

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

209803Orig1s000

Trade Name: Steglatro tablets, 5 mg and 15 mg.

Generic or Proper Name: ertugliflozin

Sponsor: Merck Sharp & Dohme Corp.

Approval Date: December 19, 2017

Indication: For the use of Steglatro (ertugliflozin) tablets as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus..

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CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
REMS	
Summary Review	X
Officer/Employee List	X
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	X
Product Quality Review(s)	X
Non-Clinical Review(s)	X
Statistical Review(s)	X
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	X
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	X
Proprietary Name Review(s)	X
Administrative/Correspondence Document(s)	X

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APPLICATION NUMBER:

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APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209803

NDA APPROVAL

Merck Sharp & Dohme Corp.
Attention: Vivian Fuh, M.D., F.A.C.P.
Executive Director, Global Regulatory Affairs
126 E. Lincoln Avenue, P.O. Box 2000
Mail Drop: RY34-B188
Rahway, NJ 07065

Dear Dr. Fuh:

Please refer to your New Drug Application (NDA) dated and received December 19, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Steglatro (ertugliflozin) tablets, 5 mg and 15 mg.

This new drug application provides for the use of Steglatro (ertugliflozin) tablets 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, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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, except with the revisions indicated, the enclosed labeling (text for the prescribing information 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 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 titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 209803.**” Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for ertugliflozin was not referred to an FDA advisory committee because this drug is not the first in its class.

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 (inclusive) because necessary studies are impossible or highly impracticable. This is because there are too few children in this age range with type 2 diabetes mellitus to study.

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

Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. This required study is listed below.

- | | |
|--------|--|
| 3311-1 | Conduct a 24-week, randomized, double-blind, placebo-controlled, parallel group study of the safety, efficacy, and pharmacokinetics (PK) of ertugliflozin as add-on to metformin background therapy for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years (inclusive), followed by a 30-week double-blind, controlled extension. Patients will be randomized to receive one of two doses of ertugliflozin or placebo once daily. The ertugliflozin doses will be determined using a population PK model derived from the Phase 3 program (in |
|--------|--|

adult subjects) for ertugliflozin. As part of the pediatric study, sparse blood samples for population PK and exposures-response analysis will be collected. An interim analysis of the PK data will be performed during this study to confirm acceptable exposure to ertugliflozin with the selected doses.

Final Protocol Submission: October 2018
Study Completion: March 2026
Final Report Submission: September 2026

Submit the protocol to your IND 106447, with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study 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 a serious risk of major adverse cardiovascular events (MACE) with Steglatro (ertugliflozin). There have been signals of a serious risk of cardiovascular events with some other medications developed for the treatment of type 2 diabetes mellitus and available data have not definitively excluded the potential for this serious risk with Steglatro (ertugliflozin).
- Assess signals of the serious risks of amputations, ketoacidosis, complicated genital infections, complicated urinary tract infections, fractures, pancreatitis, serious hypersensitivity events, malignancies, and worsening renal function.

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.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these serious risks.

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

- 3311-2 Conduct a randomized, double blind, placebo-controlled trial evaluating the effect of ertugliflozin on the incidence of major adverse cardiovascular events (MACE) in subjects 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 ertugliflozin to that observed in the placebo group is less than 1.3. This trial must also assess pregnancy outcomes and the following adverse events: amputations, ketoacidosis, complicated genital infections, complicated urinary tract infections, fractures, pancreatitis, serious hypersensitivity events, and malignancies. The estimated glomerular filtration rate (eGFR) should also be monitored over time to assess effects on renal function.

The timetable you submitted on November 21, 2017, states that you will conduct this trial according to the following schedule:

Trial Completion:	October 2019
Final Report Submission:	December 2020

Submit clinical protocols to your IND 106447 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports 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.

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, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
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>).

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).

We request that for a period of 5 years from the U.S. approval date, you submit all cases of ketoacidosis reported with Steglatro (ertugliflozin) tablets as 15-day Alert reports (as described under 21 CFR 314.80(c)(1)), and that you provide detailed analyses of events of ketoacidosis reported from clinical study and post-marketing reports in your periodic safety report (i.e., the Periodic Adverse Drug Experience Report [PADER] required under 21 CFR 314.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format). These analyses should show cumulative data relative to the date of approval of Steglatro (ertugliflozin) tablets as well as relative to prior periodic safety reports. Medical literature reviews for case reports/case series of ketoacidosis reported with Steglatro (ertugliflozin) tablets should also be provided in the periodic safety report.

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 Liz Godwin, Regulatory Project Manager, at (240) 402-3438.

Sincerely,

{See appended electronic signature page}

Mary T. Thanh Hai, M.D.
Deputy Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

Enclosures:

Content of Labeling
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/

MARY T THANH HAI
12/19/2017