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MINISTRYOFHEALTH

TANZANIAMEDICINES ANDMEDICALDEVICESAUTHORITY

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

Version number 01

3rd January, 2022

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1. Introduction

Capxcel is a generic medicine of Xeloda. Capxcel is a non-cytotoxic fluoropyrimidine carbamate medicine belonging to L01BC06 cytostatic (antimetabolite) group. Capxcel is a precursor of the cytotoxic moiety 5-fluorouracil (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 docetaxe. Capxcel is approved in Tanzania for use in adults.

1.1 Product details

Registration number	TAN 21 HM 0225
Brand name	Capxcel
Generic name, strength and form	Capecitabine 500 mg film coated tablets
ATC classification	L01BC06 cytostatic (antimetabolite)
Distribution category	POM
Country of origin	India
Associated product	State any other product of formulation, strength or site that is linked or associated with the product if applicable
Marketing Authorization Holder	Khandelwal Laboratories Pvt., Ltd 79/87, D.Lad Path, Mumbai - 400033, India **e-mail:**export@khhandelwallab.com
Local Technical Representative	Salama Pharmaceuticals Ltd. Plot No. 4, block 28, Aggrey/Nyamwezi Street, Kariakoo, Dar es Salaam, Tanzania

1.2 Assessment procedure

The application for registration of Capxcel was submitted on 11th April, 2019. The product underwent full assessment. Assessment was completed in <number> rounds of evaluation. Capxcel was registered on 3rd June, 2021

1.3 Information for users

Visual description of the finished	Biconvex circular buff coloured film coated

product	tablets
Primary packing material	Alu-Alu blister pack
Secondary packing materials	Carton box
Shelf-life and storage condition	24 months Store at a temperature not exceeding 30°C
Route of administration	Oral
Therapeutic indications	for the treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy is not indicated, e.g., patients who have received. Cumulative doses of 400 mg/m2 of doxorubicin or doxorubicin equivalents. Resistance is defined as progressive disease while on treatment, with or without an initial response, or relapse within 6 months of completing treatment with an anthracycline-containing adjuvant regimen

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 that is intended for long term use, 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: Capxcel

Composition: Capecitabine 500 mg, Ethyl Cellulose, Isopropyl Alcohol, Methylene Chloride, Lactose Anhydrous, Croscarmellose Sodium, Sodium Lauryl sulphate, Lactose Anhydrous, Colloidal Silicon Dioxide, Purified Talc, Magnesium Stearate, Instacoat brown, Isopropyl Alcohol and Methylene chloride.

Pack size: 1 x 10s
Manufacturing details: <batch number, manufacturing date, expiry date>
Storage conditions: Store at a temperature not exceeding 30°C
Manufacturer address: M/s. Khandelwal Laboaratories Pvt. Ltd, Plot B-1, Wagle Industrial Estate, Thane – 400604, Maharashtra, India.
Unique identifier: NA
Special warnings/precautions or instructions for use: <include warnings or IFU if applicable>

The details of the primary pack include:
Brand name and strength: Capxcel
Manufacturing details: <batch number, manufacturing date, expiry date>
Name of manufacturer: M/s. Khandelwal Laboaratories Pvt. 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.
Describe any approved deviation to the requirements and the justification for the deviation.

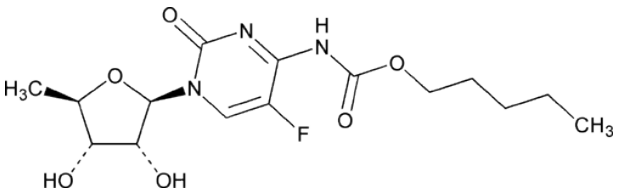
Mock labels are appended as annex I

3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

Information on quality of the API was submitted in form of Full details.

General properties
Capecitabine API is compendia in USP.
Molecular formula: $C_{15}H_{22}FN_3O_6$
Chemical name: Pentyl 1 -(5-deoxy- β-D-ribofuranosyl)-5 -fluoro-1,2- dihydro-2-oxo-4-pyrimidinecarbamate
Structure:



Capecitabine is a white to off-white crystalline powder that is freely soluble in methanol, soluble in acetonitrile and in alcohol, sparingly soluble in water. Capecitabine is not hygroscopic. Capecitabine exhibits stereoisomerism due to the presence of three chiral centers. Stereo chemical purity is controlled routinely and also in stability studies by specific optical rotation. Stability data indicates that the stereochemistry is not changed during manufacture or storage of the active substance. Manufacturing procedure employed consistently affords a single crystalline form of capecitabine as confirmed by X-ray crystallographic pattern of 3 batches of capecitabine.

Manufacture

The API manufacturing site, Mac Chem Products (India) Pvt. Ltd, N-211/10, MIDC, Boisar, District – Thane, Pin code – 401 506, Maharashtra, India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by the Office of the Commissioner, Food and Drug Control Administration M.S, Bandra – Kurla Complex, Bandra (E), Mumbai. 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, Water, Specific Optical rotation, Residual on ignition, Heavy metals, Related substances (Organic impurities) and Assay. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Capecitabine API is 60 months when packed in LDPE bag and tied with plastic fastener in aluminium bag placed in HDPE drum and stored at storage 25ºC.

Quality of the Finished Pharmaceutical Product

Formulation

Capxcel is a Description of the finished product packed in Alu-Alu blisters. Capxcel contains Capecitabine and other ingredients listed here after Ethyl Cellulose, Isopropyl Alcohol, Methylene Chloride, Lactose Anhydrous, Croscarmellose Sodium, Sodium Lauryl sulphate, Lactose Anhydrous, Colloidal Silicon Dioxide, Purified Talc, Magnesium Stearate, Instacoat brown, Isopropyl Alcohol and Methylene chloride. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 8^{th} 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 was manufactured at M/s. Khandelwal Laboratories Pvt. Ltd., Plot B-1, Wagle Industrial Estate, Thane- 400 604, Maharashtra, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on <date of GMP compliance>.

Specifications

The FPP is USP. The manufacturer controls the quality of the finished product as per USP and ICHQ3B requirements. The parameters monitored during quality control are Description, Identification, Uniformity of weight, Average Weight, Weight Variation, Uniformity of Dosage Units (By weight variation method), Dissolution, Diameter, Thickness, Organic Impurities, Related Compound, Assay (HPLC), Residual Solvent, Isopropyl alcohol and Methylene Chloride. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on three batches of the finished product stored at 30ºC + 2˚C/65% + 5 %RH for 24 months and 40ºC + 2ºC/75%+5 RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in Alu-Alu blisters at a temperature not above 30°C.

Safety and efficacy information

Safety and efficacy of Capxcel was established through bioequivalence trial. BE trial report number EL/CPA/032/2013 Version No.: 01 was submitted.

In case of BE:

Study title	Bioequivalence study of single dose of Capecitabine tablets USP 500 mg manufactured by Khandelwal Laboratories Pvt. Ltd. In comparison with Xeloda tablets containing Capecitabine USP 500 mg distributed by Genentech USA, Inc., USA in 72 locally Advanced or Metastatic Colorectar Cancer, adult, male subjects under fed condition
Study design	An open label, balanced, randomized, single dose, two treatment, two-period, two-sequence, crossover oral bioequivalence study with at least 07 days washout period between each administration under fed conditions
Study site	Clinical study site • Tata Memorial Hospital,

<table>
<tr><td></td><td>Dr. E Borges Road, Parel,
Mumbai – 400012, India.

• Sir Ganga Ram Hospital
Rajinder Nagar
New Delhi 110060, India.

• PushpanjaliCrosslay Hospital,
A-14, Pushpanjali, Vikas Marg Extn. Delhi
New Delhi

• KokilabenDhirubhai Ambani Hospital,
Rao Saheb Achhutrao
Patwardhan Marg, Four
Bunglows, Andheri (W)
Mumbai – 400053

• Max Super Speciality Hospital,
Press Enclave Road,
Saket, New Delhi 110017

Bioanalytical study site

Energetic Laboratories Pvt. Ltd.
FSM-22/1A/24-C, Rahat Nagar, Near Pathan Masjid, Sewree Cross Road, Wadala (W), Mumbai – 400031, India.</td></tr>
<tr><td>Study dates</td><td><table><tr><th>Activities</th><th>Dates</th></tr><tr><td>Period I (dosing)</td><td>27/08/2013 to 29/08/2013</td></tr><tr><td>Period II (dosing)</td><td>05/09/2013 to 07/09/2013</td></tr><tr><td>Analysis (start date)</td><td>13/09/2013</td></tr><tr><td>Analysis (completion date)</td><td>22/09/2013</td></tr></table></td></tr>
<tr><td>Primary objective</td><td>To compare the bioequivalence and characterize the pharmacokinetic profile of the sponsor’s Capecitabine tablets 500 mg manufactured by Khandelwal Laboratories Pvt. Ltd. In comparison with Xeloda tablets containing Capecitabine 500 mg distributed by Genentech USA, Inc., USA in 72 locally Advanced or Metastatic Colorectar Cancerin healthy, adult, human male subjects under fed conditions and to assess the bioequivalence</td></tr>
<tr><td>Secondary objective</td><td>To monitor the safety of the subjects</td></tr>
<tr><td>Number of participants</td><td>72 subjects</td></tr>
<tr><td>Monitored parameters</td><td>AUC, Cmax, Tmax</td></tr>
<tr><td>Investigational medicinal</td><td>Test Product</td><td>Reference product</td></tr>
</table>

products	Strength: 500 mg Batch number: TCPB20807 Expiry date: 07/2014	Strength: 500 mg Batch number: X0135A07 Expiry date: 10/2014
Analytical method	LC-MS/MS	
Statistical method	SAS® software Version 9.2	

Efficacy results are summarized as follows:

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-t (units)						
AUC0-inf (units)						
Cmax (ng/mL)						

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, Capxcel is equivalent and interchangeable with Xeloda tablets containing Capecitabine 500 mg distributed by Genentech USA, Inc., USA under acceptable in vivo experimental conditions.

4. Benefit-Risk Assessment and Conclusion

On basis ofthe 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. Capxcel 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

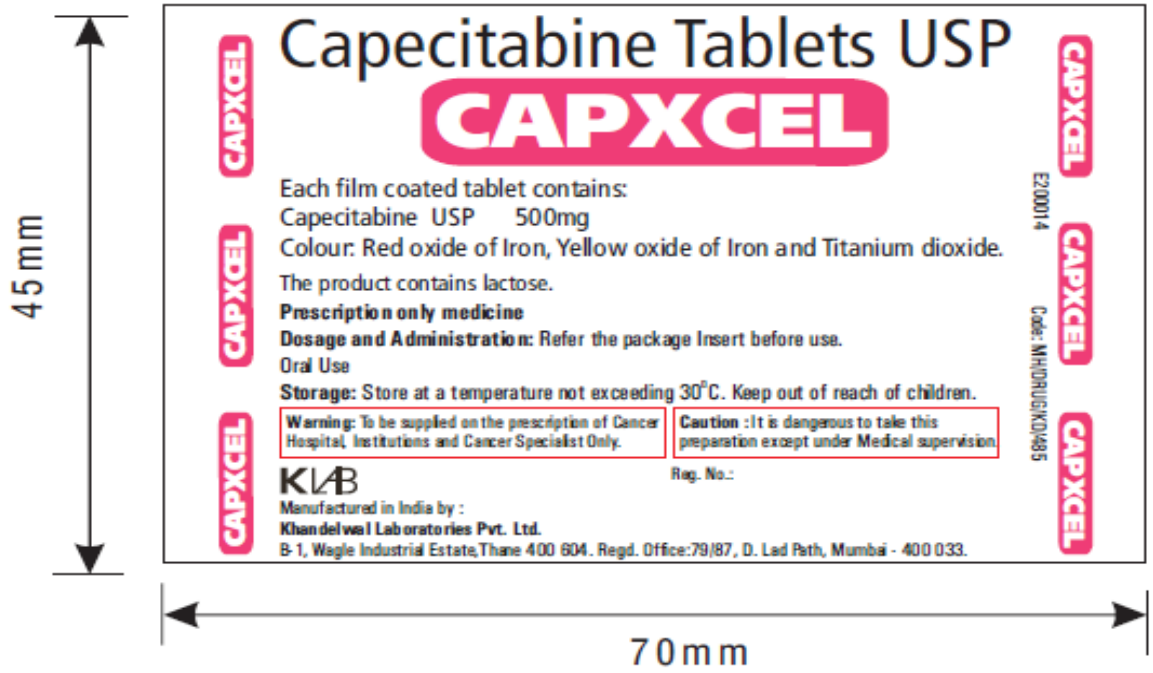
Re-registration applications

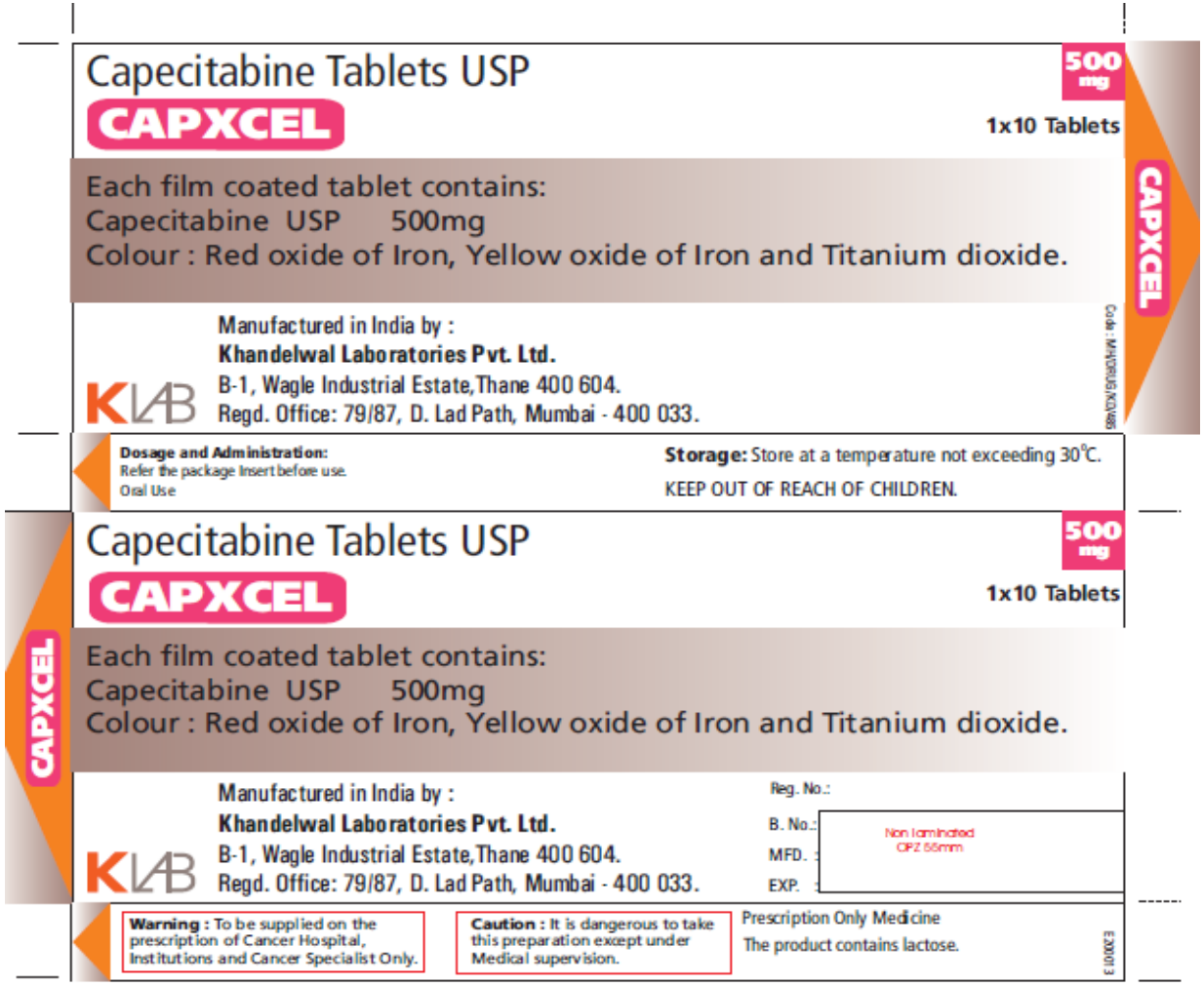
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

Version number	Date	Description of update	Section(s) Modified	Approval date

Annex I: Mock up label




Capecitabine Tablets USP
CAPXCEL
500 mg
1x10 Tablets
Each film coated tablet contains:
Capecitabine USP 500mg
Colour : Red oxide of Iron, Yellow oxide of Iron and Titanium dioxide.
Manufactured in India by :
Khandelwal Laboratories Pvt. Ltd.
B-1, Wagle Industrial Estate,Thane 400 604.
Regd. Office: 79/87, D. Lad Path, Mumbai - 400 033.
KLAB
Dosage and Administration:
Refer the package Insert before use.
Oral Use
Storage: Store at a temperature not exceeding 30°C.
KEEP OUT OF REACH OF CHILDREN.
Capecitabine Tablets USP
CAPXCEL
500 mg
1x10 Tablets
Each film coated tablet contains:
Capecitabine USP 500mg
Colour : Red oxide of Iron, Yellow oxide of Iron and Titanium dioxide.
Manufactured in India by :
Khandelwal Laboratories Pvt. Ltd.
B-1, Wagle Industrial Estate,Thane 400 604.
Regd. Office: 79/87, D. Lad Path, Mumbai - 400 033.
KLAB
Reg. No.:
B. No.:
MFD. :
EXP. :
Non Laminated
CPZ 55mm
Warning : To be supplied on the prescription of Cancer Hospital, Institutions and Cancer Specialist Only.
Caution : It is dangerous to take this preparation except under Medical supervision.
Prescription Only Medicine
The product contains lactose.