



NDA 205649/S-029

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SUPPLEMENT APPROVAL

AstraZeneca AB
C/O: AstraZeneca Pharmaceuticals LP
Attention: Elizabeth Yimam, PharmD
Regulatory Affairs Director
One MedImmune Way
Gaithersburg, MD 20878

Dear Dr. Yimam:

Please refer to your supplemental new drug applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xigduo XR (dapagliflozin and metformin hydrochloride extended-release) tablets.

We also refer to our letter dated March 31, 2026, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we have determined should be included in the labeling for metformin-containing products. This information pertains to the risk of lactic acidosis in patients with mitochondrial diseases, such as mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome and maternally inherited diabetes and deafness (MIDD), who were taking metformin products.

Supplement S-029, dated and received April 29, 2026, and your amendments, provides for revisions to the labeling for Xigduo XR, consistent with our March 31, 2026, letter and May 22, June 24, and July 10, 2026, email correspondences. The following additional edits were made during supplement review:

1. Added Section 2.7 (*Recommendations Regarding Missed Dose*) for consistency with information provided in Section 17 (*Patient Counseling Information*) and other SGLT2 inhibitor class labeling, including dapagliflozin.
2. Revised the title of the Warning and Precaution for Vitamin B₁₂ Deficiency in Section 5.6 (*Vitamin B₁₂ Deficiency*), Section 6 (*Adverse Reactions*) for consistency with the Highlights, Table of Contents and other metformin class labeling.

Supplement S-028, dated and received January 16, 2026, and your amendments, were submitted in response to our October 24, 2025, Supplement Request letter and provide for the following:

- updates to Section 5 *Warnings and Precautions* of the Prescribing Information regarding the risk of Fournier's gangrene in patients without diabetes mellitus,

- the combining of three related genitourinary infections Warnings and Precautions (Urosepsis and Pyelonephritis, Necrotizing Fasciitis of the Perineum, and Genital Mycotic Infections) into a single Warning and Precaution subsection titled, *Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), and Genital Mycotic Infections*, with corresponding changes made to the Highlights section, Table of Contents, Section 6 *Adverse Reactions*, Section 17 *Patient Counseling Information* and the Medication Guide

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.

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.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effectuated" (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 guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

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

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

² 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>.

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 supplemental applications, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.

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.³ Information and Instructions for completing the form can be found at FDA.gov.⁴

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-related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

³ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

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, contact Marisa Petruccelli, Safety Regulatory Project Manager, at (240) 402-6147.

Sincerely,

{See appended electronic signature page}

Monika Houstoun, Pharm.D., M.P.H.
Deputy Director for Safety
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology, Endocrinology,
and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
 - Prescribing Information
 - 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/

MONIKA A HOUSTOUN
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