TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR CARFILNAT (CARFILZOMIB 60 MG/VIAL) FOR INJECTION

Version number 1.0
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1. Introduction

CARFILNAT is a generic medicine of innovator product Kyprolis (Onyx Pharmaceuticals, Inc., USA). CARFILNAT is an anti-neoplastic agent contains Carfilzomib. Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor that selectively and irreversibly binds to the N terminal threonine containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome, and displays little to no activity against other protease classes. Carfilzomib had antiproliferative and proapoptotic activities in preclinical models in haematologic tumours. In animals, carfilzomib inhibited proteasome activity in blood and tissue and delayed tumour growth in models of multiple myeloma. In vitro, carfilzomib was found to have minimal neurotoxicity and minimal reaction to non-proteasomal protease. CARFILNAT is approved in Tanzania for use in adult patients.

1.1 Product details

Registration number	TAN 21 HM 0180
Brand name	CARFILNAT
Generic name, strength and form	Carfilzomib for injection 60mg/vial, each 1 ml contains 2mg of Carfilzomib
ATC classification	Antineoplastic agents, other antineoplastic agents, ATC code: L01XX45
Distribution category	POM
Country of origin	India
Associated product	N/A
Marketing Authorization Holder	Natco Pharma Limited, Nacto House, Road No.2, Banjara Hills, Hyderabad-500034, India.
Local Technical Representative	Philips Distributor's Limited, P.O.BOX 737, Dar es Salaam

1.2 Assessment procedure

The application for registration of CARFILNAT was submitted on 11 May, 2020. The product underwent full assessment. Assessment was completed in 2 (two) rounds of evaluation and the product was registered on 29 March, 2021.

1.3 Information for users

Visual description of the finished product	A white to off white lyophilized powder or cake Description for Reconstituted solution: Clear, color less solution and free from extraneous visible matter
Primary packing material	50mL clear lyo vial with a 20mm double slotted rubber stoppers and sealed with 20 mm flip-off seals Ivory coloured button

Secondary packing materials	A printed carton box
Shelf-life and storage condition	Proposed shelf life: 24 months, Store in a refrigerator (2°C – 8°C). Do not freeze and store in the original carton in order to protect from light. Proposed shelf life (after reconstitution): Chemical and physical in-use stability of reconstituted solutions in the vial, syringe or intravenous bag has been demonstrated for 24 hours at 2°C - 8°C or for 4 hours at 25°C. The elapsed time from reconstitution to administration should not exceed 24 hours. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and should not be longer than 24 hours at 2°C – 8°C.
Route of administration	intravenously by infusion administration only
Therapeutic indications	Carfilnat in combination with either lenalidomide and dexamethasone or dexamethasone alone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

2. Labelling and product information

Summary of product characteristics
The SmPC included all the relevant information to ensure correct and safe use of the medicine by healthcare providers. The complete SmPC can be accessed here.

Package insert/leaflet
The package insert is confirmed to be derived from the SmPC and contains sufficient data for the end user. Since the product is POM, the package insert contains full prescribing information as per SmPC.

Container labels
The product label information is presented in English. Details in the secondary pack label include:
Brand name: CARFILNAT

Composition: Each vial contains 60 mg carfilzomib. After reconstitution, 1 mL of solution contains 2 mg of carfilzomib. betadex sulfobutyl ether sodium, anhydrous citric acid, sodium hydroxide & water for injection

Pack size: 1 vial

Manufacturing details: batch number, manufacturing date and expiry date

Storage conditions: Store in a refrigerator (2°C – 8°C). Do not freeze and store in the original carton in order to protect from light

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Read the package leaflet before use

The details of the primary pack include:

Brand name and strength: CARFILNAT 60 mg/vial
Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Natco Pharma Limited

The content of the primary and secondary labels was aligned to the requirements of the Part V of the Compendium: Guidelines on Format and Content of Product Labels for Medicinal products. The label contains sufficient information for proper identification of the medicine and post marketing follow up of the product.

Mock labels are appended as annex I.

3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

Information on quality of the API was submitted in form of DMF.

General Information

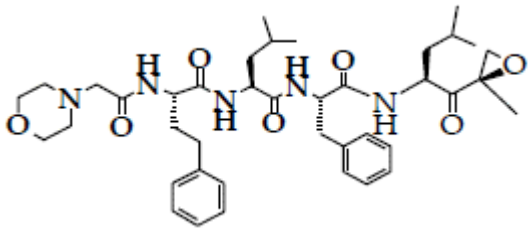
Carfilzomib API is non-compendia

Molecular formula: $C_{40}H_{57}N_5O_7$

Chemical name:

(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

Structure:



General properties

Carfilzomib appears as a white to off-white, slightly hygroscopic, crystalline powder. It is practically insoluble in water, sparingly soluble in acetonitrile and soluble in ethanol (100%). Its aqueous solubility is pH dependent and is higher at low pH values and its pKa is 5.14 and partition coefficient is 3.77.

Carfilzomib contains five chiral centres [22S, 17S, 10S, 5S, 3R] and exist in different polymorphs. The manufacturing process yield consistently the same isomer and polymorph (amorphous).

Manufacture

Carfilzomib API manufacturer is Laurus Labs Limited, Plot No. 21, Jawaharlal Nehru Pharma City, Parawada, Visakhapatnam - 531 021, Andhra Pradesh, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by Government of Andhra Pradesh Drug Control Administration. Carfilzomib API is manufactured by chemical synthesis using conventional techniques. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The API specifications were set as per in-house standards and ICHQ3A. The parameters monitored during quality control are: description, solubility, identification, specific rotation, appearance of solution, water content, residue on ignition, heavy metals, microbial enumeration tests, bacterial endotoxin, related substances, residual solvents, and assay. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Carfilzomib API is 24 months when packed in high molecular low density polyethylene bag filled with nitrogen and then vacuum seal (Heat Seal) with storage condition ‘Store at 2 to 8ºC’.

Quality of the Finished Pharmaceutical Product

Formulation

CARFILNAT is a white to off white lyophilized powder or cake. Description for Reconstituted solution: Clear, color less solution and free from extraneous visible matter

CARFILNAT contains the API Carfilzomib and other ingredients listed here after: betadex sulfobutyl ether sodium, anhydrous citric acid, sodium hydroxide, and water for injection. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, 8th Edition in terms of function and quantities.

Manufacture

The finished product manufacturer is Natco Pharma Limited – Pharma Division, Kothur – 509228 Rangareddy District Telangana, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 30 March 2020.

Specifications

The FPP is non-compendia. The manufacturer controls the quality of the finished product as per in-house standards and ICH requirements. The parameters monitored during quality control are: description, clarity and colour of solution, identification, reconstitution time, pH of reconstituted solution, uniformity of dosage units, osmolality ratio, osmolality, related substances, assay, particulate matter (visible and sub-visible), bacterial endotoxins, and sterility. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on 3 (three) batches of the finished product stored at 30 ± 2°C & RH: 75 ± 5% RH for 24 months and 40± 2°C & RH: 75% ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when packed in 50mL clear lyo vial with a 20mm double slotted rubber stoppers and sealed with 20 mm flip-off seals Ivory coloured button with storage condition 'Store in a refrigerator (2°C – 8°C)'.

Safety and efficacy information

No bioequivalence study was submitted to support the application.

The product concerned by the application contains the same active ingredient in the same concentration as the innovator product Kyprolis (Onyx Pharmaceuticals, Inc., USA). It has an identical qualitative and quantitative composition in terms of the active substance as its the innovator product.

The product is lyophilized powder for solution for infusion and contains Carfilzomib as an active substance. Excipients are betadex sulfobutyl ether sodium, anhydrous citric acid, sodium hydroxide, and water for injection. Due to the parenteral administration mode, bioequivalence can be concluded without further studies and as the composition is the same, no differences in non-clinical or clinical effects are possible.

4. Benefit-Risk Assessment and Conclusion

On basis of the data submitted, the current state of knowledge and compliance to Good Manufacturing Practice, the benefit of the product outweighs the risks associated with its use when used in accordance to the summary of product characteristics. CARFILNAT is recommended for registration.

5. Post-approval updates

Variation applications

Reference number	Date submitted	Change requested	Recommendation	Granting date

Feedback from pharmacovigilance, post marketing surveillance and enforcement activities

Type of feedback	Impact	Response

Re-registration applications

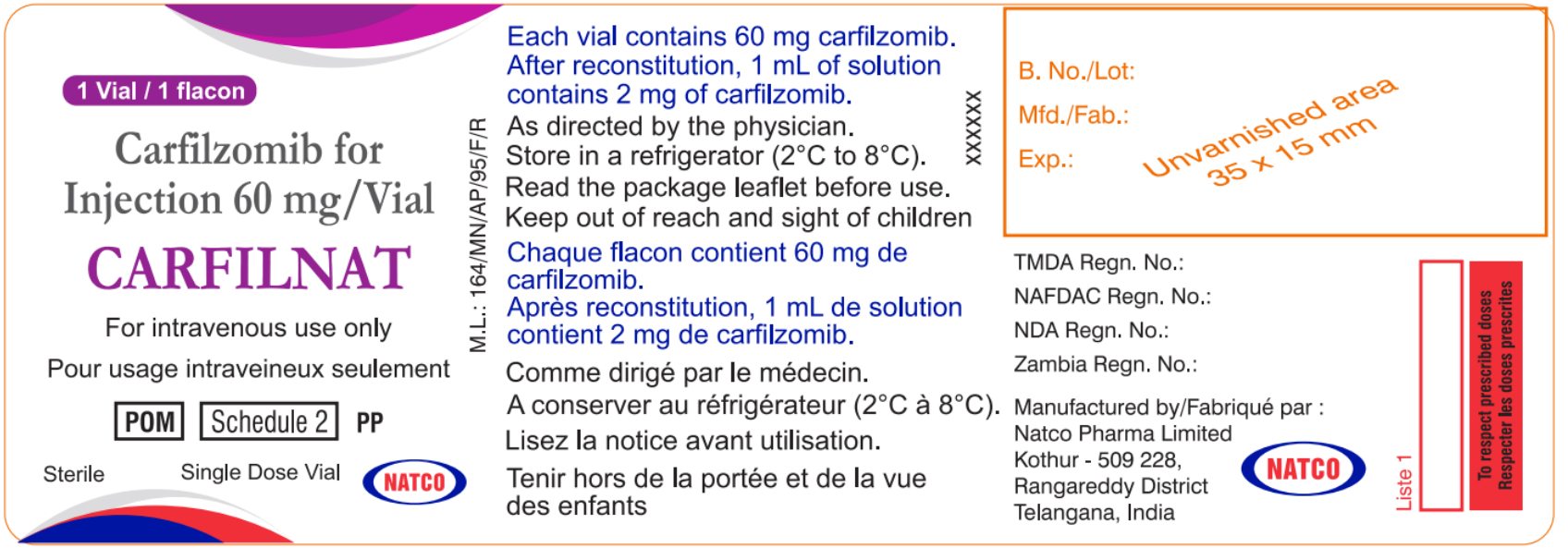
NA

PART 5: CHANGE HISTORY

Version number	**Date**	**Description of update**	**Section(s) Modified**	**Approval date**

Annex I: Mock up labels;

Primary pack label;



Secondary pack label;