CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

209936Orig1s000

Trade Name:	ALIQOPA™ for injection, 60mg
Generic or Proper Name:	copanlisib
Sponsor:	Bayer HealthCare Pharmaceuticals Inc.
Approval Date:	September 14, 2017
Indication:	For the treatment of adult patients with relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies.

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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 209936

ACCELERATED APPROVAL

Bayer HealthCare Pharmaceuticals Inc.
Attention: Anita K. Murthy, PharmD
Deputy Director Oncology 2
100 Bayer Blvd.
PO Box 915
Whippany, NJ 07981-0915

Dear Dr. Murthy:

Please refer to your New Drug Application (NDA) dated March 16, 2017, received March 16, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ALIQOPA™ (copanlisib) for injection, 60mg.

We also refer to our approval letter dated September 14, 2017 which contained the following error: PMR 3273-2 was worded incorrectly.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain September 14, 2017, the date of the original approval letter.

This new drug application provides for the use of ALIQOPA™ (copanlisib) for injection, 60mg, for the treatment of adult patients with relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

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, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" 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 container labels that are identical to the carton and immediate container labels submitted on August 3, 2017 (carton) and August 2, 2017 (container), 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 209936**." Approval of this submission by FDA is not required before the labeling is used.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Rosa Lee-Alonzo
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3211
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

ADVISORY COMMITTEE

Your application for ALIQOPA was not referred to an FDA advisory committee because the application did not raise significant efficacy or safety issues for the proposed indication.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated September 13, 2017. This requirement, along with required completion dates, is listed below.

PMR 3273-1 In order to verify the clinical benefit of Aliqopa (copanlisib), submit the complete final clinical report and datasets from a randomized, double-blind, placebo-controlled trial of Aliqopa in combination with immunochemotherapy versus immunochemotherapy alone in patients with relapsed follicular lymphoma, marginal zone lymphoma, small lymphocytic lymphoma, or lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia. The primary endpoint is progression-free survival. Enroll approximately 520 patients.

Enrollment Completed:	03/2020
Trial Completion:	03/2022
Final Report Submission:	09/2022

Submit clinical protocols to your IND 115916 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this NDA. 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 entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

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 signals of a serious risk of infections, hypertension, hyperglycemia, pneumonitis, neutropenia, gastrointestinal disorders, or severe cutaneous reactions, or to identify an unexpected serious risk of QT prolongation.

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.

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

PMR 3273-2 Characterize the long-term safety of Aliqopa (copanlisib) as monotherapy and in combination with immunotherapy and immunochemotherapy, along with safety-related concomitant medication use, in patients with hematological malignancies. Submit annual interim and final reports and integrated analysis datasets, from a prospective cohort of at least 400 patients for at least 5 consecutive years. Evaluations will include analysis of new safety concerns and increased frequency or severity of known safety concerns in the subjects exposed to copanlisib. Reports to be submitted from all sponsored studies, including ongoing studies and pharmacovigilance data, will include:

- Integrated analyses of all completed studies that includes exposure,
- Summary of safety data from individual enrolling studies that are open label,
- Serious adverse event data from safety databases for all studies, and
- Outcome of data monitoring committee decisions for blinded trials.

The timetable you submitted on September 13, 2017 states that you will conduct this trial according to the following schedule:

Statistical Analysis Plan Submission:	10/2017
Interim Report Submission (Year 1):	07/2018
Interim Report Submission (Year 2):	07/2019
Interim Report Submission (Year 3):	07/2020
Interim Report Submission (Year 4):	07/2021
Interim Report Submission (Year 5):	07/2022
Final Report Submission:	07/2023

PMR 3273-3 Complete and submit results of a study to determine the effect of Aliqopa on QT/QTc interval in subjects with advanced solid tumors and non-Hodgkin's lymphoma. The trial should be designed and conducted in accordance with the

FDA Guidance for Industry entitled, "*E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.*"

The timetable you submitted on September 13, 2017 states that you will conduct this trial according to the following schedule:

Enrollment Completed:	03/2018
Trial Completion:	12/2018
Final Report Submission:	06/2019

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of serious risks with long term use or identify an unexpected serious risk in patients with hepatic impairment, in patients with renal impairment, or from interactions with certain other drugs.

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

PMR 3273-4 In order to characterize the safety of copanlisib from a randomized controlled trial, submit the complete final clinical report and datasets from a randomized, double-blind, placebo-controlled trial of Aliqopa (copanlisib) in combination with rituximab in patients with relapsed follicular lymphoma, marginal zone lymphoma, small lymphocytic lymphoma, or lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia. Enroll at least 400 patients.

The timetable you submitted on September 13, 2017 states that you will conduct this trial according to the following schedule:

Enrollment Completed:	12/2019
Trial Completion:	12/2020
Final Report Submission:	06/2021

PMR 3273-5 Amend and complete your ongoing clinical pharmacokinetic trial to determine an appropriate safe dose of Aliqopa (copanlisib) in subjects with moderate and severe hepatic impairment and in subjects with severe renal impairment. This trial should be designed and conducted in accordance with the FDA Guidance for Industry entitled, "*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*" and the FDA Guidance for Industry entitled, "*Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*." Interim report will include subjects with moderate hepatic impairment and severe renal impairment. Final study report will include the subjects with severe hepatic impairment.

The timetable you submitted on September 13, 2017 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	12/2017
Interim Report Submission:	07/2019
Trial Completion:	12/2020
Final Report Submission:	07/2021

PMR 3273-6 Conduct a clinical pharmacokinetic (PK) trial to evaluate the effect of Aliqopa (copanlisib) on the pharmacokinetics of metformin (a sensitive MATE2-K substrate) to address the potential for PK and pharmacodynamic (such as serum lactate) interaction. This trial should be designed and conducted in accordance with the FDA Guidance for Industry entitled, "*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*."

The timetable you submitted on September 13, 2017 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	05/2018
Final Protocol Submission:	08/2018
Trial Completion:	11/2019
Final Report Submission:	05/2020

Submit clinical protocol(s) to your IND 115916 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).**

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

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).
Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products 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).

REPORTING REQUIREMENTS

We remind you that you must comply with the 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 Rosa Lee-Alonzo, Regulatory Project Manager, at (301) 348-3004.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, MD
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD PAZDUR
09/14/2017