TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR GEMCITABINE HYDROCHLORIDE (200 MG GEMCITABINE (AS HYDROCHLORIDE)) LYOPHILIZED POWDER FOR INJECTION

Version number 1.0

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1. Introduction

Gemcitabine Hydrochloride is a generic medicine of innovator product Gemzar 200 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 0296
Brand name	N/A
Generic name, strength and form	Each vial contains; Gemcitabine Hydrochloride Equivalent to Gemcitabine 200 mg
ATC classification	ATC code L01BC05- Pyrimidine analogues
Distribution category	POM
Country of origin	India
Associated product	N/A
Marketing Authorization Holder	Bahari Pharma Limited Pugu Road, Industrial Area, P.O. Box 40591, Dar es Salaam Tanzania
Local Technical Representative	N/A

1.2 Assessment procedure

The application for registration of Gemcitabine Hydrochloride was submitted on 10 March 2020. The product underwent full assessment. Assessment was completed in 3 (three) rounds of evaluation and the product was registered on 04th August 2022

1.3 Information for users

Visual description of the finished product	White to off white lyophilized plug contained in a flint glass vial
Primary packing material	10 mL type I clear glass vials with neck 20 mm with grey bromo butyl rubber stopper, and 20 mm flip off blue seal
Secondary packing materials	A printed carton box
Shelf-life and storage condition	Unopened Vial: 24 Months when stored at or below 30°C Reconstituted Solution: Within 24 hours after reconstitution when stored at temperature 25±2ºC

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 the treatment of patients with locally advanced or metastatic adenocarcinoma of the pancreas. - Gemcitabine, in combination with cisplatin is indicated as the 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, 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. - 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.

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: N/A

Composition: Gemcitabine Hydrochloride 200 mg, mannitol, sodium acetate trihydrate, sodium hydroxide, hydrochloric acid, water for injection

Pack size: 1vial

Manufacturing details: batch number, manufacturing date and expiry date

Storage conditions: Unopened Vial: 24 Months when stored at or below 30ºC
Reconstituted Solution: Within 24 hours after reconstitution when stored at temperature 25±2ºC

Manufacturer address: physical address of release site

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: Gemcitabine Hydrochloride 200 mg

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: PT Fonko International Pharmaceuticals

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.

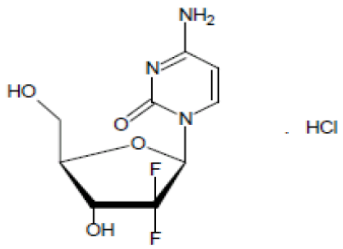
General Information

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 hydrochloride

Structure:



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 dissolved before injection; 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 Hetero Labs Limited (Unit-I), Survey.No.10, I.D.A., Gaddapotharam Village, Jinnaram Mandal, Sangareddy District, Telangana, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by Drugs Control Administration Government of Telangana-India. 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, loss on dry, 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

The re-test and shelf-life period of Gemcitabine Hydrochloride API is 12 and 60 months respectively when packed in polythene bags + triple laminated medium barrier bags with storage conditions ‘Store at temperature below 25°C, in a tight container, protect from light’.

Quality of the Finished Pharmaceutical Product

Formulation

Gemcitabine Hydrochloride is a white to off white lyophilized plug contained in a flint glass vial

Gemcitabine Hydrochloride contains the API Gemcitabine Hydrochloride and other ingredients listed here after: mannitol, sodium acetate trihydrate, sodium hydroxide, hydrochloric acid, 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 PT Fonko International Pharmaceuticals, Kawasan Industri Jababeka II, Jl. Industri Selatan V, Blok PP No.7 Cikarang Selatan, Bekasi, Jawa Barat, Indonesia. 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), Reconstitution time, Water content, Osmolality, Colour value, Light transmittance, Particulate matter, 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 stored in 10 mL type I clear glass vials with neck 20 mm with grey bromo butyl rubber stopper, and 20 mm flip off blue seal when stored at or below 30^{o}C.

In additional, stability data have been provided demonstrating that the reconstituted solution remains stable for 24 hours when stored at temperature 25±2ºC.

Safety and efficacy information

No bioequivalence study was submitted to support the application. According to Part III of the compendium: Guidelines on Therapeutic Equivalence Requirements, bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently registered product. This is the case here. Both products, generic product Gemcitabine Hydrochloride and the innovator product Gemzar 200 mg powder for solution for infusion of the same active substance, Gemcitabine Hydrochloride, and the same excipients. Therefore, it is concluded that there is no difference between the Gemcitabine Hydrochloride and Gemzar 200 mg powder for solution for infusion. A bioequivalence study is not required.

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 Hydrochloride 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;