THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR CAPAD (CAPECITABINE 500 MG) FILM COATED TABLETS

Version number 1.0
24 August, 2023

TMDA Headquarters, Plot No. 56/1, Block E, Kisasa B Centre, Hombolo 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

CAPAD 500 tablets is a generic medicinal product containing the active substance Capecitabine.The originator product is “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. CAPAD 500 tablets is approved in Tanzania for only use in adults.

Product details

Registration number	TAN 23 HM 0239
Brand name	CAPAD 500
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	Beta Drugs Ltd Kharuni-Lodhimajra Road, Vill: Nandpur, Teh: Baddi,Distt:Solan, Himachal Pradesh, India
Local Technical Representative	Dawa Medicare Ltd P.O Box 16215 Dar Es Salaam

1.1 Assessment procedure

The application for registration of CAPAD 500 was submitted on 31/10/2019. The product underwent full assessment. Assessment was completed in 5 (five) rounds of evaluation and the product was registered on 01/06/2023.

1.2 Information for users

Visual description of the finished product	Peach colour, elongated biconvex film coated tablets plain from both sides
Primary packing material	Clear Transparent PVC Foil (0.30 x 115 mm) Printed Aluminium Base (0.025 x 110 mm)
Secondary packing materials	Printed carton box
Shelf-life and storage condition	24 months,

	Do not store above 30°C. 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: CAPAD 500

Composition: Each film coated tablet contains: Capecitabine 500 mg

Pack size: 1x10 tablets

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

Storage conditions: Do not above 30°C. Protect from moisture

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Not applicable

The details of the primary pack include:

Brand name and strength: CAPAD 500

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Beta Drugs Ltd

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 CEP.

General Information

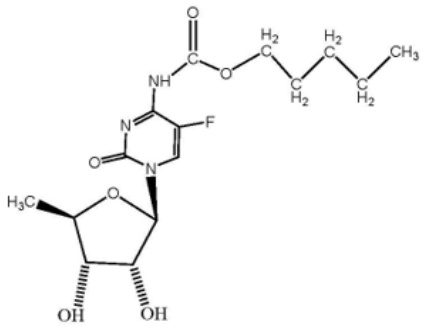
Capecitabine API is compendia in Ph.Eur., BP, USP.

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

Chemical name:

Pentyl N-[1-[(2R,3R,4S,5R)-3,4-dihydroxy-5-methyloxalan-2-yl]-5-fluoro-2-oxopyrimidin-4yl] carbamate

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, and also XRD and DSC diffractograms of the material show absence of polymorphism. 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 Kekule Life Science Ltd, Plot No. 406 A, H. No. 622, road no. 18, Jubilee Hills, Hyderabad-500033, Telangana, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificates issued by the Drugs Control Administration, Government of Telangana. 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 USP standards and ICHQ3A. The parameters monitored during quality control are: description, solubility, identification by IR and HPLC, water content, residue on ignition, heavy metals, specific optical rotation, assay (HPLC), organic impurities (HPLC), and residual solvent (GC). 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 60 months when packed in polyethylene bag with storage condition ‘Store below 25°C’.

Quality of the Finished Pharmaceutical Product

Formulation

CAPAD 500 is a peach colour, elongated biconvex film coated tablets plain from both sides.

CAPAD 500 contains the Capecitabine and other ingredients listed here after: maize starch, microcrystalline cellulose, povidone (polyvinyl pyrrolidone K30), crospovidone, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, isopropyl alcohol, wincoat white, red oxide of iron, instaglow (IG-001), isopropyl alcohol, methylene chloride. 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 Beta Drugs Ltd, Kharuni-Lodhimajra Road, Vill: Nandpur, The: Baddi, Distt: Solan, Himachal Pradesh, India. The compliance of the sites to TMDA GMP standards was confirmed through site inspection on 14-15/12/2018.

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 TLC, average weight of tablet, weight of 20 tablets, uniformity of dosage units (by weight variation), dissolution, 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 36 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 blister with storage condition ‘Do not store above 30 ^{o}C. 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	Bioequivalence Study Comparing Capecitabine Tablets USP 500 mg containing Capecitabine 500 mg manufactured by Beta Drugs Limited, India with Xeloda (Capecitabine) Tablets containing Capecitabine 500 mg manufactured by F. Hoffmann-La Roche Ltd., Basel, Switzerland at Shanghai Roche Pharmaceuticals Ltd., China.

<table>
<tr><td></td><td>An open label, randomized, two-treatment, two-period, two-sequence, single dose, crossover, comparative bioequivalence study in breast cancer or colorectal cancer patients under fed condition</td></tr>
<tr><td>Study design</td><td>An open label, randomized, two-treatment, two-period, two-sequence, single dose, crossover, comparative bioequivalence study in breast cancer or colorectal cancer patients under fed condition</td></tr>
<tr><td>Study site</td><td>Om Sai Clinical Research Pvt. Ltd.,
C.S.T. No.379/1-6, Karnal Chowki, Peth Bhag,
Sangli - 416 416, Maharashtra, India.</td></tr>
<tr><td>Study dates</td><td>
<table>
<tr><th>Activities</th><th>Dates</th></tr>
<tr><td>Clinical Phase: Group I</td><td></td></tr>
<tr><td>Period I</td><td>December 20, 2012- December 25, 2012</td></tr>
<tr><td>Period II</td><td>December 31, 2012- January 5, 2013</td></tr>
<tr><td>Period III</td><td>January 11, 2013- January 16, 2013</td></tr>
<tr><td>Period IV</td><td>January 22, 2013- January 27, 2013</td></tr>
<tr><td>Clinical Phase: Group II</td><td></td></tr>
<tr><td>Period I</td><td>December 23, 2012- December 28, 2012</td></tr>
<tr><td>Period II</td><td>January 3, 2013- January 8, 2013</td></tr>
<tr><td>Period III</td><td>January 14, 2013- January 19, 2013</td></tr>
<tr><td>Period IV</td><td>January 25, 2013- January 30, 2013</td></tr>
<tr><td>Bio-analytical Phase</td><td>February 22, 2013</td></tr>
<tr><td>Statistical Phase</td><td>March 12, 2013</td></tr>
</table>
</td></tr>
<tr><td>Primary objective</td><td>To investigate the bioequivalence of test product relative to reference product after a single oral dose administration of Capecitabine to healthy adults under fasting conditions</td></tr>
<tr><td>Secondary objective</td><td>To monitor the safety and tolerability of a single dose of Capecitabine tablets when administered</td></tr>
<tr><td>Number of participants</td><td>Planned-42 subjects
Enrolled-42 subjects
Dosed-42 subjects
Withdrawn - 06 subject
Bio-sample analyzed -42 subjects
Pharmacokinetic and statistical data analyzed – 36 subjects</td></tr>
<tr><td>Monitored parameters</td><td>Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2</td></tr>
<tr><td>Investigational medicinal products</td><td>
<table>
<tr><td>Test Product</td><td>Reference product</td></tr>
<tr><td>Strength: 500 mg
Batch number: BCTTK834Z
Expiry date:</td><td>Strength: 500 mg
Batch number: Y0423B01
Expiry date: 05/2022</td></tr>
</table>
</td></tr>
<tr><td>Analytical method</td><td>High Pressure Liquid chromatography – MS/MS – detector (LC-MS/MS) method was used for the determination of plasma concentrations of analyte</td></tr>
<tr><td>Statistical method</td><td>SAS® Version 9.2 (SAS Institute Inc., USA) procedure</td></tr>
</table>

Efficacy results are summarized as follows:

Parameter	Test	Reference	% Ratio of Geometric Means	90 % Confidence Interval	DF	CV (%)
AUCT (µg x hr/mL)	17.555	18.948	92.644	82.464 – 104.081	0.275	29.841
AUCI (µg x hr/mL)	18.683	20.099	92.956	83.315 – 103.714	0.267	28.002
Cmax (µg/mL)	4.346	4.747	91.545	81.743 – 102.522	0.196	28.999

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 Beta Drugs Limited, India is equivalent and interchangeable with Xeloda ® 500 mg Tablets (each tablet contains 500 mg of Capecitabine) of F. Hoffmann-La Roche Ltd 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. CAPAD 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: