26 January 2023
EMA/68353/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dapagliflozin Viatris

International non-proprietary name: dapagliflozin

Procedure No. EMEA/H/C/006006/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

1A9 (UGT1A9): Uridine diphosphate-glucuronosyltransferase

ACE-I: Angiotensin-converting enzyme inhibitors

AEs: Adverse events

AES atomic emission spectroscopy

ANOVA: Analysis of variance

API Active Pharmaceutical Ingredient

AR assessment report

ASM Active Substance Manufacturer

ASMF Active Substance Master File = Drug Master File

ATC: Anatomical Therapeutic Chemical

AUC: Area under the curve

AUCo-.: Represents the total drug exposure across time

AUCo_t: AUC up to the last measurable concentration

AUEC: Area under the effect curve

BDL Below the limit of detection

BP: Blood Pressure

C.V.: Cardiovascular

CEP Certificate of Suitability of the EP

CKD: Chronic Kidney Disease

CLtot: Total plasma clearance

CMS Concerned Member State

Cmax: Maximum concentration recorded

CrL: Credible interval

CoA Certificate of Analysis

CRS Chemical reference substance

CTD common technical document

CYP: Cytochrome

d :Day

DAPA: Dapagliflozin

DKA: Diabetic ketoacidosis

DKA: Diabetic Ketoacidosis

DL Detection Limit

DMF Dimethylformamide

DMSO: Dimethyl Sulfoxide

DOM Date of manufacture

DSC Differential scanning Calorimetry

ECD Electrochemical detection

EDMF European Drug Master File

EDQM European Directorate for the Quality of Medicines

ee enantiomeric excess

EP European Pharmacopoeia

ESRD: End-stage renal disease

FDA US Food and Drug Administration

FID Flame ionisation detection

FPG: Fasting plasma glucose

FPM finished product manufacturer

FTIR Fourier transmission infrared (spectroscopy)

GC Gas chromatography

GD: Guanine deaminase

GFR/ eGFR: Glomerular filtration rate/ estimated Glomerular filtration rate

GMP good manufacturing practice

HDPE high density polyethylene

HPLC High performance liquid chromatography

h/hr: Hour

HOMA: Homeostatic model assessment

ICH International conference on harmonization

ICP Inductively coupled plasma

IPA isopropyl alcohol

IPC In-process control test

IR Infra-red

Kei: Elimination rate constant

KF Karl Fischer

LADA: Latent autoimmune diabetes in adults

LD50: Median Lethal Dose

LDH: Lactate dehydrogenase

LoA Letter of Access

LOD Loss on Drying

LoD Limit of detection

LoQ Limit of Quantitation

MA Marketing Authorisation

MAH Marketing Authorisation holder

MCC microcrystalline cellulose

mcg/ml: Micro gram per milliliter

mg: Milligram

mg/kg: Milligram per kilogram

mg/kg/day: Milligram per kilogram per day

ng/mL: Nanogram per milliliter

MS Mass spectroscopy

NfG Note for Guidance

NIR Near infra-red

NLT Not less than

NMR Nuclear magnetic resonance

NMT Not more than

NT-proBNP: N-terminal pro-B-type natriuretic peptide

NYHA: New York Heart Association

PCTFE Polychlorotrifluoroethene

PDA Photo diode array

PDE Permitted Daily Exposure

Ph.Eur. European Pharmacopoeia

PKs: Pharmacokinetics

PTH: Parathyroid hormone

PVC Polyvinyl chloride

PVdC Polyvinyl dichloride

QL Quantitation limit

QOS Quality Overall Summary

RH Relative Humidity

RCT: Randomized controlled trials

RMS Reference member state

ROI residue on ignition

RRt Relative retention time

Rt Retention time

RT Room temperature

SAL Sterility assurance level

SEM Scanning electron microscopy

S.D.: Standard deviation

SGLT2: Sodium-glucose co-transporter-2

Ti/2: Term half-life

t1/2: Half-life

T2DM/ T2D: Type 2 Diabetes mellitus

THF Tetrahydrofuran

TLC Thin layer chromatography

TGA Thermo-Gravimetric Analysis

Tmax: Time to reach maximum plasma concentration

UA: Uric acid

UTI: Urinary tract infection

UV Ultra violet

XRD X-Ray Diffraction

XRPD X-Ray PowderDiffraction

lig: Microgram

tg •h/ml: Microgram hour per milliliter

pg/mL: Microgram per milliliter

N.B. → Not all abbreviations are used in this report

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Viatris Limited submitted on 7 February 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Dapagliflozin Viatris, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 16 September 2021.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in a in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

> Type 2 diabetes mellitus
> Dapagliflozin Viatris is indicated in adults and children aged 10 years and above for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise
> - as monotherapy when metformin is considered inappropriate due to intolerance.
> - in addition to other medicinal products for the treatment of type 2 diabetes.
> For study results with respect to combination of therapies, effects on glycaemic control, cardiovascular and renal events, and the populations studied, see sections 4.4, 4.5 and 5.1.
>
> Heart failure
> Dapagliflozin Viatris is indicated in adults for the treatment of symptomatic chronic heart failure with reduced ejection fraction.
>
> Chronic kidney disease
> Dapagliflozin Viatris is indicated in adults for the treatment of chronic kidney disease.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC.

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Forxiga instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Forxiga, 5mg, 10mg Film-coated tablet
- Marketing authorisation holder: AstraZeneca AB
- Date of authorisation: 11-11-2012
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/12/795

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Forxiga, 5mg, 10mg Film-coated tablet
- Marketing authorisation holder: AstraZeneca AB
- Date of authorisation: 11-11-2012
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/12/795

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Forxiga, 5mg, 10mg Film-coated tablet
- Marketing authorisation holder: AstraZeneca AB
- Date of authorisation: 11-11-2012
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/12/795
- Bioavailability study number(s): BEQ-2217-DAPA-2017

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Tomas Radimersky

The application was received by the EMA on	7 February 2022
The procedure started on	24 February 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	16 May 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	31 May 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 June 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	9 September 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	14 October 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 October 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	2 November 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	10 November 2022
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	22 December 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 January 2023
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	19 January 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Dapagliflozin Viatris on	26 January 2023

2. Scientific discussion

2.1. Introduction

This is a generic application of medicinal product Dapagliflozin 5mg and 10mg tablets according to Article 10(1) of Directive 2001/83/EC, as amended submitted through a centralised procedure. The reference product is Forxiga, 5mg, 10mg Film-coated tablet, which containing the same active substances in the same strengths and was approved approved on 11 November 2012 via the centralised procedure (EU/1/12/795).

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.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 5 mg or 10 mg of dapagliflozin as active substance.

Other ingredients are microcrystalline cellulose, lactose monohydrate, crospovidone, sodium laurylsulfate, silica colloidal anhydrous and magnesium stearate in tablet core and polyvinyl alcohol, macrogol 6000, talc, titanium dioxide and iron oxide yellow as film-coating.

The product is available in OPA/Alu/PVC-Alu blister or HDPE bottle.

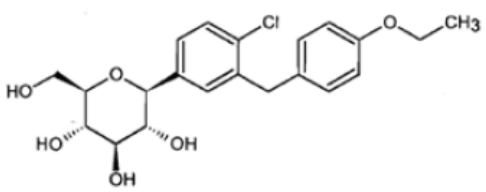
2.2.2. Active substance

2.2.2.1. General Information

The chemical name of dapagliflozin is (2S,3R,4R,5S,6R)-2-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl) tetrahydro-2H-pyran-3,4,5-triol corresponding to the molecular formula $C_{21}H_{25}ClO_6$. Dapagliflozin is supplied as dapagliflozin premix in this procedure. Premix is combination of dapagliflozin with mannitol (1:4). It has a relative molecular mass of 408.87 g/mol (dapagliflozin) and 182.172 g/mol (mannitol) and the following structure:

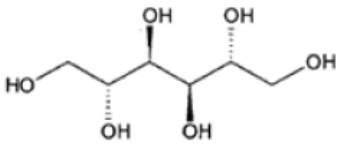
Figure 1: Active substance structure

Dapagliflozin



(2S,3R,4R,5S,6R)-2-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl) tetrahydro-2H-pyran-3,4,5-triol

Mannitol



D-Mannitol

The chemical structure of dapagliflozin premix was elucidated by a combination of elemental analysis, FTIR, ^{1}H-NMR, ^{13}C-NMR, MS and UV. The solid state properties of the active substance were measured by XRPD and DSC.

The dapagliflozin premix is a white to off white powder, slightly hygroscopic, soluble in dimethylsulfoxide, practically insoluble in cyclohexane and slightly soluble in different pH buffer 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 premix. Based on review of XRD data, dapagliflozin premix shows crystalline as well as amorphous patterns. The crystalline pattern observed is due to mannitol whereas amorphous pattern is due to dapagliflozin. The polymorphic form in dapagliflozin premix is identified by technique like X-ray diffraction or DSC. In addition, XRD test is part of release specification.

2.2.2.2. Manufacture, characterisation and process controls

The active substance is manufactured by a single manufacturer.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Dapagliflozin premix is synthesized in four main steps using commercially available well defined starting materials with acceptable specifications.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well characterised and discussed with regards to their origin.

The active substance is packed in an aluminium container, purged with nitrogen and closed with a rubber stopper. Declarations have been provided that the aluminium bottles and rubber stoppers are safe for use in contact with food.

2.2.2.3. Specifications

Specification of dapagliflozin premix is based on the specification proposed in ASMF by the active substance manufacturer.

The active substance specification includes tests for: appearance, identity (IR, HPLC), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), specific optical rotation (Ph. Eur.), and sulphated ash (Ph. Eur.).

The limits are acceptable and set in line with ICH guidelines.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. The verification of the analytical methods by the finished product manufacturer has been provided. Information regarding the reference standards used for assay and impurities testing are provided in sufficient manner.

Batch analysis data for three commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.2.2.4. Stability

Stability data from three production scale batches of the active substance from the proposed manufacturer stored in the intended commercial package for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions were also provided on one batch.

The following parameters were tested*:* description, identification (by HPLC), water content (KF), related substances (HPLC), assay (HPLC), polymorphism (XRD) and microbial quality. The analytical methods used were the same as for release and were stability indicating.

At 40 °C/75% RH an out-of-specification (OOS) result for any unknown individual impurity was reported after 6 months. Assay results and results for water content were variable at both storage conditions but showed no clear trends.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 18 months when stored below 25 °C and protected from light in the proposed container.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and Pharmaceutical development

Dapagliflozin Viatris 5 mg film-coated tablet is a yellow coloured, round shaped, biconvex film-coated tablet with diameter of approximately 7.2 mm. Debossed with '5' on one side and plain on the other side.

Dapagliflozin Viatris 10 mg film-coated tablet is a yellow coloured, diamond shaped, biconvex with dimensions of approximately 11 x 8 mm. Debossed with '10' on one side and plain on the other side.

No overage is proposed by the applicant.

The finished product has been developed to be a generic equivalent to the reference medicinal product Forxiga 5 mg or 10 mg film-coated tablets. Consequently, the objective was to prepare an immediate release film-coated tablet being essentially similar to the reference medicinal product.

The composition of the strengths is proportional.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Compatibility studies of premix with excipients have been provided and were found acceptable.

Qualitative composition and physical characterization of the reference product have been provided.

The composition of the tested and reference product is comparable. The tested product contains sodium lauryl sulphate in addition to other excipients shared between the respective products.

The dissolution profiles are accepted as similar without further mathematical evaluation.

Biowaiver of strength 5 mg has been applied. The product meets the general requirements according to Guideline on Investigation on Bioequivalence (CHMP/EWP/QWP/1401/98 Rev 01). Based on the information provided the biowaiver can be accepted.

Based on the provided information the tested and reference products are comparable.

Dissolution method used for QC was based on the US/FDA recommendation. The discriminatory power of the dissolution method has been demonstrated.

The primary packaging is OPA/Aluminium/PVC-Aluminium blister packs (common, perforated unit dose or calendar blisters) or High Density Polyethylene (HDPE) bottles with polypropylene (PP) child resistant closure. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.2.3.2. Manufacture of the product and process controls

The manufacturing process consists of the following main steps: dry mixing, wet granulation, lubrication, compression and coating. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.2.3.3. Product specifications

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: description (visual inspection), dimensions, identifications API (HPLC, UV), identification TiO_2 (in house), iron oxide (in house), water content (KF titration), dissolution (HPLC), uniformity of dosage units (Ph. Eur.), related substances (HPLC), residual solvent (GC), assay (Ph. Eur.), and microbial test (Ph. Eur.).

The specifications proposed for the control of the finished product provide an adequate control of the finished product quality after production and during shelf-life. The results presented show compliance

with specifications. Each parameter of specification has been justified based on the relevant guidelines and manufacturer experiences. The limits are acceptable.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach. The provided risk assessment (RA) complies with the ICH Q3D Guideline for Elemental Impurities Option 2b. The results of the RA show that none of the evaluated elemental impurities exceeded neither the PDE established in the ICH Q3D guideline nor the control threshold of the 30% of Product Limit. The Applicant does not consider additional control actions in the finished product. This is accepted.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) Nº 726/2004 for nitrosamine impurities in human medicines (EMA/425645/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three production scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.2.3.4. Stability of the product

Stability data from three (minimal) production scale batches of finished product stored for up to 36 months for blister and 24 months for bottle under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, water, dissolution, related substances, assay, and microbiological test. The analytical methods used were the same as for release and were stability indicating.

No significant changes have been observed.

One batch of each strength of the finished product have been subjected to photostability studies performed under conditions that are in line with the ICH Q1B guideline. The results show that the finished product is not sensitive to light. Forced degradation study was performed during validation of the HPLC method for assay and related substances. The methods are stability indicating.

In-use stability studies confirmed the shelf-life of the HDPE bottle after first opening of 90 days.

Based on available stability data, the proposed shelf-life of 24 months with no storage conditions as stated in the SmPC (section 6.3) are acceptable.

2.2.3.5. Adventitious agents

The TSE/BSE free certificate by the respective vendors has been provided. It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on the active substance has been provided using the EU/ASMF-WS.

The information about control strategy for active substance applied by the finished product manufacturer is of good quality.

The information provided about the finished product is of good quality. The finished product development has been described in detail; the information regarding dissolution method and bioequivalence has been completed. The risk assessment on potential presence of nitrosamine impurities has been provided and no risk was identified. All GMP issued raised have been resolved.

The manufacturing process is considered as standard process. Sufficient information about process control is provided. The product specifications cover appropriate parameters for this dosage form and the limits setting is acceptable. Container closure system is suitable for this dosage form. Adequate stability data are provided; therefore, the proposed shelf-life with no storage conditions is acceptable.

In conclusion, the chemical-pharmaceutical documentation in relation to Dapagliflozin Viatris 5 mg and 10 mg film-coated tablets is of sufficient quality in view of the present European regulatory requirements.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile was discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Dapagliflozin Viatris manufactured by Viatris Limited is considered unlikely to result in any significant increase in the combined sales volumes for all dapagliflozin containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.3. Discussion on non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of dapagliflozin are well known. A non-clinical clinical overview based on literature review is considered appropriate. In the overview, the applicant has also adequately discussed the impurity profile of the drug substance in the non-clinical overview.

2.3.4. Conclusion on the non-clinical aspects

The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

The MAA is approvable from the non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing dapagliflozin. To support the marketing authorisation application the applicant conducted one bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment.

No formal scientific advice by the CHMP was given for this medicinal product.

For the clinical assessment Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

GCP aspect

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

The applicant requested a biowaiver for the 5 mg strength based on the result of the bioequivalence study conducted with the 10 mg strength (Study BEQ-2217-DAPA-2017), in line with the following requirements in Guideline on the Investigation of Bioequivalence, Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/Corr**.

According to the EMA guideline on the investigation of bioequivalence, the following requirements must be met where a waiver for additional strength is claimed:

a) All the strengths (i.e. 5 mg and 10mg) of proposed pharmaceutical products are manufactured using the same manufacturing process.

b) The qualitative composition of the Dapagliflozin film-coated tablets 5 mg is same as that of Dapagliflozin film-coated tablets 10 mg

d) The composition of all strengths (i.e. 5 mg and 10 mg) are quantitatively proportional (i.e. the ratio between the amount of each excipient to the amount of active substance is same among 5 mg and 10 mg strengths).

c) Dapagliflozin demonstrates linear pharmacokinetics over the therapeutic dose range.

e) The in-vitro dissolution profile is similar under identical conditions for the additional strengths (i.e. 5 mg) and the strength of batch used in the bioequivalence studies (i.e. 10 mg).

Considering that:

- both strengths (i.e. 5 mg and 10mg) have the same manufacturing process, same qualitative composition, and composition quantitatively proportional

- the linearity in pharmacokinetics of dapagliflozin increases proportionally in dose range of 0.1 mg to 500 mg

- the in-vitro dissolution profiles are considered as similar

the requirements are met and the biowaiver for additional strength (i.e. 5mg) is justified.

Tabular overview of clinical studies

To support the application, the applicant has submitted one bioequivalence study.

- **BIOEQUIVALENCE STUDY NO. EQ-2217-DAPA-2017:** Single dose Fasting In-Vivo Bioequivalence study of Dapagliflozin Viatris Tablets 10 mg to FORXIGA® (dapagliflozin) film coated Tablets 10 mg in healthy, adult, human subjects.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study NO. EQ-2217-DAPA-2017: *Single dose Fasting In-Vivo Bioequivalence study of Dapagliflozin Tablets 10 mg to FORXIGA® (dapagliflozin) film coated Tablets 10 mg in healthy, adult, human subjects*

Methods

- **Study design**

Study NO. EQ-2217-DAPA-2017 was an open label, balanced, analyst blind, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study on 24 healthy, adult, human subjects under fasting condition.

The bioequivalence study was carried out for evaluating the following objectives:

1. Pharmacokinetic: To evaluate the comparative oral bioavailability of single dose of Dapagliflozin Tablets 10 mg with FORXIGA (dapagliflozin) film coated Tablets 10 mg in healthy, adult, human subjects under fasting condition.
2. Safety: To monitor the safety and tolerability of a single oral dose of Dapagliflozin Tablets 10 mg when administered in healthy, adult, human subjects under fasting condition.

The study was carried out in one group comprising of 24 male subjects (subject number 01 to 24).

After check-in, there was a supervised overnight fasting period of at least 10.00 hours before dosing. A pre-dose sample was taken before dosing. Thereafter, a series of blood samples were taken up to 48 hours post-dose, with the subject remaining in the CPU. After the 48 hours post-dose blood sample collection, the subjects were allowed to leave CPU after checking their vital signs and medical examination.

The test or reference products were orally administered to the subjects while in upright sitting posture, with 240 mL of 20% w/v glucose solution in water at room temperature as per the randomization schedule under the supervision of the Medical Officer followed by examination of the oral cavity.

There was a washout period of 7 days from the completion of dosing between two consecutive periods.

Concentration of dapagliflozin was measured in plasma samples of the subjects. Blood samples (1 x 5 mL) were collected in 5 mL blood collection tube containing K2EDTA as anticoagulant during each period. The venous blood samples were withdrawn pre-dose and at 0.08, 0.17, 0.33, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.33, 2.67, 3.00, 4.00, 6.00, 8.00, 12.00, 18.00, 24.00, 30.00, 36.00 and 48.00 hours post-dose (time points being relative to the investigational product dosing).

The plasma samples of subjects were analysed by a validated LC-MS/MS method.

Protocol deviations

- Time Point Deviation

  As per protocol, blood samples should be collected within two minutes of scheduled time for blood collection for in-house samples. All actual times of the sample withdrawal were recorded in the bleed sheet. However, there were following deviations from the schedule time of the collection above the permitted deviation time in the study.

Sr. No.	Subject No.	Sample Time Point (hrs)	Scheduled Time	Actual Time	Deviation in Hour	Reason for Deviation
Period 1						
1.	17	2.00	11:12 hrs	11:17 hrs	0.08	Poor blood flow
Period 2						
1.	08	3.00	12:21 hrs	12:24 hrs	0.05	Poor blood flow
2.	16	0.08	09:14 hrs	09:17 hrs	0.05	Cannula blocked
3.	24	2.67	12:13 hrs	12:16 hrs	0.05	Poor blood flow

The above deviations were duly incorporated during pharmacokinetic analysis.

A few deviations were found in the blood sampling. These deviations are not expected to significantly impact the results of the study.

No concomitant medication was reported.

- **Test and reference products**

Dapagliflozin Viatris 10mg film-coated tablets has been compared to Forxiga 10mg film-coated tablets.

- **Population(s) studied**

A total of 24 healthy adult human subjects (male, between 21 and 44 years of age and having a Body Mass Index (BMI) between 19.3 and 28.6) were enrolled. No female volunteers were included in the study.

Of these 24 subjects, 23 subjects completed both the periods of the study. Subject number 15 was withdrawn from the study in period 2 (pre-dose) on principal investigator advice due to adverse event during check-in.

The study was conducted only on Asian population. However, no clinically relevant inter-ethnic differences were observed regarding dapagliflozin pharmacokinetics and pharmacodynamics. Moreover, the design of the study was crossover, therefore the chosen population is considered acceptable.

- **Analytical methods**

Data of Dapagliflozin in human plasma samples was gathered from the study BEQ-2217-DAPA-2017 using a validated high-performance liquid chromatography tandem mass spectrometric method for dapagliflozin, to determine the concentration of dapagliflozin in the samples of all analysed subjects.

A detailed description of the operative procedures and the validation process were provided.

- **Pharmacokinetic variables**

The pharmacokinetic parameters were calculated by non-compartmental methods using SAS® version 9.4.

The following pharmacokinetic parameters (variables) of dapagliflozin were estimated after drug administration under fasting conditions

- primary variables: C_{max} and AUC_{0-t},
- secondary variables: $AUC_{0-\infty}$, $t_{1/2}$, k_{el} and residual area.

These parameters were derived individually for each subject from their dapagliflozin concentration in plasma. Actual time of blood collection was considered for pharmacokinetic calculations. For estimation of PK parameters, concentrations that were below level of quantification (BLQ) were assigned a value of zero. In the calculations of PK parameters, missing values were ignored.

- **Statistical methods**

Statistical analyses were performed. Reported summary statistics for all pharmacokinetic parameters for both the test and reference products were the minimum, maximum, arithmetic means, median, standard deviation and the coefficient of variation for untransformed data.

Log-transformed pharmacokinetic parameters (C_{max} and AUC_{0-t}) for dapagliflozin were analysed using standard analysis of variance (ANOVA) model with the main effects of "sequence, period, formulation and subject nested within sequence". Separate ANOVA model was used to analyse each of the parameters. Each ANOVA included calculation of mean square error, p-value of factors and the associated degrees of freedom. The sequence effect was tested at 5% level of significance with subjects nested within sequence as an error term. The formulation and period effects were tested at 5% level of significance.

Ninety-percent (90%) confidence intervals were calculated for the ratio of both the products averages (geometric means) by first calculating the 90% confidence intervals for the differences in the averages (least square means) of the log-transformed data and then taking the antilogarithms of the obtained confidence limits.

Criteria for conclusion of bioequivalence:

The 90% confidence intervals for C_{max} and AUC_{0-t} of dapagliflozin had to entirely fall in the acceptance range of 80.00% - 125.00% for log-transformed data to conclude the test product was bioequivalent to the reference product under fasting conditions.

Results

Table 1. Pharmacokinetic parameters for dapagliflozin (non-transformed values)

Pharmacokinetic parameter	Test (N=23)		Reference (N=23)	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$	587.68	142.88	585.24	148.76
$AUC_{(0-\infty)}$	604.82	146.72	598.92	150.68
C_{max}	99.79	18.71	97.26	16.85
T_{max}*	1.75 (0.50 – 3.00)		1.75 (1.00 – 4.00)	
AUC_{0-t}	area under the plasma concentration-time curve from time zero to 48 hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 2. Statistical analysis for dapagliflozin (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%*
$AUC_{(0-t)}$	100.78%	(97.53%, 104.14%)	6.46
C_{max}	102.11%	(98.10%, 106.29%)	7.90
* estimated from the Residual Mean Squares			

Formulation effect was found to be statistically insignificant (p-value ≥ 0.05) for C_{max} & AUC_{0-t}.

Period effect found to be statistically insignificant (p-value ≥ 0.05) for AUC_{0-t} but statistically significant (p-value < 0.05) for C_{max}.

Sequence effect found to be statistically insignificant (p-value ≥ 0.05) for C_{max} & AUC_{0-t}.

A significant period effect is caused by the fact that in one of the two periods, the plasma levels C_{max} are higher / lower than in other. This may be due to different conditions in period 1 and period 2. Some of the causes for significant period effects are volunteers, meal plan, dosing procedure and environmental conditions. However, in this study all the conditions in period 1 and period 2 were identical. These are:

- Same volunteers were enrolled in both periods. Moreover, none of the volunteers had taken any medicine between period 1 and period 2.
- Same meal plan was given to volunteers in both periods.
- Dosing procedure was same in both periods.
- Environmental conditions during dispensing and sample separation were similar in both periods.

Thus, based on the above observations, since the conditions in period 1 and period 2 were identical, the period effect appears to be insignificant in nature and may not have any clinical consequences.

The 90% confidence intervals for the ratio (Test/Reference) of C_{max} and AUC_{0-t} for dapagliflozin were within the acceptable limits of bioequivalence 80.00% - 125.00%. Thus, it is concluded that the test formulation, Dapagliflozin Tablets 10 mg is bioequivalent to reference formulation, FORXIGA® (dapagliflozin) film coated Tablets 10 mg in healthy, adult, human subjects under fasting condition.

- **Safety data**

During conduct of the study, adverse events were reported for one subject (subject number 15).

Sub. No.	Adverse Event	Date and Time of Last Dosing	Date and time of Occurrence	Time of AE since Last Dose	Date and time of Resolution	Duration of AE (From Occurrence to Resolution)	Relationship with the Study Drug	Treatment Received (Sequence)
15	Itching and rash over back	09th April 2019 09:06 hrs	12th April 2019 20:42 hrs	3 Days 11 hours 36 minutes	18th April 2019 07:54 hrs	5 days 11 hours 12 minutes	Possible	R (RT)

During the post-study safety assessment, one adverse event was reported for one subject (subject number 16) due to abnormal ECG.

Sub. No.	Adverse Event	Date and Time of Last Dosing	Date and time of Occurrence	Time of AE since Last Dose	Date and time of Resolution	Duration of AE (From Occurrence to Resolution)	Relationship with the Study Drug	Treatment Received (Sequence)
16	Abnormal ECG	16th April 2019 09:09 hrs	18th April 2019 09:38 hrs	2 days 27 hours	18th April 2019 11:16 hrs	1 hour 38 minutes	Unlikely	R (TR)

There were few out of reference range laboratory values obtained at the post-study assessment, but these were not clinically significant except for subject number 01, 02, 05, 07, 10, 11, 12, 15, 17, 19 and 21.

Sub. No.	Laboratory Parameter	Safety Assessment Results	Reference Range	Remark	Relationship with the Study Drug
01	Haemoglobin	11.5 g/dL	13.0 – 17.0 g/dL	Decreased	Unlikely
	Hematocrit	35.6%	40.0 – 50.0%	Decreased	Unlikely
02	Sodium	128.9 mmol/L	136.0 -145.0 mmol/L	Decreased	Unlikely
05	SGPT	81.0 U/L	16.0 -63.0 U/L	Increased	Possible
	SGOT	48.2 U/L	15.0 - 40.0 U/L	Increased	Possible
07	Leucocyte count	3.54 × 1000/µL	4.00 – 10.00 × 1000/µL	Decreased	Unlikely
	Sodium	126.0 mmol/L	136.0 -145.0 mmol/L	Decreased	Unlikely
10	Fasting blood sugar	122.0 mg/dL	70.0 – 110.0 mg/dL	Increased	Unlikely
11	Fasting blood sugar	143.5 mg/dL	70.0 – 110.0 mg/dL	Increased	Unlikely
	Triglycerides	221.5 mg/dL	< 150.0 mg/dL	Increased	Possible
	Total Cholesterol	254.8 mg/dL	< 200.0 mg/dL	Increased	Possible

There was no serious adverse event reported in the study.

Both formulations were well tolerated. No major side effects and no relevant differences in safety profiles were observed between the test and reference products.

2.4.2.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.3. Discussion on clinical aspects

To support the application, the applicant submitted one bioequivalence study. The study was open label, balanced, analyst blind, randomized, two-treatment, two-period, two-sequence, single dose, cross-over bioequivalence study of Dapagliflozin 10 mg film-coated tablet on 24 healthy, adult, human subjects under fasting conditions. The study was acceptable and in line with the existing EMA guidelines. Based on the results of the study, bioequivalence between the test (Dapagliflozin film-coated Tablets 10 mg) and Forxiga and reference product (Forxiga film-coated Tablets 10 mg) is demonstrated.

A biowaiver was requested for the 5 mg strength. The relevant requirements for this biowaiver described in the EMA guideline on the investigation of bioequivalence were met, therefore the biowaiver for the additional strength (i.e. 5 mg) is justified.

2.4.4. Conclusions on clinical aspects

Based on the presented bioequivalence study Dapagliflozin Viatris is considered bioequivalent with Forxiga.

2.5. The results of study BEQ-2217-DAPA-2017 with 10mg formulation can be extrapolated to other strengths 5mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6. Risk Management Plan

2.5.1. Safety concerns

Table 3. Summary of safety concerns

Summary of safety concerns	
Important identified risks	Diabetic Ketoacidosis including events with atypical presentation
Important potential risks	Bladder cancer Breast cancer Prostate cancer Lower limb amputation
Missing information	Use in patients with NYHA class IV Long-term safety in the paediatric population (aged 10 years and above)

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

Table 4. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Diabetic Ketoacidosis including events with atypical presentation	Routine risk communication: SmPC section 4.4,4.8 PL section 2, 4	Routine pharmacovigilance activities only beyond ADRs reporting and signal detection: Specific adverse reaction follow-up questionnaires for diabetes ketoacidosis
Bladder cancer	None	Routine pharmacovigilance activities only beyond ADRs reporting and signal detection: Specific adverse reaction follow-up questionnaires for bladder cancer
Breast cancer	None	Routine pharmacovigilance activities only beyond ADRs reporting and signal detection: Specific adverse reaction follow-up questionnaires for breast cancer
Prostate cancer	None	Routine pharmacovigilance activities only beyond ADRs reporting and signal detection: Specific adverse reaction follow-up questionnaires for prostate cancer
Lower limb amputation	Routine risk minimisation activities: SmPC section 4.4 PL section 2	Routine pharmacovigilance activities only beyond ADRs reporting and signal detection: Specific adverse reaction follow-up questionnaires for lower limb amputation
Use in patients with NYHA class IV	Routine risk communication: SmPC section 4.4	Routine pharmacovigilance activities
Long-term safety in the paediatric population (aged 10 years and above)	Routine risk communication: SmPC section 4.8	Routine pharmacovigilance activities

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version V 0.2 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

A bridging report, bridging the content to the reference product Forxiga 5 mg / 10 mg film-coated tablets and the layout to the leaflet for Duloxetine Mylan 30 mg hard gastro -resistant capsules, was submitted and found acceptable.

3. Benefit-risk balance

This application concerns a generic version of Dapagliflozin film-coated tablet (5 mg; 10 mg). The reference product Forxiga film-coated tablet (5 mg; 10 mg) is indicated for the treatment of:

Type 2 diabetes mellitus

Dapagliflozin Viatris is indicated in adults and children aged 10 years and above for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance.

- in addition to other medicinal products for the treatment of type 2 diabetes.

For study results with respect to combination of therapies, effects on glycaemic control, cardiovascular and renal events, and the populations studied, see sections 4.4, 4.5 and 5.1.

Heart failure

Dapagliflozin Viatris is indicated in adults for the treatment of symptomatic chronic heart failure with reduced ejection fraction.

Chronic kidney disease

Dapagliflozin Viatris is indicated in adults for the treatment of chronic kidney disease.

No nonclinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient.

From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature is considered sufficient.

The bioequivalence study forms the pivotal basis with an open label, balanced, analyst blind, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study. The study design is considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied are adequate.

The test formulation of Dapagliflozin Viatris met the protocol-defined criteria for bioequivalence when compared with Forxiga. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-∞, and Cmax were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Dapagliflozin Viatris is favourable in the following indication:

Type 2 diabetes mellitus

Dapagliflozin Viatris is indicated in adults and children aged 10 years and above for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance.
- in addition to other medicinal products for the treatment of type 2 diabetes.

For study results with respect to combination of therapies, effects on glycaemic control, cardiovascular and renal events, and the populations studied, see sections 4.4, 4.5 and 5.1.

Heart failure

Dapagliflozin Viatris is indicated in adults for the treatment of symptomatic chronic heart failure with reduced ejection fraction.

Chronic kidney disease

Dapagliflozin Viatris is indicated in adults for the treatment of chronic kidney disease.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

- ***Periodic Safety Update Reports***

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.