CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202293Orig1s024

CHEMISTRY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. NDA Supplement Number: NDA 202293 / S-024 [NDA approval date: 08-Jan-2014]

2. Submission(s) Being Reviewed: NDA 202293 / S-024 [eCTD Seq. 0815]

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	PA	03-Nov-2020	03-Nov-2020	30-Nov-2020	03-May-2021	15-Feb-2021

3. Proposed Changes: Efficacy sNDA containing final clinical data from Study D169AC0001 (DAPA-CKD-chronic kidney disease) with a request for Priority Review Designation.

- Draft Labeling in the PI, Patient Counseling Information and the Medication Guide.
- Applicant also submitted Environmental Assessment for API dapagliflozin.

4. Review #: 1

5. Clinical Review Division: OCHEN/DDLO

6. Name and Address of Applicant:

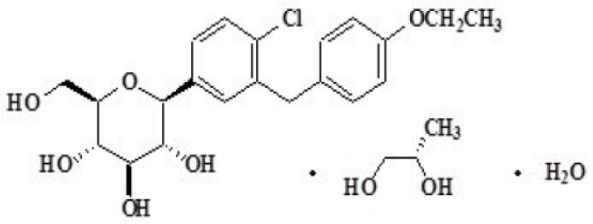
AstraZeneca AB
Karlebyhus, Astraalen
Sodertalje, Stockholm County
Sweden SE-151 85

U. S. Agent:
AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Wilmington DE 19803

7. Drug Product:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
FARXIGA (dapagliflozin)	**Tablet**	**5 mg and 10 mg**	**Oral**	**Rx**	**No**

8. Chemical Name and Structure of Drug Substance:

FARXIGA **(dapagliflozin)**  1,5-anhydro-1-*C*-[4-chloro-3-[(4ethoxyphenyl)methyl]phenyl]-, (1*S*)-, compounded with (2*S*)-1,2-propanediol, hydrate (1:1:1) Molecular formula: $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$ MW: 502.98	FARXIGA is available as a film-coated tablet for oral administration containing the equivalent of 5 mg dapagliflozin as dapagliflozin propanediol or the equivalent of 10 mg dapagliflozin as dapagliflozin propanediol, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, crospovidone, silicon dioxide, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and yellow iron oxide. Dapagliflozin is an inhibitor of Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules. SGLT2 is responsible for majority of the reabsorption of filtered glucose from the tubular lumen. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

9. Indication:

FARXIGA is a sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factors.

Limitations of use:

- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis

10. Supporting/Relating Documents:

- Environmental Assessment for Dapagliflozin

11. Consults: N/A

12. Executive Summary:

Dapagliflozin is a highly selective, reversible, oral sodium-glucose cotransporter 2 (SGLT2) inhibitor. Inhibition of SGLT2-mediated glucose reabsorption leads to pharmacologically controlled glucosuria, resulting in lowered fasting and postprandial plasma glucose, lowered

glycated hemoglobin, and reduced body weight and blood pressure. In addition to inhibition of glucose reabsorption, dapagliflozin's effects on the kidney are associated with a downstream cascade of effects that may protect against the micro- and macrovascular complications of diabetes such as heart failure (HF), other cardiovascular (CV) diseases, and nephropathy. Dapagliflozin (5 mg or 10 mg) is currently approved in over 100 countries to improve glycemic control in patients with type 2 diabetes mellitus (T2DM), including in the United States (US) since January 2014 (FARXIGA® NDA 202293). On 18 October 2019 FARXIGA was approved to reduce the risk of hospitalization for heart failure in adults with T2DM and established cardiovascular disease or multiple cardiovascular risk factors. FARXIGA was also approved for reducing the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure with reduced ejection fraction (NYHA class II-IV) on 5 May 2020. Dapagliflozin can be given as monotherapy or in combination with other medicinal products indicated for the treatment of T2DM.

The subject supplement is based on the following:

- *Recently completed Phase III study D169AC00001/DAPA-CKD entitled Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease. The study was powered to be a single pivotal indication seeking phase III study.*

- *Recently approved (October 18, 2019 S-018) Phase IIIb studyD1693C00001/ DECLARE-TIMI 58 (hereafter referred to as 'DECLARE'). DECLARE evaluated the effect of dapagliflozin compared to placebo on CV and renal outcomes in abroad T2DM population with or without established CV disease. DECLARE was designed to address post-marketing requirements in the US (PMRs 2121-5 and 2121-6) and was a Category 3 post-authorization safety study (PASS) in the EU (PAM 005).*

With this supplemental new drug application (sNDA), applicant seeks marketing approval for the use of FARXIGA:

(b) (4)

DAPA-CKD includes patients with CKD and T2DM or without diabetes. As such, it is the first SGLT2 inhibitor trial in CKD to include patients without diabetes.

Nonannotated Draft Labeling

The applicant proposed to revise the Draft Labeling Text in the PI, Patient Counseling Information and the Medication Guide. The applicant proposed to change the Indications and Usage as follows:

1 INDICATIONS AND USAGE

No CMC related changes were made to the PI, Patient Counseling Information and the Medication Guide.

Environmental Assessment (EA)

Applicant submitted the EA in Section 1.12.14 requesting a categorical exclusion from the need to prepare an environmental assessment in accordance with 21 CFR 25.31 (b).

> Applicant stated that "*To the best of the sponsor's knowledge, no extraordinary circumstances, as referenced in 21 CFR 25.21, exist relative to this action*".

Applicant's request for Categorical Exclusion may be granted.

13. Conclusions & Recommendations:

This supplement is recommended for approval from the CMC review perspective.

14. Comments/Deficiencies to be Conveyed to Applicant: N/A

15. Primary Reviewer:

Pallaiah Thammana, Ph. D., Senior CMC reviewer, Branch 1, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

16. Secondary Reviewer:

Ramesh Raghavachari, Ph. D., Branch Chief, Branch 1, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ

Pallaiah Thammana

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Ramesh Raghavachari

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/s/

SABRY SOUKEHAL
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On behalf of OPQ