U.S. FOOD & DRUG ADMINISTRATION

Lem Moyé, M.D., Ph.D
(b) (6) [redacted]

November 20, 2023

Re: Docket No. FDA-2022-P-2708

Dear Dr. Moyé:

This letter responds to your citizen petition, which was received by the Food and Drug Administration (FDA or Agency) on November 1, 2022 (Petition). The Petition requests that, in connection with the FDA-approved drug Farxiga (dapagliflozin[1]), FDA: (1) reexamine the results of the DECLARE (dapagliflozin effect on cardiovascular events) clinical trial, with particular attention to the use of the combined endpoint of cardiovascular (CV) death and hospitalization for heart failure; (2) answer the 22 questions reflected on pages 13 to 15 of the Petition; and (3) reexamine Farxiga's "indication for the use of dapagliflozin to reduce CV death and hospitalization for heart failure" (Petition at 1) if FDA's answers to the 22 questions suggest "that the interpretation of the DECLARE trial is invalid because of the improper construction of a combined endpoint" (Petition at 1).

FDA has carefully considered your Petition, and your Petition is denied.

Farxiga has four approved indications:

(1) To reduce the risk of sustained eGFR [estimated glomerular filtration rate] decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.

(2) To reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure in adults with heart failure.

(3) To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors.

(4) As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[2]

[1] Your Petition refers to dapaglifozin. We interpret it to refer to Farxiga (dapaglifozin) (new drug application 202293). For purposes of this response, dapaglifozin and Farxiga are used interchangeably.
[2] FDA-approved labeling for Farxiga, available at https://www.accessdata fda.gov/spl/data/129852e5-b1f1-488e-99fe-aa8d0d4fd07a/129852e5-b1f1-488e-99fe-aa8d0d4fd07a.xml (9/2023).

The DECLARE trial supported the October 2019 approval of the third indication above, namely: "To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors."[3] Such indication does not include reduction in the risk of CV death. The DECLARE trial was not relied on to support approval of the two indications that include reductions in CV death. FDA reviewed the data for the DECLARE trial carefully and did not have concerns regarding its methodology or use of the combined endpoint of CV death and hospitalization for heart failure. The Agency's reviews are available on FDA's website at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=202293 (see 10/18/2019 review for SUPPL-18). Additionally, the clinical trials that support the other approved indications, including the indications that include CV death, for Farxiga are discussed in the FDA-approved labeling for the drug.[4]

The specific questions about the DECLARE trial (posed beginning on page 13 of your Petition) seem to be premised on the idea that the DECLARE trial "serve[s] as a basis for the approval of dapagliflozin for the reduction of CV death" (Petition at 15, Question 22). As noted above, the DECLARE trial was not relied on to support approval of the two indications that include reductions in CV death. Therefore, FDA is not responding to the specific questions.

Therefore, for the reasons described above and in accordance with 21 CFR 10.30(e), your Petition is denied.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
Date: 2023.11.20 16:01:04 -05'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

[3] Id.
[4] Id.