BLA 761234

BLA APPROVAL

Bristol-Myers Squibb Company
Attention: Andro Shenouda, PharmD
Director, Global Regulatory Strategy Lead - Oncology
P.O. Box 5326
Princeton, NJ 08543

Dear Dr. Shenouda:

Please refer to your biologics license application (BLA) dated July 19, 2021, and your amendments, submitted under section 351(a) of the Public Health Service Act for Opdualag (nivolumab and relatlimab-rmbw) solution for intravenous infusion.

LICENSING

We have approved your BLA for Opdualag (nivolumab and relatlimab-rmbw) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Opdualag under your existing Department of Health and Human Services U.S. License No. 1713. Opdualag is indicated for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture nivolumab and relatlimab drug substances at Bristol-Myers Squibb Company in Devens, MA. The final formulated drug product will be manufactured, filled, labeled, and packaged at Catalent Indiana LLC, Bloomington, IN. You may label your product with the proprietary name, Opdualag, and market it as 240 mg of nivolumab and 80 mg of relatlimab per 20 mL in a single-dose vial.

DATING PERIOD

The dating period for Opdualag shall be 36 months from the date of manufacture when stored at 2°C to 8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substances shall be 36 months from the date of manufacture when stored at -60 ± 10°C.

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substances under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Opdualag to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Opdualag, or in the manufacturing facilities, will require the submission of information to your BLA for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

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.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format.[1] Content of labeling must be identical to 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 (October 2009)*.[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

We acknowledge your March 17, 2022, submission containing final printed carton and container labeling.

ADVISORY COMMITTEE

Your application for Opdualag was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for a drug/biologic of this class or in the intended population for which external input was necessary.

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[1] See 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 at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 11 years because necessary studies are impossible or highly impracticable. This is due to the rarity of metastatic melanoma in pediatric populations less than 12 years of age. In addition, due to differences in the biology of melanoma in populations less than 12 years of age, extrapolation of results from studies in adults and adolescents is not appropriate.

We are deferring submission of your pediatric studies for ages 12 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 Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of this postmarketing studies must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

4222-1 Conduct Study CA224069 (A Phase 1/2 Study of the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of Relatlimab Plus Nivolumab in Pediatric and Young Adult Participants with Recurrent or Refractory Classical Hodgkin Lymphoma and Non-Hodgkin Lymphoma) to further characterize the safety, pharmacokinetics, pharmacodynamics and efficacy of relatlimab in combination with nivolumab in participants 0 to <30 years of age with relapsed or refractory Hodgkin lymphoma and an exploratory assessment in Non-Hodgkin lymphoma. Include at least 6 patients 0-11 years old and 6 patients 12-17 years old.

Final Protocol Submission:	02/2021 (completed)
Study Completion:	03/2028
Final Report Submission:	09/2028

4222-2 Conduct a study, Study 2 (Modeling and Simulation/Extrapolation Study), to further characterize the pharmacokinetics and evaluate the dose regimen of nivolumab and relatlimab combination therapy in pediatric lymphoma.

Study Completion:	01/2029
Final Report Submission:	02/2029

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(s) to your IND 136382 with a cross-reference letter to this BLA. Reports of these required pediatric postmarketing studies must be submitted as a BLA or as a supplement to your approved BLA 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 COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4222-3 Re-evaluate the lot release and stability acceptance criteria for the potency (cell-based) - relatlimab test for relatlimab drug substance and Opdualag drug product after the manufacture of 30 drug product lots with the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final report.

The timetable you submitted on January 7, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/2027

4222-4 Develop an endotoxin release method for the drug product which mitigates the low endotoxin recovery (LER) effect and to submit the results of the LER study performed at room temperature with 3 lots of drug product, the endotoxin method qualification with 3 lots of drug product and the updated endotoxin method. The updated endotoxin method will replace the rabbit pyrogen testing upon approval of the supplement.

The timetable you submitted on January 18, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/2022

[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.

Submit clinical protocols to your IND 136382 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

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*.[4]

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.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80).

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

POST APPROVAL FEEDBACK MEETING

New biological products 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 Christina Leach, Regulatory Health Project Manager, at 240-402-6571 or christina.leach@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Marc R. Theoret, MD
Supervisory Associate Director (Acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Carton and 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/

MARC R THEORET
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