THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR ADREA (HYDROXYUREA 500MG) HARD GELATIN CAPSULES

Version number 1.0
21 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

ADREA capsules is a generic medicinal product containing the active substance Hydroxyurea. The reference product is “HYDREA 500 mg (Hydroxyurea) Capsules by Bristol-Myers Squibb. Hydroxyurea is an orally active antineoplastic agent. Although the mechanism of action has not yet been clearly defined, Hydroxyurea appears to act by interfering with synthesis of DNA. ADREA capsules is approved in Tanzania for use only in adults.

Product details

Registration number	TAN 23 HM 0277
Brand name	ADREA
Generic name, strength, and form	Each hard gelatin capsule contains: Hydroxyurea 500 mg
ATC classification	L01XX05 Other antineoplastic agents
Distribution category	POM
Country of origin	India
Associated product	N/A
Marketing Authorization Holder	Beta Drugs Ltd. Works: Kharuni-Lodhimajra Road, Vill: Nandpur, Teh: Baddi, Distt: Solan, Himachal Pradesh, India
Local Technical Representative	M/s Generics & Specialities Limited P.O.Box 1469, Dar es Salaam

1.1 Assessment procedure

The application for registration of ADREA was submitted on DD/MM/YYYY. The product underwent full assessment. Assessment was completed in 4 (four) rounds of evaluation and the product was registered on 01/06/2023.

1.2 Information for users

Visual description of the finished product	Grey/Pink “Size 0” coloured hard gelatin capsules containing white to off white powder
Primary packing material	PVC-Aluminium blister pack
Secondary packing materials	Printed carton box
Shelf-life and storage condition	24 months, Do not store above 30 °C. Protect from light and moisture
Route of administration	Oral
Therapeutic indications	The treatment of chronic myeloid leukemia; -as pre-TKI treatment phase before confirmation of BCR-ABL fusion with an immediate need for therapy due to high

	leukocyte and thrombocyte counts. -as palliative care in patients in blastic phase with leucocytosis and thrombocytosis The treatment of cancer of the cervix in conjuction with radiotherapy

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: ADREA

Composition: Each hard gelatin capsule contains: Hydroxyurea 500 mg

Pack size: 2x5 tablets

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

Storage conditions: Do not store above 30 ^{o}C. Protect from light and moisture

Manufacturer address: Physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: It contain lactose
The details of the primary pack include:

Brand name and strength: ADREA

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 Ingredient

General Information

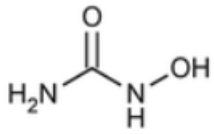
Hydroxyurea API is compendia in Ph.Eur., BP, USP.

Molecular formula: $CH_4N_2O_2$

Chemical name:

N-Carbamoylhydroxylamine

Structure:



General properties

Hydroxyurea is a white or off-white powder, somewhat Hygroscopic, decomposes in the presence of moisture, melts at temperature exceeding 133°C with decomposition It dissolves in dilute solutions of mineral acids and alkali hydroxides. No polymorphism has been confirmed. Nevertheless, as Hydroxyurea is classified as a BCS class I molecule, which is a high soluble API according to BCS, therefore neither particle size and distribution nor polymorphism are considered to be critical.

Manufacture

Hydroxyurea API manufacturer is Khandelwal Laboratories Pvt. Ltd, B-1, Wagle Industrial Estate Thane -400604, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Food & Drug Administration Thane. Hydroxyurea 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 standards and ICHQ3A. The parameters monitored during quality control are: Description, solubility, identification by IR and TLC, urea

and related compounds, other related substances, heavy metals, chlorides, sulphated ash, residue on ignition, loss on drying, water, assay, residue solvent. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Hydroxyurea API is 60 months when packed in LDPE bag with storage condition 'Do not store above 30°C, store in an airtight container, protected from light'.

Quality of the Finished Pharmaceutical Product

Formulation

ADREA is a grey/pink "Size 0" coloured hard gelatin capsules containing white to off white powder.

ADREA contains the Hydroxyurea other ingredients listed here after: lactose anhydrous, crospovidone, magnesium stearate, sodium lauryl sulphate, hard gelatin capsule of size '0' having grey/pink color (gelatin, brilliant blue, carmoisine, erythrosine, tartrazine, titanium dioxide). 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 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 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, average fill content, average weight of capsule, uniformity of dosage unit by uniformity of weight), dissolution, assay, related substances, and microbiological limit. 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 PVC - Aluminum foil blister pack with storage condition 'Do not store above 30°C, protect from light and moisture'.

Safety and efficacy information

Safety and efficacy of ADREA was established through bioequivalence trial.

BE trial report number OS/HYDR/05-19/18 was submitted.
In case of BE:

<table>
<tr><td>Study title</td><td>A Randomized, Single dose, Open Label, Bioequivalence Study Comparing Hydroxyurea Capsules USP 500 mg containing Hydroxyurea 500 mg of Beta Drugs Limited, India with HYDREA 500 mg (Hydroxyurea) Capsules containing Hydroxyurea 500 mg of Bristol-Myers Squibb Australia Pty Ltd., Australia in Normal Healthy Human Subjects under Fasting Condition</td></tr>
<tr><td>Study design</td><td>An open label, randomized, two-period, two-treatment, two-sequence single dose crossover bioequivalence study on 36 healthy adult human subjects with wash out period of 5 days between two periods under fasting condition</td></tr>
<tr><td>Study site</td><td>OM SAI CLINICAL RESEARCH PVT. LTD.
C.S.T. No.379/1-6, Kamal 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>Period I (dosing)</td><td>Group I (Subject No. 01- 18) : 03rd July, 2019
Group II (Subject No. 19 - 36): 06th July, 2019</td></tr>
<tr><td>Period II (dosing)</td><td>Group I (Subject No. 01- 18): 08th July, 2019 Group II (Subject No. 19 - 36): 11th July, 2019</td></tr>
<tr><td>Validation and Analysis</td><td>14/07/2019 to 19/07/2019</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 Hydroxyurea 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 Hydroxyurea capsules when administered in 36 healthy adult human subjects under fasting condition</td></tr>
<tr><td>Number of participants</td><td>Planned-36 subjects
Enrolled-36 subjects
Dosed-36 subjects
Withdrawn - 00 subject
Bio-sample analyzed -36 subjects</td></tr>
</table>

	Pharmacokinetic and statistical data analyzed – 36 subjects	
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: BHUCI824Z Expiry date: 08/2020	Strength: 500 mg Batch number: 9M03768 Expiry date: 04/2021
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® PROC MIXED (SAS Institute Inc., USA) procedure	

Efficacy results are summarized as follows:

Hydroxyurea

Average of PK parameters of two periods of Test and Reference Formulation

Pharmacokinetic Parameters	Test Product (B) N=36	Reference Product (A) N=36
C_{max} (µg/mL)	13.70	12.94
AUC_{0-t} (µg × hr/mL)	55.606	52.152
AUC_{0-inf} (µg × hr/mL)	57.498	53.669

90 % Confidence Interval from Log Transformed Data

Pharmacokinetic Parameters	Acceptance Criteria	Confidence Interval
LnC_{max}	80-125%	100.397 – 111.658
$LnAUC_{0-t}$	80-125%	95.527 – 120.892
$LnAUC_{0-inf}$	80-125%	96.333 – 120.980

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, Hydroxyurea Capsules USP 500 mg containing Hydroxyurea 500 mg of Beta Drugs Limited, India is equivalent and interchangeable with HYDREA 500 mg (Hydroxyurea) Capsules containing Hydroxyurea 500 mg of Bristol-Myers Squibb Australia Pty Ltd., Australia 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. ADREA 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

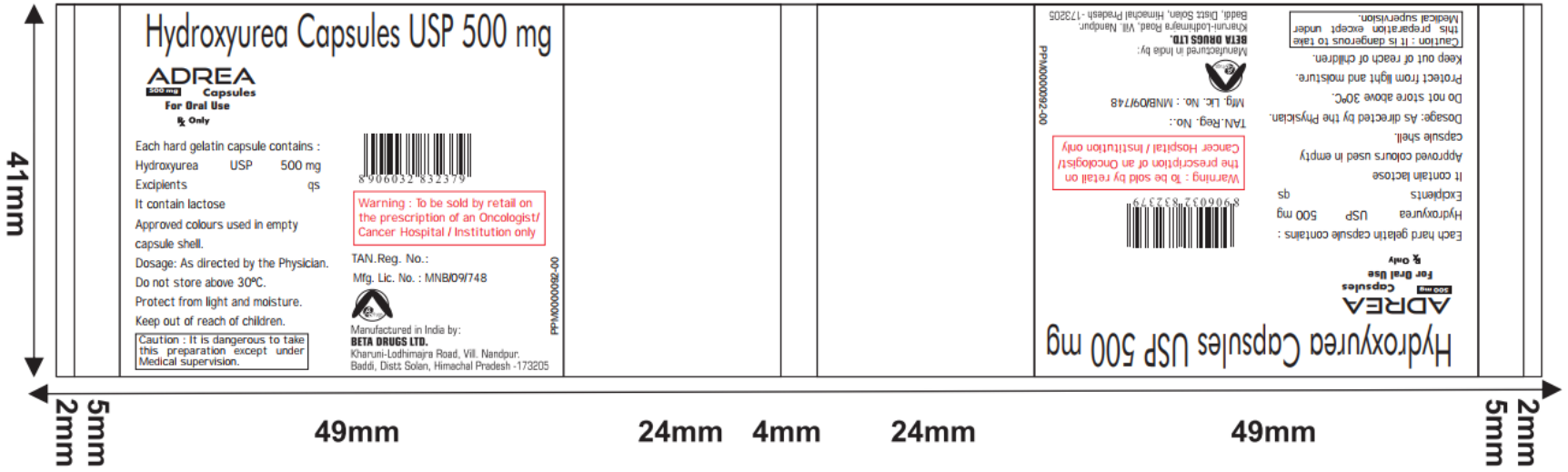
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

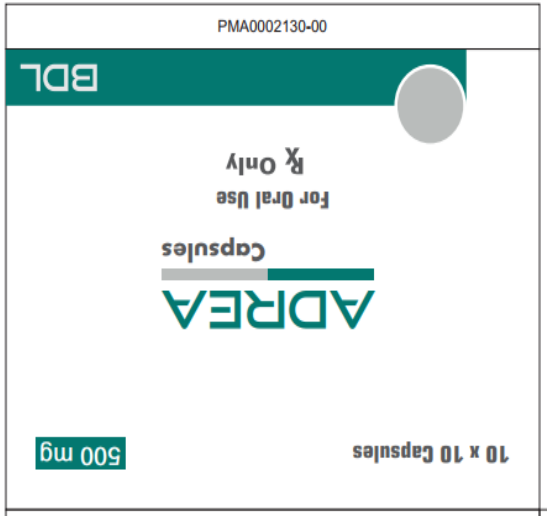
Version number	Date	Description of update	Section(s) Modified	Approval date

Annex I: Mock up labels;

Primary pack label;



Secondary pack label:



ARTWORK FORMAT

BETA DRUGS LTD.

Registered Office: Office No- 1101, 11th floor , Peninsula Park off. Andheri Link Road, Extension of Fun Republic LaneAndheri West, Mumbai-400053 ,email: sales@adleylab.com

Generic Name:	Hydroxyurea Capsules USP	Brand Name: Adrea-500	
Artwork No.	APMA0002130-00	Specification of Carton :	
Market	Export	350 GSM ITC SAPPHIRE GLOSS LAMINATION	
Customer	Beta Drugs Ltd.		
Material code	PMA0002130-00		
CC No.	CC/19/05/RA/008		
Superceded Material Code No.	N/A	Dimension	90 x 65 x 80 mm
		Colour Job	5 Color

Prepared by: Pack.Dev.Department	Checked by: RA Department	Checked by: P.D. Department	Checked by: QC Department	Approved by: QA Department

10 x 10 Capsules POM 500 mg

Hydroxyurea
Capsules USP 500 mg

ADREA
Capsules

For Oral Use

℞ Only

BDL

Each hard gelatin capsule contains :
Hydroxyurea USP 500 mg
Excipients qs
It contain lactose
Approved colours used in empty capsule shell.
Dosage: As directed by the Physician.
Do not store above 30ºC.
Protect from light and moisture.
Keep out of reach of children.

Caution : It is dangerous to take this preparation except under Medical supervision.

Warning : To be sold by retail on the prescription of an Oncologist/ Cancer Hospital / Institution only

10 x 10 Capsules POM 500 mg

Hydroxyurea
Capsules USP 500 mg

ADREA
Capsules

For Oral Use

℞ Only

BDL

Mfg. Lic. No. : MNB/09/748
TAN.Reg. No.:
Batch No. :
Mfg. Date :
Exp. Date :

8 906032 832379

Manufactured in India by:
BETA DRUGS LTD.
Kharuni-Lodhimajra Road, Vill. Nandpur.
Baddi, Distt Solan, Himachal Pradesh-173205

Effective date: 03/10/2022