THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR IRNIZET 500 (IRINOTECAN HYDROCHLORIDE 20 MG/ML) CONCENTRATE FOR SOLUTION FOR INFUSION

Version number 01
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1. Introduction

IRNIZET 500 is a generic medicine of Campto 20mg/ml concentrate for solution for infusion of Pfizer Limited. IRNIZET 500 is an antioneoplastic medicine belonging to cytostatic topoisomerase I inhibitor (ATC Code: L01CE02) group. IRNIZET 500 exerts is activity by inhibiting DNA topoisomerase I. IRNIZET 500 is approved in Tanzania for use only in adults.

1.1 Product details

Registration number	TAN 21 HM 0414
Brand name	IRNIZET 500
Generic name, strength, and form	Each mL contains Irinotecan Hydrochloride Trihydrate 20 mg [500 mg/25 mL]
ATC classification	Cytostatic topoisomerase I inhibitor. ATC Code: L01CE02
Distribution category	POM
Country of origin	India
Associated product	IRNIZET 40, IRNIZET 300, IRNIZET 100
Marketing Authorization Holder	Aurobindo Pharma Limited Plot No.2, Maitrivihar, Ameerpet, Hyderabad, Zip Code: 500 038, Telangana State, India.
Local Technical Representative	Generic & Specialities limited, P. O. Box 1469, Dar es Salaam

1.2 Assessment procedure

The application for registration of IRNIZET 500 was submitted in 19/10/2020. The product underwent full assessment. Assessment was completed in 2 (two) rounds of evaluation and the product was registered on 09 October 2021.

1.3 Information for users

Visual description of the finished product	Clear colourless to slightly yellow solution, essentially free from visible particles
Primary packing material	Type-I tubular, amber glass vial, stoppered with Dark Grey bromo butyl rubber stopper and sealed with aluminum seal with polypropylene disc
Secondary packing materials	A printed carton box
Shelf-life and storage condition	36 months, Do not store above 30°C. Do not Freeze. Store in the original package in order to protect from light Shelf life after reconstitution Chemical and physical in-use stability has been demonstrated in glucose 50 mg/mL (5%) and in sodium chloride 9 mg/mL (0.9%) for 72 hours at

	2-8 °C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions
Route of administration	Intravenous use only (Iv administration)
Therapeutic indications	Irinotecan is indicated for the treatment of patients with advanced colorectal cancer. • In combination with 5-fluorouracil (5-FU) and folinic acid (FA) in patients not having undergone previous chemotherapy for advanced cancer. • As a single agent in patients who have not been successful with an established treatment regimen containing 5-FU. Irinotecan in combination with Cetuximab is indicated for the treatment of patients with metastatic colorectal cancer (KRAS wild-type) with expression of epidermal growth factor receptor (EGFR) who have not received prior treatment for metastatic disease or after failure of a cytotoxic therapy that included Irinotecan (see section 5.1). Irinotecan in combination with 5-FU, FA and Bevacizumab is indicated as first-line treatment for patients with colon or rectum metastatic carcinoma. Irinotecan in combination with a Capecitabine with or without Bevacizumab is indicated as first-line treatment for patients with metastatic colorectal carcinoma.

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: IRNIZET 500

Composition: Each mL contains Irinotecan Hydrochloride Trihydrate 20 mg [500 mg/25 mL]

Pack size: 25 mL

Manufacturing details: batch number, manufacturing date, and expiry date

Storage conditions: Do not store above 30°C. Do not Freeze. Store in the original package in order to protect from light

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Must diluted before use

The details of the primary pack include:

Brand name and strength: IRNIZET 500

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Aurobindo 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 Ingredients

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

Irinotecan Hydrochloride Trihydrate

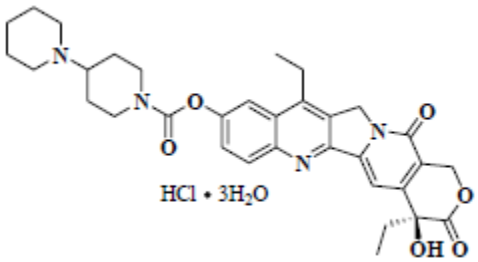
General Information
Irinotecan Hydrochloride Trihydrate API is compendia in USP, Ph.Eur., and BP.

Molecular formula: $C_{33}H_{38}N_4O_6.HCl.3H_2O$

Chemical name:

(+)-(4S)-4,11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino) carbonyloxy]-1H-pyrano [3´,4´:6,7]indolizino[1,2-b]quinoline-3,14-(4H,12H)- dione hydrochloride trihydrate

Structure:



General properties

The active substance is a pale-yellow crystalline powder, which is soluble in dimethyl sulphoxide, sparingly soluble in water, slightly soluble in ethanol and chloroform, and insoluble in acetone. The water content is 8.0 to 9.0% w/w. Two asymmetric carbons are present in the molecule.

The active substance displays polymorphism. Nonetheless, this is not considered important as the active substance is present in solution in the finished product. The active is present in the drug product dissolved in water, hence the polymorphic form and particle size distribution are not considered as critical quality aspects.

Manufacture

Irinotecan Hydrochloride Trihydrate API manufacturer is Laurus Labs Limited, Plot No. 21, Jawaharlal Nehru Pharma City, Parawada, Visakhapatnam-531021, Andhra Pradesh, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Drug Control Administration, Andhra Pradesh. Irinotecan Hydrochloride Trihydrate 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

Specifications

The API specifications were set as per Ph. Eur and In-house standards and ICHQ3A. The parameters monitored during quality control are: description, melting point, identification (IR, HPLC, Chloride, water content), assay (HPLC), appearance of solution, enantiomeric purity (HPLC), related compounds (HPLC), water determination (KF), light absorption, polymorphic identity (XRPD), sulphated ash, loss on drying, residual solvents (GC), microbial enumeration tests, bacterial endotoxins. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The shelf-life period of Irinotecan Hydrochloride Trihydrate API is 60 months when packed in the original packing material and stored in tight, light resistant containers at controlled room temperature.

Quality of the Finished Pharmaceutical Product

Formulation

IRNIZET 500 is a clear colourless to slightly yellow solution, essentially free from visible particles.

IRNIZET 500 contains Irinotecan Hydrochloride Trihydrate and other ingredients listed here after: Sorbitol, Lactic acid, Sodium hydroxide (for pH adjustment), Hydrochloric acid (for pH adjustment), Water for Injections. 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 manufacturers are Eugia Pharma Specialities Limited, Survey No. 550, 551 & 552, Kolthur Village, Shamirpet Mandal, Medchal-Malkajgiri District, Telangana, India. The compliance of the sites to TMDA GMP standards was confirmed through site inspection on 04/10/2018.

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, identification of the API (HPLC, UV), extractable volume, color absorbance, color absorbance, appearance of solution, clarity and degree of opalescence of liquid, degree of coloration of liquid, particulate contamination, related substances (HPLC), assay (HPLC), bacterial endotoxin, sterility, and pH. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on 6(six) batches of the finished product stored at 30 ± 2°C & RH: 75 ± 5% RH for 36 months and 40± 2°C & RH: 75% ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 36 months when stored in type-I tubular, Amber glass vial, stoppered with Dark Grey bromo butyl rubber stopper and sealed with aluminum seal with polypropylene disc with storage condition ‘Do not store above 30°C. Do not Freeze. Store in the original package in order to protect from light’.

Safety and efficacy information

IRNIZET 500 concentrate for solution for infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the part III: guidelines on therapeutic equivalence requirements, which states that a bioequivalence study is not required if the solutions for injection that contain the same active ingredients and excipients in the same concentrations as currently registered products and which are administered by the same route(s). The quantitative composition of IRNIZET 500 is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product

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. IRNIZET 500 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

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 labels;

Primary pack label;

Secondary pack label

Effective date: 03/10/2022