NDA 216951/Original 1

NDA APPROVAL

GlaxoSmithKline Intellectual Property (No. 2) Limited England
Attention: Susan Nolt
Associate Director, Global Regulatory Affairs
1250 S Collegeville Road, UP4000
Collegeville, PA 19426

Dear Ms. Nolt:

Please refer to your new drug application (NDA) dated and received February 1, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Jesduvroq (daprodustat) tablets.

NDA 216951 provides for the use of Jesduvroq (daprodustat) tablets for the following indications (b) (4)

- NDA 216951/Original 1 – for the treatment of anemia due to chronic kidney disease in adults who have been receiving dialysis for at least four months.
- (b) (4)

The subject of this action letter is NDA 216951/Original 1. (b) (4)

APPROVAL & LABELING

We have completed our review of NDA 216951/Original 1, as amended. It is approved for the treatment of anemia due to chronic kidney disease in adults who have been receiving dialysis for at least four months, 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) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

CONTAINER LABELING

Submit final printed container labeling that are identical to the enclosed container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Container Labeling for Approved NDA 216951/Original 1**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Jesduvroq (daprodustat) tablets shall be 36 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F).

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 deferring submission of your pediatric study until February 2030, because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act/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)(4)(C) of the Federal Food, Drug, and Cosmetic Act/FDCA. The required study is listed below.

[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.

4400-1 Conduct a trial to evaluate the pharmacokinetics, pharmacodynamics and safety of Jesduvroq for the treatment of anemia associated with chronic kidney disease in children and adolescents aged 3 months to under 18 years requiring dialysis. Submit datasets at the time of the final clinical study report submission.

Study Completion:	08/2029
Final Report Submission:	02/2030

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol to your IND 101291, with a cross-reference letter to this NDA. Reports of this required pediatric postmarketing study must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. 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 Federal Food, Drug, and Cosmetic Act (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 a known serious risk of major adverse cardiovascular events (MACE), thrombotic vascular events, hospitalization for heart failure, and serious gastrointestinal bleeding; a signal of a serious risk of malignancy and eye disorders (proliferative retinopathy, macular edema, choroidal neovascularization); and to identify an unexpected serious risk of hepatic injury, pregnancy and maternal complications, fetal and neonatal adverse effects, and adverse infant outcomes related to the use of Jesduvroq in adults with dialysis dependent chronic kidney disease.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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

4400-2 Conduct a prospective observational study in the United States to characterize the long-term safety (at least 5 years follow up) of Jesduvroq in adults with dialysis-dependent chronic kidney disease treated with the approved dosing regimen of Jesduvroq versus an ESA comparator arm. Specific safety outcomes of interest include: the risk of major adverse cardiovascular events (MACE) defined as all-cause mortality, non-fatal myocardial infarction and non-fatal stroke; thrombotic vascular events to include vascular access thrombosis; hospitalization for heart failure; serious gastrointestinal bleeds, eye disorders (proliferative retinopathy, macular edema, choroidal neovascularization), and hepatic injury. The study population should include adults previously treated with erythropoiesis-stimulating agents (ESAs) and adults naïve to ESAs. The effect of baseline and maximum achieved hemoglobin on the specified safety outcomes should be evaluated.

The timetable you submitted on January 30, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	08/2023
Final Protocol Submission:	02/2024
Interim Report Submission:	07/2028
Study Completion:	07/2031
Final Report Submission:	07/2032

Submit an integrated safety dataset and patient level data including Jesduvroq dosing, treatment-emergent serious adverse events (SAEs), adverse events leading to treatment discontinuation, and outcomes of SAEs with your final report.

4400-3 Conduct an observational study (at least 5 years follow up) to assess the risk for malignancy (hematological and non-hematological) in adults with dialysis-dependent chronic kidney disease with anemia treated with Jesduvroq versus an ESA comparator arm. The study should include an assessment of primary malignancies among adults with no cancer history (including assessment by type and location), and the impact of Jesduvroq

on progression-free survival, and overall survival in adults with prior cancers.

The timetable you submitted on January 30, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2024
Final Protocol Submission:	06/2025
Study Completion:	10/2031
Final Report Submission:	10/2032

4400-4 Conduct a worldwide descriptive study to collect prospective and retrospective data on women exposed to Jesduvroq during pregnancy to assess the risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Assess infant outcomes through at least the first year of life. The minimum number of patients will be specified in the protocol.

The timetable you submitted on January 30, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	08/2023
Final Protocol Submission:	02/2024
Interim Report Submission:	09/2027
Study Completion:	08/2029
Final Report Submission:	09/2030

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit clinical protocol(s) to your IND 101291 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and 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).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format – Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[5]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

REPORTING REQUIREMENTS

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

REQUESTED PHARMACOVIGILANCE

We request that you submit a summary and analyses of all serious adverse events of gastrointestinal erosion and hypertensive crisis associated with the use of Jesduvroq in the narrative portion of your periodic adverse drug experience report (PADER) required

[5]. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

under 21 CFR 314.80(c)(2), quarterly during the first three years post-approval and annually thereafter, through the 5th year following the initial U.S. approval date.

The summary analyses should include an assessment of all new information obtained during the reporting interval and cumulatively since initial U.S. approval related to these adverse events (i.e., gastrointestinal erosion and hypertensive crisis) with the aim of further characterizing these risks (e.g., intended use of Jesduvroq, temporal association, action taken, outcome, de-challenge/re-challenge, confounders, underlying risk factors, use in unapproved populations such as non-dialysis-dependent patients, and assessment of causality).

We also request that, in the narrative portion of your annual PADER, you submit annual reports of Jesduvroq utilization rates, including use in the non-dialysis dependent population and among females of reproductive potential (i.e., females aged 15 to 50 years) calculated cumulatively from the initial U.S. approval date annually through the 5th year following the initial U.S. approval date.

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, contact Caden Brennen, Safety Regulatory Project Manager at 301-796-6591 or at Caden.Brennen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, MD, MMSc
Director
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

- Container Labeling

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/

HYLTON V JOFFE
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