THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR GEMCITABINE (AS HYDROCHLORIDE) 38 MG/ML, CONCENTRATE FOR SOLUTION FOR INFUSION

Version number 01, 06/01/2023

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

Gemcitabine Hydrochloride is a generic medicine of innovator product Gemzar 1000 mg powder for solution for infusion by Lilly Deutschland GmbH, Germany.Gemcitabine Hydrochloride is a nucleoside (pyrimidine) analogue that exhibits antitumor activity. Gemcitabine (dFdC) is metabolised intracellularly by nucleoside kinase to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is due to inhibition of DNA synthesis by two mechanisms of action by dFdCDP and dFdCTP. First, dFdCDP inhibits ribonucleotide reductase, which is uniquely responsible for catalysing the reactions that produce deoxynucleoside triphosphates (dCTP) for DNA synthesis. Inhibition of this enzyme by dFdCDP reduces the concentration of deoxynucleosides in general and, in particular, dCTP. Second, dFdCTP competes with dCTP for incorporation into DNA (self-potentiation). Gemcitabine Hydrochloride is approved in Tanzania for use only in adult patients.

1.1 Product details

Registration number	TAN 22 HM 0475
Brand name	N/A
Generic name, strength and form	One ml of the reconstituted solution for infusion contains 38 mg gemcitabine (as hydrochloride)
ATC classification	pyrimidine analogues ATC code: L01BC05
Distribution category	POM
Country of origin	India
Associated product	N/A
Marketing Authorization Holder	Shilpa Medicare Limited, #12-6-214/A1, Hyderabad Road, Raichur – 584135, Karnataka, India
Local Technical Representative	Medox Pharmaceutical Dar es Salaam Limited Plot No. 19, Malik Road, Upanga, Dar es Salaam

1.2 Assessment procedure

The application for registration of Gemcitabine Hydrochloride was submitted on 21/10/2021. The product underwent full assessment. Assessment was completed in two rounds of evaluation and the product was registered on 05/12/2022

1.3 Information for users

Visual description of the finished product	clear and colourless to light straw colored solution
Primary packing material	30 ml glass vial colourless type-I moulded glass vial with bromobutyl rubber stopper and with 20 mm crimp
Secondary packing materials	Carton box alongside with a package insert
Shelf-life and storage condition	24 months Store in a refrigerator (2°C - 8°C)

Route of administration	Intravenous
Therapeutic indications	- Gemcitabine is indicated for the treatment of locally advanced or metastatic bladder cancer in combination with cisplatin. - Gemcitabine is indicated for treatment of patients with locally advanced or metastatic adenocarcinoma of the pancreas. - Gemcitabine, in combination with cisplatin is indicated as first line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). Gemcitabine monotherapy can be considered in elderly patients or those with performance status 2. - Gemcitabine is indicated for the treatment of patients with locally advanced or metastatic epithelial ovarian carcinoma, in combination with carboplatin, in patients with relapsed disease following a recurrence-free interval of at least 6 months after platinum-based, first- line therapy. - Gemcitabine, in combination with paclitaxel, is indicated for the treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated

2. Labelling and product information

Summary of product characteristics

The SmPC included all the relevant information to ensure correct and safe use of the medicineby 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: N/A

Composition: Gemcitabine Hydrochloride, Sodium Hydroxide, Hydrochloric Acid, Water for Injection and Nitrogen

Pack size: 1vial

Manufacturing details: batch number, manufacturing date and expiry date

Storage conditions: Unopened Vial: 24 Months when stored in a refrigerator 2°C - 8°C

Manufacturer address: Shilpa Medicare Limited, Plot No. S-20 to S-26, Pharma SEZ; TSIIC, Green Industrial Park, Polepally Village, Jadcherla Mandal, Mahaboobnagar District, Telangana State-509301, India

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Cytotoxic Agent, see enclosed leaflet
The details of the primary pack include:
Brand name and strength: One ml of the reconstituted solution for infusion contains 38 mg gemcitabine (as hydrochloride)
Manufacturing details: batch number, manufacturing date and expiry dateName of manufacturer: Shilpa Medicare 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.

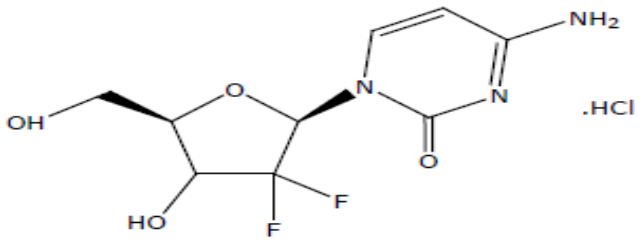
3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

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

General Information

Gemcitabine Hydrochloride API is compendia in USP, BP, Ph. Eur.Molecular formula: $C_9H_{12}ClF_2N_3O_4$
Chemical name:
4-Amino-1-(2-deoxy-2,2-difluoro-β-d-erythro-pentofuranosyl) pyrimidin-2(1H)-one hydrochlorideStructure:



General properties

Gemcitabine Hydrochloride is a white or almost white powder, which is soluble in water, slightly soluble in methanol and practically insoluble in acetone. The finished product is a solution for infusion; therefore, the particle size and polymorphic form of the drug substance will not have an impact on the drug product.

Manufacture

Gemcitabine Hydrochloride API manufacturer is Shilpa Medicare Limited, 1A & 1A 'P', 1B, 2, 2A, 2B, 3A to 3E, 4A, 5A, 4B, & 5B, Deosugur Industrial Area Deosugur - 584170, Raichur, Dist: Raichur, Karnataka, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by Office of Drugs control department for the state of Karnataka. Gemcitabine Hydrochloride 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 Ph. Eur and ICH guidelines. The parameters monitored during quality control are: Appearance, solubility, identification (by IR), test for chloride, specific optical rotation, appearance of solution, sulphated ash, pH, heavy metals, related substances (HPLC), assay (HPLC), residual solvents (GC), and bacterial endotoxins. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

Appropriate stability data have been provided supporting a suitable retest period of 60 months when stored in the proposed packaging.

Quality of the Finished Pharmaceutical
ProductFormulation

Gemcitabine Hydrochloride is presented as clear and colourless to light straw colored solution

Gemcitabine Hydrochloride contains the API Gemcitabine Hydrochloride and other ingredients listed here after: Sodium Hydroxide, Hydrochloric Acid, Water for Injection and Nitrogen. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, 8^{th} Edition in terms of function and quantities.

Manufacture

The finished product manufacturer is Shilpa Medicare Limited, Plot No. S-20 to S-26, Pharma SEZ; TSIIC, Green Industrial Park, Polepally Village, Jadcherla Mandal, Mahaboobnagar District, Telangana State-509301, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection.

Specifications

The FPP is compendia in USP. 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, Identification (HPLC and UV), Clarity of solution, Uniformity of dosage units (weight variation), Related substances (HPLC), Assay (HPLC), Osmolality, Colour value, Light transmittance, Particulate matter, Bacterial endotoxins, and Sterility. Compliance to the standard was established using batch analysis data and stabilitydata

Stability and container closure system

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing. Based on available stability data, the proposed shelf-life of 24 months with storage recommendation “Store in a refrigerator (2°C - 8°C)” is satisfactory.

Safety and efficacy information

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

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. Gemcitabine Hydrochlorideis recommended for registration.

5. Post-approval updatesVariation applications

Referenc enumber	Date submitte d	Change requested	Recommendation	Grantin gdate

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;

Effective date 03/10/2022