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(54) Title: THE PARENTERAL COMPOSITION COMPRISING CARFILZOMIB

(57) Abstract: The present invention relates to a parenteral composition comprising carfilzomib or a pharmaceutically acceptable salt thereof. Furthermore, the composition is obtained using an effective process.

# THE PARENTERAL COMPOSITION COMPRISING CARFILZOMIB

## Field of the invention

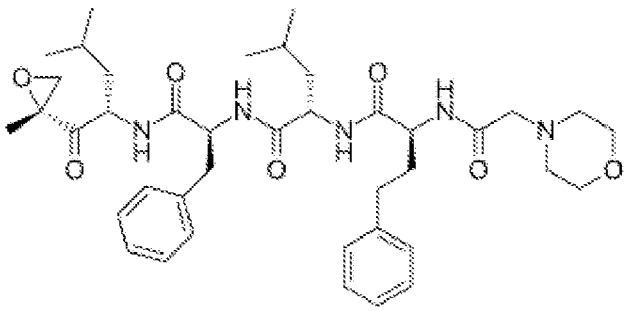
The present invention relates to a parenteral composition comprising carfilzomib or a pharmaceutically acceptable salt thereof. Furthermore, the composition is obtained using an effective process.

## Background of the invention

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body.

Multiple myeloma is a cancer that forms in a type of white blood cell called a plasma cell. Plasma cells help you fight infections by making antibodies that recognize and attack germs. Multiple myeloma causes cancer cells to accumulate in the bone marrow, where they crowd out healthy blood cells. The clinical features are bone pain, renal impairment, immunodeficiency, anemia and presence of abnormal immunoglobulins.

Carfilzomib is a modified tetrapeptidyl epoxide, isolated as the crystalline free base. 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- phenyl butanamido)-4-methylpentanamide. Carfilzomib has the following structure:



Formula I

Carfilzomib is a selective proteasome inhibitor indicated for the treatment of cancer, particularly multiple myeloma.

Carfilzomib is commercially marketed under the name Kyprolis® in single dose vials containing either 30 mg or 60 mg of the active ingredient. Each vial, in addition to lyophilized

carfilzomib, also contains sulfobutylether beta-cyclodextrin, citric acid and sodium hydroxide for pH adjustment (target pH 3.5).

U.S. Patent No.7,417,042, discloses a process for the preparation of carfilzomib. U.S. Patent No. 8,367,617, discloses crystalline carfilzomib, a citrate salt of carfilzomib, and amorphous carfilzomib.

WO2016116882 (A2) discloses a pharmaceutical composition comprising carfilzomib, one or more sugars, an acidifying agent.

As carfilzomib has low aqueous solubility, the development of a stable parenteral composition comprising carfilzomib is very challenging.

Therefore, there is still need for a parenteral composition comprising carfilzomib that has desired stability and solubility.

Surprisingly, in the present invention, a stable parenteral composition of carfilzomib has been developed using the non-aqueous environment which overcomes the above drawbacks.

**Detailed description of the Invention**

The main object of the present invention is to provide a stable composition comprising carfilzomib or pharmaceutically acceptable salt thereof.

Another object of the present invention is to provide desired solubility, permeability, pharmacokinetics and/or pharmacodynamics properties.

The present invention provides a process for producing a lyophilized pharmaceutical composition comprising carfilzomib.

The term “parenteral” as used herein means modes of administration other than enteral and topical administration, usually by injection, and comprising intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrastemal injection, and infusion.

According to one embodiment of the present invention, a parenteral composition comprising carfilzomib or a pharmaceutically acceptable salt thereof, at least one acid stabilizers and at least one surfactants.

Surprisingly, it has been found that the antimicrobial activity and stability of the carfilzomib is dependent on the pH value of the composition.

So, chemical stability can be substantially improved by lowering the pH value and by increasing the buffer capacity in order to provide an adjusted and robustly maintained pH value. It has been surprisingly found that using acid stabilizer provide very stable composition comprising carfilzomib.

According to one embodiment of the present invention, the acid stabilizers are selected from the group comprising succinic, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, lactic, phosphoric, sulfuric, tartaric, maleic, malic, mandelic, methanesulfonic, p-toluenesulfonic, chloroacetic acids or mixtures thereof. Preferably, the acid stabilizer is succinic or acetic or mixtures thereof.

According to one embodiment of the present invention, the pH of the acid stabilizers is from 2 to 4, preferably pH of the acid stabilizers is 3.5.

Surfactants offer many advantages. One of these is the use of surfactants becomes inevitable to reduce the interfacial tension between the medium and the drug and to increase solubility of drugs. Since carfilzomib has low molarity, the choice of surfactant is of great importance.

Suitable the surfactants are selected from the group comprising macrogol 15 hydroxystearate, macrogolglycerol ricinoleate 35, polyoxyethylene sorbitan esters (polysorbate), sodium lauryl sulphate, propylene glycol, glyceryl oleate, tocopherol, ascorbyl palmitate, citric acid, polyethoxylated fatty acid esters, polyoxyethylene hydrogenated castor oil, sorbitan esters, docusate sodium, nonoxynol or mixtures thereof.

According to one embodiment of the present invention, the surfactant is macrogol 15 hydroxystearate or macrogolglycerol ricinoleate 35 or mixtures thereof.

Due to stability issues, carfilzomib containing compositions must be lyophilized before storage and reconstituted before use.

According to one embodiment of the present invention, the composition is a stable lyophilized powder for injection.

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.

Lyoprotectant is added to a formulation in order to protect the active ingredient during both freezing and drying process. Lyoprotectants are selected from the group comprising amino acids and sugars.

According to one embodiment of the present invention, the composition further comprises at least one the lyoprotectant which is selected from amino acids.

Suitable the amino acids are selected from the group comprising L-cysteine, glycine, proline, 4-hydroxyproline, L-serine, sodium glutamate, alanine, arginine, lysine hydrochloride, di- or tri-amino acids or mixtures thereof.

According to one embodiment of the present invention, the amino acid is L-cysteine.

In the formulation, using sugars as lyoprotectant with acid causes non-volatile sugar acids. It may create stability problems for the composition comprising carfilzomib.

According to one embodiment of the present invention, the composition is free of sugars. Said sugars is mannitol or sucrose or glucose or lactose or trehalose or glycine or dextrose or maltose or sorbitol or dextran or raffinose.

According to one embodiment of the present invention, the composition further comprises the solvents and co-solvents which is selected from the group comprising tertiary butyl alcohol, water for injection, dimethyl sulfoxide (DMSO), N,N- dimethylacetamide (DMA), acetonitrile, lower alkanols, ethyl acetate, propylene glycol (PG), polyethylene glycol, glycerine or mixtures thereof.

Buffering agents encompasses those agents which maintain the composition pH in an acceptable range prior to lyophilization. Many buffering agents covering a wide pH range are available for selection in the formulations.

According to one embodiment of the present invention, the composition further comprises at least one the buffering agent which is selected from the group comprising sodium hydroxide (NaOH), sodium phosphate, acetate, citrate, glycine, histidine, potassium phosphate, diethanolamine, tris or mixtures thereof.

According to one embodiment of the present invention, the composition further comprises chelating agent for increase the solubility like ethylenediaminetetraacetic acid (EDTA), optionally.

According to one embodiment of the present invention, the composition is ready-to-dilute. The composition is for use in treating cancer.

According to an embodiment of the present invention, the cancer is selected from the group comprising multiple myeloma, head and neck cancers, esophagus cancer, gastric cancer, colorectal cancer, colon cancer, rectum cancer, liver cancer, gallbladder cancer, cholangiocarcinoma, biliary tract cancer, pancreatic cancer, lung cancer, breast cancer, ovarian cancer, cervical cancer, endometrial cancer, vaginal cancer, vulvar cancer, renal cancer, urothelial cancer, prostate cancer, testicular tumor, osteosarcoma, soft-tissue sarcoma, leukemia, myelodysplastic syndrome, malignant lymphoma, adult T-cell leukemia, skin cancer, brain tumor, pleural mesothelioma, and unknown primary cancer.

According to one embodiment of the present invention, the cancer is multiple myeloma.

**Example 1:**

| Agents | Examples |
|---|---|
| Active agent | Carfilzomib |
| Acid stabilizers | Succinic acid, acetic acid or mixtures thereof |
| Surfactants | macrogol 15 hydroxystearate, macrogolglycerol ricinoleate 35 or mixtures thereof |
| Lyoprotectant | L-cysteine |
| Buffering agent | NaOH |
| Co-Solvent | Tert-butyl alcohol |
| Solvent | Water for injection |

**Process**

a) dissolving surfactant(s) in water for injection,
b) adding tert-butyl alcohol in step (a) mixture,
c) adding L-cysteine and adjusting to pH 1.7 with acid stabilizer(s),
d) cooling the mixture until 5°C,
e) adding carfilzomib gradually until a clear solution is obtained,
f) adjusting to pH 3.5 with NaOH,
g) this solution is filtered through a 0.45µ membrane filter
h) filling in vials as per the fill volume
i) Vials are loaded in a lyophilizer and freeze dried.

## CLAIMS

1. A parenteral composition comprising carfilzomib or a pharmaceutically acceptable salt thereof, at least one acid stabilizers and at least one surfactants.

2. The parenteral composition according to claim 1, wherein the acid stabilizers are selected from the group comprising succinic, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, lactic, phosphoric, sulfuric, tartaric, maleic, malic, mandelic, methanesulfonic, p-toluenesulfonic, chloroacetic acids or mixtures thereof.

3. The parenteral composition according to claim 2, wherein the acid stabilizer is succinic or acetic or mixtures thereof.

4. The parenteral composition according to claim 3, wherein the pH of the acid stabilizers is from 2 to 4, preferably pH of the acid stabilizers is 3.5.

5. The parenteral composition according to claim 1, wherein the surfactants are selected from the group comprising macrogol 15 hydroxystearate, macrogolglycerol ricinoleate 35, polyoxyethylene sorbitan esters (polysorbate), sodium lauryl sulphate, propylene glycol, glyceryl oleate, tocopherol, ascorbyl palmitate, citric acid, polyethoxylated fatty acid esters, polyoxyethylene hydrogenated castor oil, sorbitan esters, docusate sodium, nonoxynol or mixtures thereof.

6. The parenteral composition according to claim 5, wherein the surfactant is macrogol 15 hydroxystearate or macrogolglycerol ricinoleate 35 or mixtures thereof.

7. The parenteral composition according to claim 1, wherein the composition is lyophilized powder for injection.

8. The parenteral composition according to claim 7, wherein further comprising at least one the lyoprotectant which is selected from amino acids.

9. The parenteral composition according to claim 8, wherein the amino acids are selected from the group comprising L-cysteine, glycine, proline, 4-hydroxyproline, L-serine, sodium glutamate, alanine, arginine, lysine hydrochloride, di- or tri-amino acids or mixtures thereof.

10. The parenteral composition according to claim 9, wherein the amino acid is L-cysteine.

11. The parenteral composition according to any preceding claim, wherein the composition is free of sugars.

12. The parenteral composition according to claim 11, wherein said sugars is mannitol or sucrose or glucose or lactose or trehalose or glycine or dextrose or maltose or sorbitol or dextran or raffinose.

13. The parenteral composition according to any preceding claim, wherein further comprising the solvents and co-solvents which is selected from the group comprising tertiary butyl alcohol, water for injection, dimethyl sulfoxide (DMSO), N,N-dimethylacetamide (DMA), acetonitrile, lower alkanols, ethyl acetate, propylene glycol (PG), polyethylene glycol, glycerine or mixtures thereof.

14. The parenteral composition according to any preceding claim, wherein further comprising at least one the buffering agent which is selected from the group comprising sodium hydroxide (NaOH), sodium phosphate, acetate, citrate, glycine, histidine, potassium phosphate, diethanolamine, tris or mixtures thereof.

15. The parenteral composition according to any preceding claim, wherein further comprising chelating agent optionally, preferably chelating agent is EDTA.

16. The parenteral composition according to any preceding claim, wherein the composition is ready-to-dilute.

17. The parenteral composition according to any preceding claim for use in treating cancer.

18. The parenteral composition according to claim 17, wherein the cancer is multiple myeloma.