THEUNITEDREPUBLICOFTANZANIA

MINISTRYOFHEALTH

TANZANIAMEDICINES ANDMEDICALDEVICESAUTHORITY

PUBLIC ASSESSMENT REPORT FOR DOXEL 20 (DOCETAXEL 20 MG/1ML CONCENTRATE FOR SOLUTION FOR INFUSION

Version number 1
3rd January, 2023

TMDA Headquarters, Plot No. 56/1, Block E, Kisasa B Centre, Swaswa Road, P. O. Box 1253, Dodoma – Tanzania, Telephone: +255 (26) 2961989/2061990/+255 (22) 2450512/2450751/2452108, Email: info@tmda.og.tz, Website: **www.tmda.go.tz**
Toll free: 0800110084

1. Introduction

Doxel 20 Concetrate for Solution for Infusion is a generic medicine of Taxotere. Doxel 20 Concetrate for Solution for Infusion is an antioneoplastic medicine belonging to L01CD02; antineoplastic and immunomodulating agents, taxanes group. Doxel 20 concentrate for solution for Infusion. Docetaxel is an antineoplastic agent which acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly which leads to a marked decrease of free tubulin. The binding of docetaxel to microtubules does not alter the number of protofilaments. Docetaxel has been shown in vitro to disrupt the microtubular network in cells which is essential for vital mitotic and interphase cellular functions. Doxel 20 Concetrate for Solution for Infusion is approved in Tanzania for use in adults, elderly.

1.1 Product details

Registration number	TAN 21 HM 0291
Brand name	Doxel 20 Concentrate for Solution for Infusion
Generic name, strength and form	Docetaxel anhydrous, 20 mg Concentrate for Solution for Infusion
ATC classification	Taxanes, ATC Code: L01CD02
Distribution category	POM
Country of origin	Italy
Associated product	State any other product of formulation, strength or site that is linked or associated with the product if applicable
Marketing Authorization Holder	Eurolab (Pty) Ltd, Woodmead Office Park, 3 Stirrup Lane, Van Reenens Avenue,Woodmead, 2144 South Africa
Local Technical Representative	BB Pharma Consultancy Limited, Mabibo External, EPZA, P.O.BOX 31338, Dar es salaam; Tanzania

1.2 Assessment procedure

The application for registration of Doxel 20 Concentrate for Solution for Infusion was submitted on 15th October, 2019. The product underwent full assessment. Assessment was completed in two rounds of evaluation. Doxel 20 Concentrate for Solution for Infusion was registered on 20th August, 2021

1.3 Information for users

Visual description of the finished product	Clear, oily, pale yellow solution
Primary packing material	Colorless glass (USP type 1) with Bromo butyl rubber stopper with Aluminum metallic cap with flip off
Secondary packing materials	Carton box
Shelf-life and storage condition	24 months Do not store above 30oC
Route of administration	I.V
Therapeutic indications	**Breast cancer** Docetaxel in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with: • operable node- positive breast cancer. • operable node- negative breast cancer. For patients with operable node-negative breast cancer, adjuvant treatment should be restricted to patients eligible to receive chemotherapy according to internationally established criteria for primary therapy of early breast cancer (see section 5.1). Docetaxel in combination with doxorubicin is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy for this condition. Docetaxel monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic therapy. Previous chemotherapy should have included an anthracycline or an alkylating agent. Docetaxel in combination with trastuzumab is indicated for the treatment of patients with metastatic breast cancer whose tumours over express HER2 and who previously have not received chemotherapy for metastatic disease. Docetaxel in combination with capecitabine is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. **Non-small cell lung cancer**

	Docetaxel is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy. Docetaxel in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer, in patients who have not previously received chemotherapy for this condition. **Prostate cancer** Docetaxel in combination with prednisone or prednisolone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer. Docetaxel in combination with androgen-deprivation therapy (ADT), with or without prednisone or prednisolone, is indicated for the treatment of patients with metastatic hormone-sensitive prostate cancer. **Gastric adenocarcinoma** Docetaxel in combination with cisplatin and 5-fluorouracil is indicated for the treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for metastatic disease. **Head and neck cancer** Docetaxel in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck

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 that is intended for long term use 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: DOXEL 20

Composition: Each single dose vial contains 20 mg Docetaxel per 1 mL (20 mg/1mL), Citric acid Anhydrous, Povidone (Kollidon 12 PF), Polisorbate 80 (Montanox 80 P.P.I), Ethanol absolute, Nitrogen

Pack size: 5 mL

Manufacturing details: <batch number, manufacturing date, expiry date>

Storage conditions: Do not store above 30ºC**,** Store in the original package in order to protect from light**,** do not refrigerate or freeze

Manufacturer address: Actavia Italy, S.P.A, Nerviano Plant, Via Pasteur 10, 20014 Nerviano, (Milano), Italy.

Unique identifier: NA

Special warnings/precautions or instructions for use: <include warnings or IFU if applicable>

The details of the primary pack include:

Brand name and strength: DOXEL 20 (Docetaxel 20 mg/1mL)

Manufacturing details: <batch number, manufacturing date, expiry date>

Name of manufacturer: Actavia Italy, S.P.A

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.

Describe any approved deviation to the requirements and the justification for the deviation.

Mock labels are appended as annex I

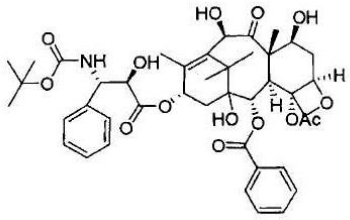
3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

Information on quality of the API was submitted in form of CEP

General properties
Docetaxel API is compendia in USP/BP
Molecular formula: C43H53NO14
Chemical name: (2R, 3S)-N-Carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5beta, 20-epoxy-1,2alpha,4,7beta, 10beta, 13alpha-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate

Structure:



Docetaxel is a white to off-white crystalline powder, practically insoluble in water; freely soluble in anhydrous ethanol and tetrahydrofuran; and soluble in methylene chloride, methanol, acetone and ethylacetate. Its partition coefficient (log P) is 4.26. Docetaxel anhydrous has eleven chiral centres resulting in a considerable number of potential stereoisomers. Docetaxel exhibits polymorphism. XRD results confirm that the same crystalline form is consistently obtained by API manufacturers (Phyton Biotech LLC and Scinopharm Taiwan, Ltd)

Manufacture
The API manufacturing site, Phyton Biotech LLC, 1527 Cliveden Avenue, Canada-V3M 6P7 Delta, British Columbia and Scinopharm Taiwan, Ltd, No. 1, Nan-KE 8th Road, Taiwan – 74144 Shan-Hua, Tainan were noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by EDQM. Docetaxel 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 BP, in-house standards and ICHQ3A. The parameters monitored during quality control are: Description, identification, specific optical rotation, appearance of solution, sulphated ash, related substance, water content, assay (HPLC), residual solvents, microbial limit test, bacterial endotoxin.

Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Docetaxel API is 36 months when packed in polyethylene bag in an aluminum bag with desiccant pack and stored at below 25ºC.

Quality of the Finished Pharmaceutical Product

Formulation

DOXEL 20 is a clear, oily, pale-yellow solution. DOXEL 20 contains Docetaxel and other ingredients listed here after Citric acid Anhydrous, Povidone (Kollidon 12 PF), Polisorbate 80 (Montanox 80 P.P.I), Ethanol absolute, Nitrogen. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 8th in terms of function and quantities.

Manufacture

The finished product was manufactured at Actavis Italy S.P.A, Nerviano Plant Via Pasteur 10 20014 Nerviano (Milan), Italy. The compliance of the site to TMDA GMP standards was confirmed through desk-review.

Specifications

The FPP is non-compendia. The manufacturer controls the quality of the finished product as per in-house and ICHQ3B requirements. The parameters monitored during quality control are: Appearance, Visible particles, Sub-visible particles (≥ 10µm, ≥ 25µm) Coloration, Clarity, pH (solution 1/10 (v/v) in water, Extractable volume (80mg/4ml) Water (KF), Identification of Docetaxel (TLC, HPLC), Assay of Docetaxel (HPLC), Assay of alcohol (GC), Related substances (HPLC), Bacterial endotoxins (LAL) 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 three batches of the finished product stored at 30°C±2°C/65%±5%RH for 24 months and 40°C±2°C/75%±5%RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in Colorless glass vial (USP type 1) with Bromo butyl rubber stopper at “Do not store above 30^{o}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 Taxotere from Sanofi-Aventis Australia Pty Ltd). It has an identical qualitative and quantitative composition in terms of the active substance as its the innovator product.

The product is concentrate for solution for infusion and contains Docetaxel as an active substance. Excipients are Citric acid Anhydrous, Povidone (Kollidon 12 PF), Polisorbate 80 (Montanox 80 P.P.I), Ethanol absolute, Nitrogen. 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. DOXEL 20 is recommended for registration.

5. Benefit-Risk Assessment and Conclusion

On basis ofthe 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. <Brand name> is recommended for registration.

6. 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

Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

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

Annex I: Mock up label