THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

# PUBLIC ASSESSMENT REPORT FOR DAPAGLIFLOZIN (10 MG DAPAGLIFLOZIN (AS PROPANEDIOL)) FILM-COATED TABLETS

**Version number 1.0**
**21 August, 2023**

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## 1. Introduction

Dapagliflozin tablets is a pink, biconvex, diamond-shaped, film-coated tablets with “C389” engraved on one side and plain on the other side containing the 10 mg Dapagliflozin (as Propanediol) per tablet. The reference product is Forxiga 10 mg film-coated tablets of AstraZeneca. The drug substance dapagliflozin competitively, reversibly, and highly selectively inhibits Sodium- glucose co-transporter 2 (SGLT2). SGLT2s are expressed in the kidney and on the epithelial lining of the Si segment of the proximal convoluted tubule. Physiologically, these transporters are responsible for approximately 90% of renal glucose absorption. By blocking SGLT2 with Dapagliflozin, reabsorption of glucose into the bloodstream is diminished. Dapagliflozin promotes glucose filtration through the kidneys and into the urine to be eliminated from the body. Dapagliflozin tablets is approved in Tanzania for use in adults and children aged 10 years and above.

**Product details**

| | |
|---|---|
| Registration number | TAN 23 HM 0298 |
| Brand name | N/A |
| Generic name, strength, and form | Each film-coated tablet contains: dapagliflozin propanediol equivalent to 10 mg dapagliflozin |
| ATC classification | A10BK01: Drugs used in diabetes, sodium-glucose cotransporter 2 (SGLT2) inhibitors) |
| Distribution category | POM |
| Country of origin | India |
| Associated product | N/A |
| Marketing Authorization Holder | Cipla Ltd.<br>Cipla House,<br>Peninsula Business Park,<br>Ganpatrao Kadam Marg, Lower Parel,<br>Mumbai 400 013 India |
| Local Technical Representative | JD PHARMACY LIMITED,<br>P17/53 Uhuru Street, Kariakoo,<br>Dar es Salaam,<br>Tanzania |

### 1.1 Assessment procedure

The application for registration of Dapagliflozin tablets was submitted on 22/10/2021. 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 | Pink, biconvex, diamond-shaped, film-coated tablets with “C389” engraved on one side and plain on the other side |

| | |
|---|---|
| Primary packing material | HDPE Bottle |
| Secondary packing materials | Carton |
| Shelf-life and storage condition | 24 months, Store in tightly closed container. Do not store above 30 °C. |
| Route of administration | Oral |
| Therapeutic indications | Indication(s): Dapagliflozin is indicated:<br>• as an adjunct to diet and exercise to improve glycaemic control in<br>adults with type 2 diabetes mellitus.<br>• to reduce the risk of hospitalization for heart failure in adults with<br>type 2 diabetes mellitus and established cardiovascular disease<br>(CVD) or multiple cardiovascular (CV) risk factors.<br>Heart failure<br>Dapagliflozin is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (nyha class ii-iv) with reduced ejection fraction. |

## 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: Not applicable

Composition: Each film-coated tablet contains: dapagliflozin propanediol equivalent to 10 mg dapagliflozin

Pack size: 30 tablets

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Store in tightly closed container. Do not store above 30 °C.

Manufacturer address: physical address of release site

Unique identifier:

Special warnings/precautions or instructions for use: <The tablet contains Lactose, Do not use if printed inner seal of bottle is broken or missing>

The details of the primary pack include:

Brand name and strength: Not applicable

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Cipla 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

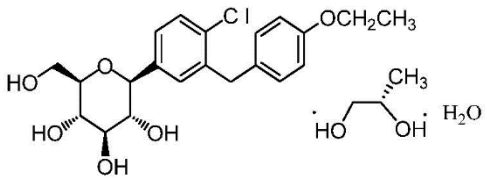
Dapagliflozin Propanediol API is non-compendia.

Molecular formula: $C_{21}H_{25}ClO_6.C_3H_8O_2.H_2O$

Chemical name:

D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl) methyl] phenyl]-, (1S)-, compounded with (2S)-1,2-propanediol, hydrate

Structure:



## General properties

Dapagliflozin Propanediol is a white to off white powder. It dissolves in methanol and practically insoluble in Cyclohexane and water. Dapagliflozin exhibits stereoisomerism due to the presence of five chiral centres. Enantiomeric purity is controlled routinely by specific optical rotation.

Polymorphism has been observed for dapagliflozin. The polymorphic form in dapagliflozin is identified by X-ray diffraction and DSC. Dapagliflozin according to the BCS the API is a class 3 compound (low permeability, high solubility). Thus, solid-state properties such as polymorphism and PSD of the API are not considered critical for the performance of the FPP.

## Manufacture

Dapagliflozin Propanediol API manufacturer is MSN Laboratories Private Limited, Sy. No. 317, 320, 321, 322,323, 604 & 605, Rudraram (Village), Patancheru (Mandal), Sangareddy District, Telangana, Pin code: 502 329, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Drugs Control Administration, Government of Telangana. Dapagliflozin Propanediol 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 in-house standards and ICHQ3A. The parameters monitored during quality control are: Description, Solubility, Water content, Specific Optical Rotation, Residue on ignition, Related Substances, Assay (on anhydrous basis), Residual Solvents, Propylene Glycol Content, Acetic acid content, Polymorphic Identification. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Dapagliflozin Propanediol API is 60 months when packed in double LDPE bags with storage condition ‘Store between 20$^{o}$C – 25$^{o}$C, protect from light and moisture (excursions are allowed between 15°C and 30°C)’.

## Quality of the Finished Pharmaceutical Product

## Formulation

Dapagliflozin tablets is a pink, biconvex, diamond-shaped, film-coated tablets with “C389” engraved on one side and plain on the other side

Dapagliflozin tablets contains the Dapagliflozin Propanediol other ingredients listed here after: Microcrystalline cellulose, Copovidone, Isopropyl alcohol, Anhydrous lactose, Silicon dioxide, Magnesium stearate, Purified water, film-coating (Polyvinyl alcohol-part hydrolysed, Titanium dioxide, Macrogol / PEG, Talc, Iron oxide red). The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, 8$^{th}$ 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 manufacturers are Cipla Limited, Unit III, Plot No. L-139 to L-146, Verna Industrial Estate, Verna, Salcette, Goa – 403 722. India. The compliance of the sites to TMDA GMP standards was confirmed through site inspection on DD/MM/YYYY.

**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, Water Content, Disintegration, Uniformity of Dosage Units, Degradation Products, Assay, Residual Solvent, Polymorphic Identity, microbial enumeration. 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 HDPE container with storage condition 'Store in tightly closed container. Do not store above 30 $^{o}$C'.

**Safety and efficacy information**

Safety and efficacy of Dapagliflozin tablets was established through bioequivalence trial.

**<u>Fed Conditions:</u>**

BE trial report number ARL/17/388 was submitted.
In case of BE:

| | |
|---|---|
| Study title | A Randomized, Open Label, Balanced, Two Treatment, two period, Two Sequence, Single Dose, Crossover Bioequivalence Study of Dapagliflozin Tablets 10 mg of Cipla Ltd., India with Farxiga (dapagliflozin) Tablets 10 mg of AstraZeneca Pharmaceuticals LP Wilmington, DE 19850, in Normal, Healthy, Adult, Male and Female Human Subjects under Fed Conditions. |
| Study design | A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover design bioequivalence studies under fed condition. |
| Study site | Accutest Research Laboratories (I) Pvt. Ltd, (Unit-I) 4th Floor, The Grand Monarch, Near Seema Hall, Anand Nagar Road, Satellite, |

<table>
<tr><td></td><td colspan="2">Ahmedabad-380015, India.</td></tr>
<tr><td>Study dates</td><td colspan="2"><table><tr><th>Activities</th><th>Dates</th></tr><tr><td>Period I (dosing)</td><td>11 November 2017</td></tr><tr><td>Period II (dosing)</td><td>18 November 2017</td></tr><tr><td>Analysis (start date)</td><td>24 November 2017</td></tr><tr><td>Analysis (completion date)</td><td>16 December 2017</td></tr></table></td></tr>
<tr><td>Primary objective</td><td colspan="2">To demonstrate the bioequivalence between Test Product (T): Dapagliflozin Tablets 10mg and Reference Product (R): Farxiga (dapagliflozin) Tablets 10 mg in normal, healthy, adult, male and female human subjects, under fed conditions</td></tr>
<tr><td>Secondary objective</td><td colspan="2">To monitor the safety and tolerability of a single oral dose of investigational medicinal products (IMPs).</td></tr>
<tr><td>Number of participants</td><td colspan="2">Planned-60 subjects<br>Enrolled-60 subjects<br>Dosed-60 subjects<br>Withdrawn - 09 subject<br>Bio-sample analyzed -60 subjects<br>Pharmacokinetic and statistical data analyzed – 51 subjects</td></tr>
<tr><td>Monitored parameters</td><td colspan="2">Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2</td></tr>
<tr><td rowspan="2">Investigational medicinal products</td><td>Test Product</td><td>Reference product</td></tr>
<tr><td>Strength: 10 mg<br>Batch number: GC70902 (Mother Batch No. GC70895)<br>Expiry date: MM/YYYY</td><td>Strength: 10 mg<br>Batch number: HM0336<br>Expiry date: MM/YYYY</td></tr>
<tr><td>Analytical method</td><td colspan="2">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 colspan="2">SAS® (SAS Institute Inc., USA) procedure</td></tr>
</table>

Efficacy results are summarized as follows:

**Table 01: Geometric Means, Ratios and 90% Confidence Intervals for Dapagliflozin (N=51)**

| Parameters | *Geometric mean | | % Ratio | 90% Confidence Interval for ln transformed data | |
|---|---|---|---|---|---|
| | Test (T) | Reference (R) | T/R | Lower Limit | Upper Limit |
| $AUC0_{-inf}$ | 663.1836 | 651.3778 | 101.8124 | 98.4535 | 105.2859 |
| $AUC_{0-t}$ | 612.2655 | 597.7249 | 102.4327 | 98.7709 | 106.2302 |
| $C_{max}$ | 84.0231 | 87.3274 | 96.2163 | 88.9881 | 104.0317 |

**Geometric mean was taken as the antilog (exponential) of the Least squares mean of the ln transformed data.*

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, Dapagliflozin Tablets 10 mg of Cipla Ltd., India is equivalent and interchangeable with Farxiga (dapagliflozin) Tablets 10 mg of AstraZeneca Pharmaceuticals LP Wilmington, DE 19850, under acceptable in vivo experimental conditions.

BE trial report number ARL/17/387 was submitted.
In case of BE:

<table>
<tr><td>Study title</td><td>Randomized, Open Label, Balanced, Two Treatment, two period, Two Sequence, Single Dose, Crossover Bioequivalence Study of Dapagliflozin Tablets 10 mg of Cipla Ltd., India with Farxiga (dapagliflozin) Tablets 10 mg of AstraZeneca Pharmaceuticals LP Wilmington, DE 19850, in Normal, Healthy, Adult, Male and Female Human Subjects under Fasting Conditions</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>Accutest Research Laboratories (I) Pvt. Ltd, (Unit-I) 4th Floor, The Grand Monarch, Near Seema Hall, Anand Nagar Road, Satellite,<br>Ahmedabad-380015, 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>07 November 2017</td></tr><tr><td>Period II (dosing)</td><td>14 November 2017</td></tr><tr><td>Analysis (start date)</td><td>21 November 2017</td></tr><tr><td>Analysis (completion date)</td><td>15 December 2017</td></tr></table></td></tr>
<tr><td>Primary objective</td><td>To demonstrate the bioequivalence between Test Product (T): Dapagliflozin Tablets 10mg and Reference Product (R): Farxiga (dapagliflozin) Tablets 10 mg in normal, healthy, adult, male and female human subjects, under fasting conditions</td></tr>
<tr><td>Secondary objective</td><td>To demonstrate the bioequivalence between Test Product (T): Dapagliflozin Tablets 10mg and Reference Product (R): Farxiga (dapagliflozin) Tablets 10 mg in normal, healthy, adult, male and female human subjects, under fasting conditions.</td></tr>
<tr><td>Number of participants</td><td>Planned-80 subjects<br>Enrolled-71 subjects<br>Dosed-80 subjects<br>Withdrawn - 09 subject<br>Bio-sample analyzed -80 subjects</td></tr>
</table>

| | | |
|---|---|---|
| | Pharmacokinetic and statistical data analyzed – 71 subjects | |
| Monitored parameters | Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2 | |
| Investigational medicinal products | Test Product | Reference product |
| | Strength: 500 mg<br>Batch number: BHUCI824Z<br>Expiry date: 08/2020 | Strength: 500 mg<br>Batch number: 9M03768<br>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:

**Table 01: Geometric Means, Ratios and 90% Confidence Intervals for Dapagliflozin (N=73)**

| Parameters | *Geometric mean | | % Ratio | 90% Confidence Interval for ln-transformed data | |
|---|---|---|---|---|---|
| | Test (T) | Reference (R) | T/R | Lower Limit | Upper Limit |
| $AUC_{0-inf}$ | 611.8750 | 610.3340 | 100.2525 | 98.3923 | 102.1479 |
| $AUC_{0-t}$ | 566.2263 | 561.3429 | 100.8699 | 98.9064 | 102.8725 |
| $C_{max}$ | 93.6601 | 92.7568 | 100.9738 | 95.1085 | 107.2009 |

**Geometric mean was taken as the antilog (exponential) of the Least squares mean of the ln-transformed data.*

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, Dapagliflozin Tablets 10 mg of Cipla Ltd., India is equivalent and interchangeable with Farxiga (dapagliflozin) Tablets 10 mg of AstraZeneca Pharmaceuticals LP Wilmington, DE 19850, 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. Dapagliflozin Propanediol 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**

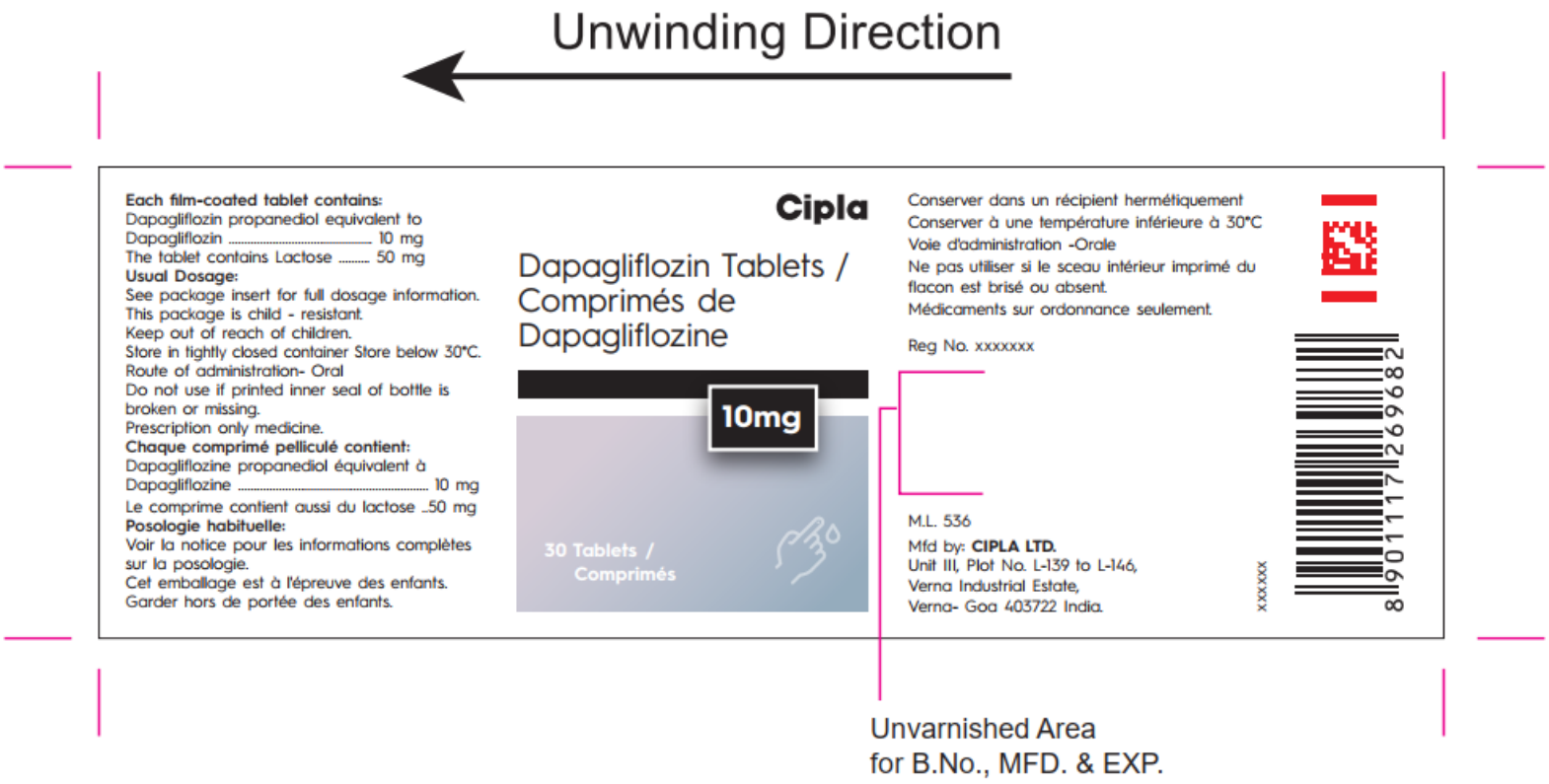
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

**PART 5: CHANGE HISTORY**

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

**Annex I: Mock up labels;**

Primary pack label;




Effective date: 03/10/2022

Effective date: 03/10/2022