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(54) Title: NOVEL COMPOSITIONS OF CARFILZOMIB

(57) Abstract: The invention relates to novel parenteral compositions of Carfilzomib or its pharmaceutically acceptable salts, solvates and hydrates thereof. More specifically, the invention relates to cyclodextrin free lyophilized formulations of Carfilzomib.

NOVEL COMPOSITIONS OF CARFILZOMIB

Field of Invention

The invention relates to stable parenteral compositions of Carfilzomib or its pharmaceutically acceptable salts, solvates and hydrates thereof, wherein the compositions are free of cyclodextrins.

Background of the invention

Carfilzomib is an anti-cancer drug acting as a selective proteasome inhibitor. Chemically, it is a tetrapeptide epoxyketone and an analog of epoxomicin. The chemical name for Carfilzomib is (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide. Carfilzomib has molecular weight of 719.9 and molecular formula is $C_{40}H_{57}N_5O_7$. Carfilzomib is practically insoluble in water, and very slightly soluble in acidic conditions.

The U.S. Food and Drug Administration (FDA) approved Carfilzomib Injection in July 2012 under the brand name Kyprolis®. Kyprolis®, a peptide epoxy ketone proteasome inhibitor is indicated for the treatment of patients with multiple myeloma who have received at least two prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of the last therapy. Carfilzomib irreversibly binds to the N-terminal threonine-containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome. Carfilzomib has been shown to have antiproliferative and proapoptotic activities in vitro in solid and hematologic tumor cells. The compound has also been shown to inhibit proteasome activity in blood and tissue and delay tumor growth in models of multiple myeloma, hematologic, and solid tumors.

U.S Patent Nos. 7,417,042; 7,491,704; 8,207,125; 8,207,126; 8,207,127 and 8,207,297 to Smyth Mark et al., disclose Carfilzomib and a pharmaceutically acceptable salt thereof and a method of treating cancer.

U.S Patent No. 7,737,112 to Lewis Evan et al., discloses Carfilzomib compositions formulated with cyclodextrins. It was found that the solubility of proteasome inhibitors, such as the peptide epoxy ketones is significantly enhanced when formulated with cyclodextrin.

U.S Patent application nos. 2013/303465 and 2013/303482 to Lewis Evan et al., disclose compositions comprising of one or more peptide proteasome inhibitors and a cyclodextrin, or a mixture of cyclodextrins, to increase the solubility and stability of proteasome inhibitors and facilitate both their manufacture and administration.

Kyprolis for Injection is available for intravenous use only. It is a sterile, white to off-white lyophilized powder and is available as a single-use vial. Each vial of Kyprolis contains 60 mg of Carfilzomib, 3000 mg sulfobutylether beta-cyclodextrin, 57.7 mg citric acid, and sodium hydroxide for pH adjustment to 3.5.

Carfilzomib is difficult to formulate due to its low aqueous solubility. It is formulated with cyclodextrins such as sulfobutylether beta-cyclodextrin and showed improved solubility and stability. However, cyclodextrin containing formulations of Carfilzomib make the product more expensive. Another disadvantage associated with the prior art formulations is the limited availability of sulfobutylether beta-cyclodextrin. Hence, there exists a need to develop Carfilzomib formulations free of cyclodextrins.

Summary of the invention

One aspect of the present invention relates to stable parenteral compositions of Carfilzomib or its pharmaceutically acceptable salts, solvates and hydrates thereof, wherein the compositions are free of cyclodextrins.

Another aspect of the invention relates to stable parenteral compositions of Carfilzomib or its pharmaceutically acceptable salts, solvates and hydrates thereof, wherein the composition comprises of sugars and other pharmaceutically acceptable adjuvants.

Yet another aspect of the present invention is to provide stable parenteral compositions comprising of Carfilzomib or its pharmaceutically acceptable salts, solvates, hydrates thereof, sugars, acidifying agent, suitable solvent or mixture of solvents in suitable proportion and other pharmaceutically acceptable adjuvants thereof.

Another aspect of the present invention provides manufacturing process for preparing stable cyclodextrin free compositions of Carfilzomib or its pharmaceutically acceptable salts, solvates and hydrates thereof.

Detailed description of the invention

As used herein, "cyclodextrins" include alpha-, beta- and gamma-cyclodextrin, derivatives of these cyclodextrins such as methyl or hydroxypropyl β-cyclodextrins (HPCD), methyl-and-ethyl-β-cyclodextrin, substituted cyclodextrins include those substituted with one or more hydrophilic groups, such as monosaccharide (e.g., glucosyl, maltosyl), carboxyalkyl (e.g., carboxymethyl, carboxyethyl), hydroxyalkyl-substituted (e.g., hydroxyethyl, 2-hydroxypropyl) and sulfoalkylether beta-cyclodextrins, sulfobutylether beta-cyclodextrin (SBECD) and the like.

As used herein the term "solvent" refers to the liquid component of a formulation that is capable of dissolving or suspending one or more solutes. The term "solvent" can refer to a single solvent or a mixture of solvents. The solvent, as mentioned, can be any liquid in which the material dissolves. The solvent can be a single substance or a mixture of solvents. Depending on the formulation or the freeze-drying process, it may be desirable to include one or more solvents in the liquid formulation.

As used herein, the term “acidifying agent” is intended to mean a compound used to provide an acidic medium.

The term "lyophilized" refers to freeze drying processes in which a material is frozen at cold temperatures and reduced pressure to sublimate water and other solvents present.

The term “free of cyclodextrins” refers to lyophilized composition of Carfilzomib comprising less than 5%, preferably 2% and more preferably less than 1% cyclodextrins.

The stable parenteral compositions of Carfilzomib comprise lyophilized composition of Carfilzomib and a diluent, preferably supplied as a kit comprising both the components.

One embodiment of the invention relates to a lyophilized composition of Carfilzomib comprising:

(i) Carfilzomib or its pharmaceutically acceptable salts, solvates, hydrates thereof,
(ii) One or more sugars
(iii)One or more solvents
(iv)Optionally other pharmaceutically acceptable adjuvants, wherein the composition is free of cyclodextrins

Another embodiment of the invention relates to lyophilized composition of Carfilzomib comprising:

(i) Carfilzomib or its pharmaceutically acceptable salts, solvates, hydrates thereof,

(ii) Sugars such as mannitol, sucrose and the like,

(iii)Solvents such as acetonitrile, t-butyl alcohol (TBA), N, N-Dimethyl acetamide, ethanol, water and the like.

(iv)Optionally other pharmaceutically acceptable adjuvants, wherein the composition is free of cyclodextrins.

In another embodiment, the lyophilized composition of Carfilzomib additionally comprises acidifying agents. Alternately, the acidifying agents may be present in the diluent composition.

Another embodiment of the invention comprises:

(i) Carfilzomib or its pharmaceutically acceptable salts, solvates, hydrates thereof,

(ii) Sugars such as mannitol, sucrose and the like,

(iii)Acidifying agents such as tartaric acid, citric acid, aspartic acid, maleic acid, ascorbic acid, succinic acid and the like

(iv)Solvents such as acetonitrile, t-butyl alcohol (TBA), N,N-Dimethyl acetamide, ethanol, water and the like

(v) Optionally other pharmaceutically acceptable adjuvants.

In one preferred embodiment, the formulation may additionally comprise buffer, anti-oxidants, cryostabilizers, pH adjusting agents and preservatives. In a further preferred embodiment, the formulations of the present invention comprise sugar such as mannitol, sucrose and the like; suitable solvents such as t-butyl alcohol (TBA), acetonitrile, N,N-dimethyl acetamide, water and the like; suitable acids such as tartaric acid, citric acid, aspartic acid, maleic acid, ascorbic acid, succinic acid and the like; and optionally other pharmaceutically acceptable adjuvants thereof.

Another aspect of the present invention provides suitable ratio of Carfilzomib to sugars by weight. The ratio of Carfilzomib to sugars ranges from 1:0.5 to 1:100.

Suitable sugars include the following but not limited to mannitol, glucose, sucrose, lactose, trehalose, glycine, dextrose, maltose, sorbitol, dextran, raffinose and the like.

Suitable solvents include, but are not limited to N-methylpyrrolidone (NMP), dimethylformamide (DMF), dimethyl sulfoxide (DMSO), N,N-dimethylacetamide (DMA), tetrahydrofuran (THF), tetrahydropyran, dioxane, trioxane and other cyclic mono-, di- and tri-ethers, lower alkanols (such as ethanol, propanol, isopropanol, sec-butanol, t-butyl alcohol (TBA), and n-butyl alcohol), ethyl acetate, propylene glycol (PG), polyethylene glycol, glycerine, acetone, acetonitrile, ethoxy ethanol, methanol or other organic solvents and mixtures of suitable solvents thereof or their equivalents. Water can also be used as a solvent. Mixtures of solvents are used in a suitable proportion and suitable quantity to achieve desirable effect.

Examples of suitable acidifying agents include but not limited to tartaric acid, citric acid, aspartic acid, maleic acid, ascorbic acid, succinic acid, glutaric acid, malic acid, carbonic acid, acetic acid, phosphoric acid, aconitic acid, lactic acid, hydrochloric acid, sulfuric acid, fumaric acid, propionic acid, and the like. Compositions of the present invention will have a pH from 2 to 8. Preferably the pH would be from 2 to 6.

The pharmaceutical compositions of the present invention may optionally include one or more anti-oxidants and preservatives such as butylated hydroxyanisole (BHA), butylated hydroxyl toluene (BHT), citric acid, tocopherol, monothioglycerol, ascorbic acid, propyl gallate, phenylmercuric nitrate, thiomersal, benzalkonium chloride, benzethonium chloride, phenol, cresol, chlorobutanol, aminoacids and mixtures thereof.

The lyophilized product is intended to be reconstituted with a suitable diluent. Components of the diluent comprise water, ethanol, acidifying agent, polyethylene glycols or blends containing one or more polyethylene glycols of different grades, propylene glycol, polyvinylpyrrolidone, or agents to adjust solution osmolarity or other parenterally acceptable sugars, polyols, electrolytes or any suitable adjuvants thereof.

The inventors have surprisingly found that the presence of sugar in combination with suitable solvent and acidifying agent yields a stable formulation overcoming the disadvantages associated with the prior art.

The physical stability of the bulk solution of the invention formulation is summarized in Table 1. Apart from the excipients specifically listed in the table, solvents and other excipients described previously were also used to prepare the formulation solutions.

Table 1:

Formulation No.	**Sugar**	**Acidifying agent**	**Carfilzomib: Sugar**	**pH of the solution**	**Physical Stability**
F1	Mannitol	Tartaric acid	1:10	2.9	7 hrs
F2	Mannitol	Tartaric acid	1: 25	3.6	5 hrs
F3	Mannitol	Citric acid	1:10	2.8	4 hrs
F4	Mannitol	Citric acid	1: 25	3.6	1 hr
F5	Mannitol	Maleic acid	1:10	2.8	> 12hrs
F6	Mannitol	Maleic acid	1: 25	2.5	> 12hrs
F7	Sucrose	Tartaric acid	1:10	3.2	> 12hrs
F8	Sucrose	Tartaric acid	1: 25	3.2	> 12hrs
F9	Sucrose	Citric acid	1:10	3.3	> 12hrs
F10	Sucrose	Citric acid	1: 25	3.4	> 12hrs
F11	Sucrose	Maleic acid	1:10	2.4	> 12hrs

F12	Sucrose	Maleic acid	1: 25	2.2	> 12hrs
F13	Sucrose	Ascorbic acid	1:10	3.7	> 12hrs
F14	Sucrose	Ascorbic acid	1: 25	3.3	> 12hrs
F15	Sucrose	Succinic acid	1:10	3.5	> 12hrs
F16	Sucrose	Succinic acid	1: 25	3.7	> 12hrs

The formulations set forth in examples F1 to F16 as shown in the table 1 were prepared with different acidifying agents in combination with sugars.
The formulations set forth in examples F5 to F16 were prepared with sucrose/ mannitol and various acidifying agents such as tartaric acid, citric acid, maleic acid, ascorbic acid and succinic acid. These formulations have Carfilzomib to sugar ratio between 1:10 and 1:25 and were found to be stable up to 12 hours.

The invention further relates to a process of preparing formulations of Carfilzomib comprising

(i) Dissolving Carfilzomib in solvent till a clear solution is obtained
(ii) Dissolving sugar and optionally acidifying agent in water.
(iii)Mixing both the solutions.
(iv)Filtering of the solution through 0.22μ sterile filters and filling in vial
(v) Freeze drying the vials

The following examples further describe certain specific aspects and embodiments of the present invention and demonstrate the practice and advantages thereof. It is to be understood that the examples are given by way of illustration only and are not intended to limit the scope of the invention in any manner.

Table 2: Lyophilization cycle

Step #	Lyophilization Step	Shelf Temp (°C)	Process Time (min)	Cumulative Time (min)	Ramp / Hold	Vacuum mtorr
1	Freezing	-15	2	2	R	-
2	Freezing	-50	60	62	R	-
3	Freezing	-50	300	362	H	-
4	Freezing	-25	120	482	R	-
5	Freezing	-25	60	542	H	-
6	Freezing	-50	60	602	R	-
7	Freezing	-50	400	1002	H	-
Transition from Freezing to Primary Drying						
8	Primary Drying	-50	60	1062	R	400
9	Primary Drying	-42	30	1092	R	278
10	Primary Drying	24	1700	2792	R	278
11	Primary Drying	30	90	2882	R	188
12	Primary Drying	30	120	3002	H	150
13	Primary Drying	36	250	3252	R	150
14	Primary Drying	40	300	3552	R	50
15	Primary Drying	45	120	3672	R	50
16	Primary Drying	45	400	4072	R	20
17	Primary Drying	45	100	4172	R	350
18	Secondary Drying	45	300	4472	R	20

Example 1

S.No	Ingredients	F1	F2
		Qty/vial	Qty/vial
1	Carfilzomib	60 mg	60 mg
2	Tartaric acid	49.98 mg	49.98 mg
3	Mannitol	600 mg	1500 mg

4	Tert-Butyl alcohol (TBA)	6 mL	6 mL
5	Water	4.8mL	4.8mL

Manufacturing Process:

1. Carfilzomib was dissolved in Tert-Butyl alcohol.
2. Mannitol and tartaric acid were dissolved in water
3. The mannitol solution was heated to 30°C.
4. The solution of step 1 was added to mannitol solution obtained in step 3 slowly with stirring.
5. The solution thus obtained was stirred for 30 minutes or until a clear solution is obtained.
6. The solution was filtered through 0.22µ sterile filters and filled in vials as per the fill volume.
7. Vials were loaded in a lyophilizer and freeze dried.

Example 2

S.No	**Ingredients**	**F3**	**F4**
		Qty/vial	**Qty/vial**
1	Carfilzomib	60 mg	60 mg
2	Citric acid	64.20 mg	64.20 mg
3	Mannitol	600 mg	1500 mg
4	Tert-Butyl alcohol (TBA)	6 mL	6 mL
5	Water	4.8mL	4.8mL

Manufacturing Process:

1. Carfilzomib was dissolved in Tert-Butyl alcohol.
2. Mannitol and citric acid were dissolved in water .
3. The mannitol solution was heated to 30°C. .
4. The solution of step 1 was added to mannitol solution obtained in step 3 slowly with stirring.

5. The solution thus obtained was stirred for 30 minutes or until a clear solution is obtained.
6. The solution was filtered through 0.22µ sterile filters and filled in vials as per the fill volume.
7. Vials were loaded in a lyophilizer and freeze dried.

Example 3

S.No	Ingredients	F5	F6
		Qty/vial	Qty/vial
1	Carfilzomib	60 mg	60 mg
2	Maleic acid	38.64 mg	38.64 mg
3	Mannitol	600 mg	1500 mg
4	Tert-Butyl alcohol (TBA)	6 mL	6 mL
5	Water	4.8mL	4.8mL

Manufacturing Process:

1. Carfilzomib was dissolved in Tert-Butyl alcohol.
2. Mannitol and maleic acid were dissolved in water.
3. The mannitol solution was heated to 30°C.
4. The solution of step 1 was added to mannitol solution obtained in step 3 slowly with stirring.
5. The solution thus obtained was stirred for 30 minutes or until a clear solution is obtained.
6. The solution was filtered through 0.22µ sterile filters and filled in vials as per the fill volume.
7. Vials were loaded in a lyophilizer and freeze dried.

Example 4

S.No	Ingredients	F7	F8
		Qty/vial	Qty/vial
1	Carfilzomib	60 mg	60 mg
2	Tartaric acid	49.98 mg	49.98 mg
3	Sucrose	600 mg	1500 mg
4	Tert-Butyl alcohol (TBA)	6 mL	6 mL
5	Water	4.8mL	4.8mL

Manufacturing Process:

1. Carfilzomib was dissolved in Tert-Butyl alcohol.
2. Sucrose and tartaric acid were dissolved in water .
3. The sucrose solution was heated to 30°C. .
4. The solution of step 1 was added to sucrose solution obtained in step 3 slowly with stirring.
5. The solution thus obtained was stirred for 30 minutes or until a clear solution is obtained.
6. The solution was filtered through 0.22µ sterile filters and filled in vials as per the fill volume.
7. Vials were loaded in a lyophilizer and freeze dried.

Example 5

S.No	Ingredients	F9	F10
		Qty/vial	Qty/vial
1	Carfilzomib	60 mg	60 mg
2	Citric acid	64.20 mg	64.20 mg
3	Sucrose	600 mg	1500 mg
4	Tert-Butyl alcohol (TBA)	6 mL	6 mL
5	Water	4.8mL	4.8mL

Manufacturing Process:

1. Carfilzomib was dissolved in Tert-Butyl alcohol.
2. Sucrose and citric acid were dissolved in water .
3. The sucrose solution was heated to 30°C. .
4. The solution of step 1 was added to sucrose solution obtained in step 3 slowly with stirring.
5. The solution thus obtained was stirred for 30 minutes or until a clear solution is obtained.
6. The solution was filtered through 0.22µ sterile filters and filled in vials as per the fill volume.
7. Vials were loaded in a lyophilizer and freeze dried.

Example 6

S.No	Ingredients	F11	F12
		Qty/vial	Qty/vial
1	Carfilzomib	60 mg	60 mg
2	Maleic acid	38.64 mg	38.64 mg
3	Sucrose	600 mg	1500 mg
4	Tert-Butyl alcohol (TBA)	6 mL	6 mL
5	Water	4.8mL	4.8mL

Manufacturing Process:

1. Carfilzomib was dissolved in Tert-Butyl alcohol.
2. Sucrose and maleic acid were dissolved in water .
3. The sucrose solution was heated to 30°C.
4. The solution of step 1 was added to sucrose solution obtained in step 3 slowly with stirring.
5. The solution thus obtained was stirred for 30 minutes or until a clear solution is obtained.
6. The solution was filtered through 0.22µ sterile filters and filled in vials as per the fill volume.

7. Vials were loaded in a lyophilizer and freeze dried.

Example 7

S.No	Ingredients	F13	F14
		Qty/vial	Qty/vial
1	Carfilzomib	60 mg	60 mg
2	Ascorbic acid	58.80 mg	58.80 mg
3	Sucrose	600 mg	1500 mg
4	Tert-Butyl alcohol (TBA)	6 mL	6 mL
5	Water	4.8mL	4.8mL

Manufacturing Process:

1. Carfilzomib was dissolved in Tert-Butyl alcohol.
2. Sucrose and ascorbic acid were dissolved in water.
3. The sucrose solution was heated to 30°C.
4. The solution of step 1 was added to sucrose solution obtained in step 3 slowly with stirring.
5. The solution thus obtained was stirred for 30 minutes or until a clear solution is obtained.
6. The solution was filtered through 0.22µ sterile filters and filled in vials as per the fill volume.
7. Vials were loaded in a lyophilizer and freeze dried.

Example 8

S.No	Ingredients	F15	F16
		Qty/vial	Qty/vial
1	Carfilzomib	60 mg	60 mg
2	Succinic acid	39.30 mg	39.30 mg
3	Sucrose	600 mg	1500 mg
4	Tert-Butyl alcohol (TBA)	6 mL	6 mL

5	Water	4.8mL	4.8mL

Manufacturing Process:

1. Carfilzomib was dissolved in Tert-Butyl alcohol.
2. Sucrose and succinic acid were dissolved in water .
3. The sucrose solution was heated to 30°C.
4. The solution of step 1 was added to sucrose solution obtained in step 3 slowly with stirring.
5. The solution thus obtained was stirred for 30 minutes or until a clear solution is obtained.
6. The solution was filtered through 0.22µ sterile filters and filled in vials as per the fill volume.
7. Vials were loaded in a lyophilizer and freeze dried.

Example 9

S.No	Ingredients	Qty/vial
1	Carfilzomib	60 mg
2	Sucrose	100 mg
3	Acetonitrile	2mL
4	Water	q.s to 3 mL

Manufacturing Process:

1. Carfilzomib was dissolved in acetonitrile, and the solution was cooled to 5±3°C.
2. Sucrose was dissolved in water, and the solution was cooled to 5±3°C.
3. The solution of step 2 was added to solution of step 1, while maintaining the temperature at 5±3°C.
4. The solution was filtered through 0.22µ sterile filters and filled in vials as per the fill volume.
5. Vials were loaded in a lyophilizer and freeze dried.

We Claim

1. A lyophilized composition of Carfilzomib for parenteral administration that is free of cyclodextrins.

2. A lyophilized composition of Carfilzomib comprising:
   (i) Carfilzomib or its pharmaceutically acceptable salts, solvates, hydrates thereof,
   (ii) One or more sugars
   (iii) An acidifying agent
   (iv) One or more solvents, and
   (v) Optionally other pharmaceutically acceptable adjuvants,
   wherein the composition is free of cyclodextrins.

3. A lyophilized composition of Carfilzomib comprising:
   (i) Carfilzomib or its pharmaceutically acceptable salts, solvates, hydrates thereof,
   (ii) One or more sugars
   (iii) One or more solvents, and
   (iv) Optionally other pharmaceutically acceptable adjuvants,
   wherein the composition is free of cyclodextrins.

4. The composition of claims 2 and 3, wherein the ratio of Carfilzomib to sugars ranges from 1:0.5 to 1:100 by weight.

5. The composition of claims 2 and 3, wherein the sugar is selected from mannitol, sucrose, glucose, lactose, trehalose, glycine, dextrose, maltose, sorbitol, dextran and raffinose.

6. The composition of claims 2 and 3, wherein the solvent is selected from acetonitrile, tertiary butyl alcohol, dimethyl sulfoxide (DMSO), N,N-

dimethylacetamide (DMA), lower alkanols, ethyl acetate, propylene glycol (PG), polyethylene glycol, glycerine and water.

7. A stable parenteral composition of Carfilzomib comprising the lyophilized composition of claim 3 along with a diluent, wherein the diluent comprises of an acidifying agent and suitable solvents.

8. The compositions according to claims 2 and 7, wherein the acidifying agent is selected from tartaric acid, citric acid, aspartic acid, maleic acid, ascorbic acid and succinic acid.