THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR CAPECITABINE 500 MG FILM COATED TABLETS

Version number 1.0
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1. Introduction

Shilpa's Capecitabine 500 mg Film Coated Tablets is a generic medicinal version of "XELODA® 500 mg tablets" by Roche. Capecitabine is a non-cytotoxic fluoropyrimidine carbamate, which functions as an orally administered precursor of the cytotoxic moiety 5-fluorouracil (5-FU). Capecitabine has been designed and developed as a pro-drug to the known cytotoxic agent 5-FU and becomes cytotoxic only after conversion to 5-FU. Capecitabine is activated via several enzymatic steps. The enzyme involved in the final conversion to 5-FU, thymidine phosphorylase (ThyPase), is found in tumour tissues, but also in normal tissues, albeit usually at lower levels. In human cancer xenograft models capecitabine demonstrated a synergistic effect in combination with docetaxel, which may be related to the upregulation of thymidine phosphorylase by docetaxel. Capecitabine 500 mg tablets is approved in Tanzania for only use in adults.

Product details

Registration number	TAN 23 HM 0238
Brand name	N/A
Generic name, strength, and form	Each film coated tablet contains: Capecitabine 500 mg
ATC classification	L01BC06-Fluoropyrimidine Carbamate, antimetabolites
Distribution category	POM
Country of origin	India
Associated product	N/A
Marketing Authorization Holder	Shilpa Medicare Limited No.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

1.1 Assessment procedure

The application for registration of Capecitabine 500 mg tablets was submitted on 03/12/2021. The product underwent full assessment. Assessment was completed in 2 (two) rounds of evaluation and the product was registered on 01/06/2023.

1.2 Information for users

Visual description of the finished product	Dark pink colored, capsule shaped, biconvex film coated tablet debossed with CAP one side and 500 on other side.
Primary packing material	PVC/PVdC-Alu blister
Secondary packing materials	Printed carton box

Shelf-life and storage condition	24 months, Do not store above 30°C, store in the original package in order to protect from moisture
Route of administration	Oral
Therapeutic indications	Capecitabine is indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer. Capecitabine is indicated for the treatment of metastatic colorectal cancer. Capecitabine is indicated for first-line treatment of advanced gastric cancer in combination with a platinum-based regimen. Capecitabine in combination with docetaxel 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. Capecitabine is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.

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: Each film coated tablet contains: Capecitabine 500 mg
Pack size: 30 tablets

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

Storage conditions: Do not store above 30°C, store in the original package in order to protect from moisture

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: contains anhydrous lactose

The details of the primary pack include:

Brand name and strength: N/A

Manufacturing details: batch number, manufacturing date and expiry date

Name 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

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

General Information

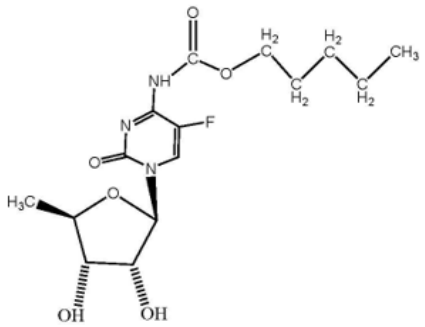
Capecitabine API is compendia in Ph.Eur., BP, USP.

Molecular formula: $C_{15}H_{22}FN_3O_6$

Chemical name:

Pentyl [1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-2-oxo-1, 2-dihydropyrimidine-4-yl] carbamate Pentyl 1-(5-deoxy- β-D-ribofuranosyl)-5-fluro-1, 2-dihydro-2-oxo-4-pyrimidinecarbamate Carbamic acid, [1-(5-deoxy- β-D-ribofuranosyl)-5-fluoro 1, 2-dihydro-2-oxo-4-pyrimidinyl]-,pentyl ester [1-(5-Deoxy- β-D-ribofuranosyl)-5-fluoro-1, 2-dihydro-2-oxo-4-pyrimidinyl]carbamic acid pentyl ester 5'-Deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine

Structure:



General properties

Capecitabine is a white to off white powder, which is freely soluble in methanol, soluble in alcohol and acetonitrile and sparingly soluble in water. No polymorphic forms are described in literature, though Capecitabine API manufactured by Shilpa Medicare Limited show single crystalline form and this was proven by data performed on three batches of the API by XRD analysis. The molecule contains four chiral centers.

The submitted solubility data across physiological proves that the molecule is highly soluble according to BCS system.

Manufacture

Capecitabine API manufacturer is Shilpa Medicare Limited, Plot Nos. 33, 33A, 40 to 47, Raichur Industrial Growth Center, Wadloor Road, Chicksugar Cross Chichsugur- 584 134, Raichur, Karnataka, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificates issued by the Drugs Control Department of Karnataka. Capecitabine 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./In- House standards and ICHQ3A. The parameters monitored during quality control are: description, solubility, identification by IR and specific optical rotation, water content, sulfated ash, heavy metals, specific optical rotation, assay (HPLC), organic impurities (HPLC), residual solvent (GC), microbial examination, and particle size distribution. Compliance to these specifications were established via batch analysis data and stability studies.

<u>Stability and container closure system</u>

The re-test period of Capecitabine API is 48 months when packed in polyethylene bag with storage condition ‘Store below 25°C’.

Quality of the Finished Pharmaceutical Product

Formulation

Capecitabine 500 mg tablets is a dark pink colored, capsule shaped biconvex film coated tablet debossed with CAP on one side and 500 on other side

Capecitabine 500 mg tablets contains the Capecitabine and other ingredients listed here after: Lactose Anhydrous, Microcrystalline cellulose (Avicel pH 101), Microcrystalline cellulose (Avicel pH 102), Croscarmellose sodium, Hydroxy propyl methyl cellulose, Magnesium stearate, Opadry Pink 03A84408 (Hypromellose/HPMC 2910, Titanium dioxide, Talc, Iron oxide red, and Iron oxide yellow), Purified Water. 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. Ingredient, Lactose is of safety concern therefore appropriate warnings were included in the product label.

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-509301, India. The compliance of the sites to TMDA GMP standards was confirmed through site inspection on DD/MM/YYYY.

Specifications

The FPP is compendia. The manufacturer controls the quality of the finished product as per USP standards and ICH requirements. The parameters monitored during quality control are: Description, Identification by IR and HPLC, average weight of tablet, uniformity of dosage units (by weight variation), dissolution, disintegration time, organic impurities, assay, water content, residual solvents, and microbial contamination. 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 Alu-PVC/PVDC blisters with storage condition ‘Do not store above 30 ^{o}C, , store in the original package in order to protect from moisture’

Safety and efficacy information

Safety and efficacy of CAPAD 500 was established through a bioequivalence trial.

BE trial report number : OS/CAPE/06-19/02 was submitted.

Study title	A multicenter , open label, balanced , randomized , two treatment,

	three period, three sequence, reference replicate crossover, single dose, oral bioequivalence study of Capecitabine film Coated 500 mg of Shilpa Medicare Limited, India and Xeloda® Film Coated Tablets 500 mg (Capecitabine) marketed by Roche Registration Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1 TW United Kingdom following single oral dose of 2000 mg (4x500mg) in adult human cancer patients under Fed conditions.
Study design	As this was a multi-center study, study was carried out at different clinical sites (Hospitals). Adult human colon, colorectal or breast cancer patients were identified as per the screened results, inclusion and exclusion criteria. The patients who met the all the inclusion and none of the exclusion criteria were enrolled into the study. √ The study medication was administered on the morning of Day 1 (Period 01), Day 2 (Period 02) and Day 3 (Period 03). The pre-dose blood sample (00.00) was drawn within one hour prior to the scheduled dosing and post-dose until 08.00 hours after dosing in each period.
Study site	(a) Clinical Facility (Name and full mailing address) Apple Hospital, Udhna Darwaja, Ring Road, Surat-395002, Gujarat, India. Artemis Hospitals Sector 51, Gurgaon – 122001 Haryana, India. Erode Cancer Center, Velavan Nagar, Perundurai Road, ThindalMedu, Hindal Erode – 638 012, Tamil, Nadu, India. City Cancer Centre, 33, 25, 33, Ch Venkata, Krishnayya Street, Suryaraopet, Vijayawada – 520002, Andhra Pradesh, India Mahatma Gandhi Cancer Hospital & Rese arch Institute, M. V. P. Colony, Visakhapatnam- 530017, Andhra Pradesh, India. PDEA's AyurvedRugnalaya& Sterling Multi Specialty Hospital, Sector No. 27, Near Bhel Chowk, NigdiPradhikaran, Pimpri-Chinchwad, Pune - 411044, Maharashtra, India. Sapthagiri Institute of Medical Sciences and Research Centre, #15, Chikkasandra, Hesaraghatta

	Main Road, Bengaluru - 560090, Karnataka, India. Curie Manavata Cancer Centre, Opp. Mahamarg Bus Stand, Mumbai Naka, Nashik - 422004, Maharashtra, India. Unique Hospital – Multispecialty and Research Institute, Opp. Kiran Motor, Near Canal, Civil Hospital Char Rasta, Sosyo Circle Lane, Off Ring Road, Surat- 395002, Gujarat, India. Care Hospital, 3 Farmland, Panchsheel Square Ramdaspeth, Wardha Road, Nagpur – 420012, Maharashtra, India SNR Galaxy Hospitals, LR Nagar, Ring Road, Hyderabad – 500074, Telangana, INDIA. Manas Hospital (Sankalp Speciality Healthcare Pvt Ltd), Manas Hospital, Opposite Tupsakhre Lawns, Mumbai Naka, Matoshree Nagar, Nashik, Maharashtra 422002, INDIA. KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Nehrunagar, Belgaum-590010, Karnataka, India (b) <u>Clinical Laboratories (Name and full mailing address)</u> (c) <u>Analytical Laboratories (Name and full mailing address)</u> QPS Bioserve India Pvt. Limited # 6-56/6/1A, Opp. IDPL Factory, Balanagar, Hyderabad – 500 037, Telangana, India. Ph: +(91) 40-4377 0873 / 1875 Fax: +(91) 40-4377 0877 (d) <u>Company performing pharmacokinetic/statistical analysis (Name and full mailing address)</u> QPS Bioserve India Pvt. Limited # 6-56/6/1A, Opp. IDPL Factory, Balanagar, Hyderabad – 500 037, Telangana, India.
Study dates	Study Phases / Start Date / End Date Clinical Phase / 07/02/2017 (FPFV) / 07/06/2017 (LPLV) Bioanalytical Phase / 28/06/2017 / 09/08/2017 Statistical Phase / 28/08/2017 / 30/08/2017

Primary objective	To assess the bioequivalence of Capecitabine Film Coated Tablets 500 mg of Shilpa Medicare Limited, India with Xeloda® (Capecitabine) Tablets 500mg marketed by Roche Registration Limited 6 Falcon Way, Shire Park, Welwyn Garden City,AL7 1TW, United Kingdom, following a single oral 2000mg (4x500mg) dose administration in adult human cancer patients under fed conditions.	
Secondary objective	To monitor the safety and tolerability of a single dose of Capecitabine tablets when administered	
Number of participants	Planned- Enrolled- Dosed- Withdrawn - Bio-sample analyzed - Pharmacokinetic and statistical data analyzed –	
Monitored parameters	Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2	
Investigational medicinal products	Test Product	Reference product
	Strength: 500 mg Batch number: SMTA16007 Expiry date: 11/2018	Strength: 500 mg Batch number: X4030B03 Expiry date: 03/2018
Analytical method	High Pressure Liquid chromatography – MS/MS – detector (LC-MS/MS) method was used for the determination of plasma concentrations of analyte	
Statistical method	SAS® Studio 3.6 (Basic Edition), (SAS® Institute Inc. USA)	

Efficacy results are summarized as follows:

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-t (units)	7569.182	7525.279	101.99	97.34 – 106.87	178	16.4
AUC0-inf (units)	7630.395	7525.279	101.40	97.04 – 105.95	172	15.3
Cmax (units)	6306.726	6277.957	100.46	88.87 – 113.56	178	48.1

The acceptance limits of 80 – 125% are met by the AUC and Cmax values. Furthermore, the safety profile of the test product is similar to that of reference product. Therefore, Capecitabine 500 mg Tablet (each tablets contains 500 mg of Capecitabine) of Shilpa Medicare Limited, India is equivalent and interchangeable with Xeloda® Film Coated Tablets 500 mg (Capecitabine) marketed by Roche Registration Limited, United Kingdom under acceptable in vivo experimental conditions.

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. Capecitabine 500 mg Tablets 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