



NDA 204629

NDA APPROVAL

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Daniel T. Coleman, Ph.D.
Sr. Associate Director; Drug Regulatory Affairs
900 Ridgebury Road; P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA) dated and received March 5, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Jardiance (empagliflozin) tablets, 10 mg and 25 mg.

We acknowledge receipt of your amendments dated April 12, 24, and 25, May 1, 3, and 7, June 3, 17, 18, and 27, July 3, 19, and 30, August 9, 14, 15, and 16, September 9 and 23, October 1, 2, 11, 14, 15, 29, and 30, November 1, 8, and 19, and December 20, 2013, and February 5 and 28, March 17, June 3, 5, and 18, and July 3 (2), 23, and 31, 2014.

The June 3, 2014, submission constituted a complete response to our March 4, 2014, action letter.

This new drug application provides for the use of Jardiance (empagliflozin) tablets, 10 mg and 25 mg 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 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 (text for the package insert and text for the patient package insert). 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 *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 204629.**” 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.

ADVISORY COMMITTEE

Your application for empagliflozin tablets was not referred to an FDA advisory committee because this drug is not the first in its class and the safety profile is similar to that of other drugs approved for this indication.

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 studies for ages 10 to 17 years (inclusive) 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.

2755-1 A single-dose pharmacokinetic and pharmacodynamics trial of empagliflozin in pediatric patients 10 to 17 years (inclusive) with type 2 diabetes mellitus.

Study Completion: June 2015
Final Report Submission: December 2015

2755-2 A 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of empagliflozin for the treatment of pediatric patients 10 to 17 years (inclusive) with type 2 diabetes mellitus as an add-on to metformin, followed by a 28-week double-blind, placebo- or active-controlled extension period. The efficacy and safety study should have at least 30% of randomized subjects 10 to 14 years (inclusive) of age and at least one-third (but not more than two-thirds) of subjects in both age subsets (10 to 14 years [inclusive] and 15 to 17 [inclusive]) will be female. Secondary safety endpoints should include the effect of empagliflozin on mineral and bone metabolism, and the effect of empagliflozin on growth. This trial should not be initiated until after the data from the juvenile animal study have been submitted to and reviewed by the Agency.

Final Protocol Submission: November 2015
Study Completion: February 2019
Final Report Submission: August 2019

2755-3 A study to evaluate empagliflozin toxicity in juvenile rats.

Study Completion: November 2014
Final Report Submission: May 2015

Submit the protocol to your IND 102145, 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.

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 Jardiance (empagliflozin).

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 a signal of a serious risk of major adverse cardiovascular events with Jardiance (empagliflozin).

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 this serious risk.

Finally, 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 Jardiance (empagliflozin), as well as signals of serious risks of liver toxicity, bone fractures, nephrotoxicity/acute kidney injury, breast cancer, bladder cancer, lung cancer, melanoma, complicated genital infections, complicated urinary tract infections/pyelonephritis/urosepsis, serious events related to hypovolemia and serious hypersensitivity reactions, which may potentially be long-term effects of Jardiance (empagliflozin).

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

- 2755-4 A randomized, double-blind, placebo-controlled trial evaluating the effect of empagliflozin 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 empagliflozin to that observed in the placebo group is less than 1.3. The long-term effects of empagliflozin on the incidence of liver toxicity, bone fractures, nephrotoxicity/acute kidney injury, breast cancer, bladder cancer, lung cancer, melanoma, complicated genital infections, complicated urinary tract infections/pyelonephritis/urosepsis, serious events related to hypovolemia and serious hypersensitivity reactions should also be assessed. Estimated glomerular filtration rate (eGFR) should also be monitored over time to assess for worsening renal function.

The timetable you submitted by email on July 9, 2014, states that you will conduct this trial according to the following schedule:

Trial Completion:	June 2015
Final Report Submission:	December 2015

Submit the protocol(s) to your IND 102145, 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 36-month expiry dating period is granted for Jardiance (empagliflozin) tablets when stored at 25°C (77°F); 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 Patricia Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
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/

CURTIS J ROSEBRAUGH
08/01/2014