further comprise water in an amount of equal or less than 25 %w/v

7) The stable ready-to-use liquid pharmaceutical formulation of claim 1 wherein the pH of the formulation is above 5.

8) The stable ready-to-use liquid pharmaceutical formulation of claim 1 wherein the pH of the formulation is adjusted with acids, bases or the like.

9) The stable ready-to-use liquid pharmaceutical formulation of claim 1, wherein the buffer if present, is selected from citric acid buffer, acetic acid buffer, maleic acid buffer, lactic acid buffer, succinic acid buffer, and tartaric acid buffer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2016/000006

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/69 A61K47/10
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/116286 A2 (INNOPHARMA LLC [US]; SOPPIMATH KUMARESH [US]; PEJAVER SATISH [US]; PAT) 22 September 2011 (2011-09-22) Formulations I-III; paragraphs [0010], [0032], [0045]; tables 1,5	1-9
X	US 2012/172808 A1 (SOPPIMATH KUMARESH [US] ET AL) 5 July 2012 (2012-07-05) paragraphs [0055], [0070]; claims 1,5,6; tables 1,5,15,16	1-6,8,9
A	US 2014/073583 A1 (HIPPALGAONKAR KETAN [US] ET AL) 13 March 2014 (2014-03-13) page 1, column 2, lines 6-11, paragraphs 65,68,83,87,121; claim 1; example 2	1-9

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2016/000006

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		WO 2015038431 A1	19-03-2015