



NDA 202293/S-018  
NDA 205649/S-011

**SUPPLEMENT APPROVAL  
FULFILLMENT OF POST MARKETING  
REQUIREMENTS**

AstraZeneca AB  
c/o AstraZeneca Pharmaceuticals LP  
Attention: Sally Walsh  
Director, Regulatory Affairs  
One MedImmune Way  
Gaithersburg, MD 20878

Dear Ms. Walsh:

Please refer to your supplemental new drug applications (sNDAs) dated and received December 18, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Farxiga (dapagliflozin) tablets and Xigduo XR (dapagliflozin and metformin HCL) extended release tablets.

These Prior Approval supplemental new drug applications provide for revisions to labeling based on the results of Study D1693C0001, Dapagliflozin Effect on Cardiovascular Events (DECLARE), which was conducted to assess cardiovascular outcomes and to assess the risk of bladder cancer associated with dapagliflozin.

**APPROVAL & LABELING**

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

**WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS**

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.<sup>1</sup> Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling

---

<sup>1</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.<sup>2</sup>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable since the disease is rare in children. For a meaningful study to be conducted, the population would require a diagnosis of type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factors. The number of pediatric patients fitting these criteria is small, and a clinical trial for the new indication is therefore not feasible.

### **FULFILLMENT OF POSTMARKETING REQUIREMENTS**

The supplemental application for NDA 202293 contained the final reports for the following postmarketing requirements listed in the January 8, 2014, approval letter for NDA 202293.

2121-5 A randomized, double-blind, placebo-controlled trial (the DECLARE trial) evaluating the effect of dapagliflozin on the incidence of major adverse

---

<sup>2</sup> We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with dapagliflozin to that observed in the placebo group is less than 1.3. The long-term effects of dapagliflozin on the incidence of liver toxicity, bone fractures, nephrotoxicity/acute kidney injury, breast and bladder cancer, complicated genital infections, complicated urinary tract infections/pyelonephritis/urosepsis, serious events related to hypovolemia and serious hypersensitivity reactions should also be assessed. The estimated glomerular filtration rate (eGFR) should also be monitored over time to assess for worsening of renal function.

- 2121-6 To assess the risk of bladder cancer associated with dapagliflozin, conduct adequate follow-up beyond completion of the cardiovascular outcomes trial (DECLARE) to observe a total of 66 events of bladder cancer, with 80% power to exclude a relative risk of 2.0 for dapagliflozin versus placebo, assuming a 2-sided alpha of 5%.

We have reviewed your submission and conclude that the above requirements were fulfilled.

We remind you that there are postmarketing requirements listed in the December 4, 2015, supplement approval letter, and the April 24, 2017, post-approval postmarketing requirement letter that are still open for NDA 202293.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and*

*Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*<sup>3</sup>

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.<sup>4</sup> Information and Instructions for completing the form can be found at FDA.gov.<sup>5</sup> For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.<sup>6</sup>

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Richard Whitehead, M.S., Regulatory Project Manager, at (301) 796-4945.

Sincerely,

*{See appended electronic signature page}*

Patrick Archdeacon, M.D.  
Associate Director for Therapeutics (Acting)  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**ENCLOSURES:**

- Content of Labeling
  - Prescribing Information
  - Medication Guides

---

<sup>3</sup> When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

<sup>4</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

<sup>5</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

<sup>6</sup> <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>

-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
-----

/s/  
-----

PATRICK ARCHDEACON  
10/18/2019 04:48:51 PM  
signing as associate director