DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202293

NDA APPROVAL

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Director, Global Regulatory Sciences - U.S.
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) dated December 27, 2010, received December 28, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Farxiga (dapagliflozin) tablets 5 mg and 10 mg.

We acknowledge receipt of your amendments dated January 5, 12, 28 (2), and 31, February 1 and 16, March 23 and 30, April 11, 12, 13, 14, 22 and 27, May 9, 13, 16,18, 20 (2), 23, and 24, June 2, 3 (2), 8, 13 (2), 14, 16, 17, 22, 24, and 30, July 13 and 25, August 1, 12, 17, 19, 22, 26, 29, and 30, September 2 (2), 7, 9, 14, 19, 20, and 26, October 18, 20, and 27, November 2, 8, 9, 10 (2), 16 (2), and 22, and December 2, 6, 7, 12, 19, and 29, 2011, and January 10, 11, 19, and 24, February 7, March 30 (2), April 2, 27, and 30, May 9 and 30, June 4 and 27, July 17, August 6 and 31, October 26, November 21, and December 12, 2012, and January 30, February 4 and 28, May 13, July 11 and 16, August 7, September 3, 5, 6, 9, and 17, October 4, 10, 16 (2), 18, 22, and 25, November 4, 5, and 21, and December 6, 18, 24, 26, and 31, 2013. We also acknowledge receipt of your email dated January 7, 2014, which includes the agreed-upon labeling.

The July 11, 2013, submission constituted a complete response to our January 17, 2012, action letter.

This new drug application provides for the use of Farxiga (dapagliflozin) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (package insert and Medication Guide). 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*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels submitted on December 24, 2013, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 202293**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 through 9 years because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group **and** is not likely to be used in a substantial number of pediatric patients in this group.

We are deferring submission of your pediatric studies for ages 10 to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

2121-1 Complete a randomized, multicenter, parallel, single-dose study to explore the pharmacokinetics (PK) and pharmacodynamics (PD) of dapagliflozin in children, 10 to 17 years of age with type 2 diabetes mellitus (T2DM) receiving one of the three dose levels of dapagliflozin over the range of 2.5 to 10 mg. At least 30% of randomized subjects in each dose group will be 10 - 15 years of age.

Final Protocol Submission:	April 2012
Study Completion:	August 2014
Final Report Submission:	February 2015

2121-2 A 26-week randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of dapagliflozin for the treatment of pediatric subjects ages 10 to <18 years of age with type 2 diabetes mellitus (T2DM), as add-on to metformin or as monotherapy, followed by a 26-week double-blind, placebo- or active-controlled extension period (Week 26 to Week 52). At least 30% of randomized subjects will be 10 to 14 years of age and at least one-third and not more than two-thirds of subjects in both age subsets (10 to 14 years and 15 to <18 years) will be female. Secondary safety endpoints should include the effect of dapagliflozin on mineral and bone metabolism, and the effect of dapagliflozin on growth.

Final Protocol Submission:	August 2015
Study Completion:	February 2020
Final Report Submission:	August 2020

Submit the protocol(s) to your IND 068652, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess signals of serious risks of bladder cancers, serious hepatic abnormalities and adverse pregnancy outcomes in patients treated with Farxiga (dapagliflozin).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2121-3 Conduct a study to evaluate dapagliflozin in an orthotopic rodent bladder tumor promotion model.

The timetable you submitted on December 20, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	November 2014
Study Completion:	November 2015
Final Report Submission:	August 2016

2121-4 An assessment and analysis of all foreign and domestic spontaneous reports of serious hepatic abnormalities and pregnancy outcomes in patients treated with dapagliflozin. The enhanced pharmacovigilance study should continue for 5 years.

The timetable you submitted on December 20, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	September 2014
Interim Report Submissions:	March 2015
	March 2016
	March 2017
	March 2018
	March 2019
Study Completion:	September 2019
Final Report Submission:	March 2020

Finally, we have determined that only a clinical trial (rather than an observational study) will be sufficient to assess a signal of a serious risk of bladder cancer in patients treated with Farxiga (dapagliflozin). Furthermore, there have been signals of a serious risk of cardiovascular events with some medications developed for the treatment of type 2 diabetes mellitus and available data have not definitively excluded the potential for this serious risk with Farxiga (dapagliflozin). As such, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of major adverse cardiovascular events with antidiabetic medications, including Farxiga (dapagliflozin).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

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

The timetable you submitted on December 20, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	submitted May 9, 2013
Trial Completion:	June 2019
Final Report Submission:	June 2020

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%.

The timetable you submitted on December 20, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	January 2015
Trial Completion:	June 2024
Final Report Submission:	December 2024

Submit the protocol(s) to your IND 068652, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

EXPIRY DATING PERIOD

A 24-month expiry dating period is granted for Farxiga (dapagliflozin) tablets when stored at 25°C (77°F) with excursions permitted from 15° to 30°C (59° to 86 °F).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new

biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Abolade (Bola) Adeolu, Regulatory Project Manager, at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, MD, MPH
Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

Enclosures:
Package Insert
Medication Guide
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CURTIS J ROSEBRAUGH
01/08/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 202293/S-017
NDA 205649/S-010
NDA 209091/S-003

SUPPLEMENT APPROVAL

AstraZeneca AB
Attention: Sally Walsh and Ajay Parashar, B.Pharm., M.S., M.D.D., RAC
Director, Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Walsh and Mr. Parashar:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received October 12, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Farxiga (dapagliflozin) tablets, Xigduo XR (dapagliflozin and metformin HCl extended-release) tablets, and Qtern (dapagliflozin and saxagliptin) tablets.

We also refer to our letter dated August 29, 2018, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for the sodium-glucose cotransporter-2 (SGLT-2) inhibitors drug class, of which, Farxiga, Xigduo XR, and Qtern are members. This information pertains to the risk of necrotizing fasciitis of the perineum (also known as Fournier's gangrene).

These supplemental new drug applications provide for revisions to the labeling for Farxiga, Xigduo XR, and Qtern consistent with our August 29, 2018, Safety Labeling Change Notification letter, and the comments sent to you in our October 5, 17, and 18, 2018, correspondence.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revisions listed below.

The pagination has been revised so that the Qtern and Xigduo XR Medication Guide page numbers begin with page number 1.

WAIVER OF HIGHLIGHTS SECTION

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the prescribing information, Medication Guide), with the addition of any labeling 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 titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

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 MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, 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.

Because none of these criteria apply to your application, you are exempt from this requirement.

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 (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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 http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). We also request that you submit all reports (foreign and domestic) of Fournier's gangrene, regardless of labeling status, as 15-day expedited safety reports for a period of ten years from the date of this letter.

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

Sincerely,

{See appended electronic signature page}

William Chong, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Farxiga Prescribing Information
Farxiga Medication Guide
Xigduo XR Prescribing Information
Xigduo XR Medication Guide
Qtern Prescribing Information
Qtern Medication Guide

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/

WILLIAM H CHONG
10/26/2018