CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

215039Orig1s000

Trade Name:	Vijoice (alpelisib) tablets
Generic or Proper Name:	alpelisib
Sponsor:	Novartis Pharmaceuticals Corporation
Approval Date:	April 5, 2022
Indication:	Vijoice (alpelisib) tablets are indicated for the treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PIK3CA-Related Overgrowth Spectrum (PROS) who require systemic therapy.

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 215039

CORRECTED ACCELERATED APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Nupur Mittal, PharmD
Sr. Global Program Regulatory Manager
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Mittal:

Please refer to your new drug application (NDA) dated October 6, 2021, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vijoice (alpelisib) tablets, 50mg, 125 mg, 200 mg.

We also refer to our approval letter dated April 5, 2022, which contained the following error(s): inclusion of the phrase, [redacted] (b) (4) in Section 14, CLINICAL STUDIES.

This corrected action letter incorporates the correction of the error. The effective action date will remain April 5, 2022, the date of the original letter.

This NDA provides for the use of Vijoice (alpelisib) tablets for the treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PIK3CA-Related Overgrowth Spectrum (PROS) who require systemic therapy.

This indication is approved under accelerated approval based on response rate and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

APPROVAL & LABELING

We have completed our review of this application. 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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, 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.*[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on March 21, 2022, 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 titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 215039**." 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 VIJOICE® (alpelisib) tablets shall be 36 months from the date of manufacture when stored at USP controlled room temperature 20°-25°C (68°-77°F); excursions permitted between 15°C and 30°C (59°-86°F).

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 April 5, 2022. This requirement, along with required completion dates, is listed below.

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

4260-1 Conduct a multiregional clinical trial to verify and describe the clinical benefit of alpelisib film-coated tablets, through more precise estimation of confirmed objective response rate and mature response duration per blinded independent review, in adult and pediatric patients 2 years of age and older with PIK3CA-Related Overgrowth Spectrum (PROS), including those with severe manifestations of PROS. Responding patients will be followed for at least 36 months from the onset of response, or until disease progression, whichever comes first. Evaluate a sufficient number of patients to characterize response rate and durability of response by PIK3CA mutation type (frequent hotspot mutations vs. other less frequent mutations), PROS subtype, and age (2 – 5 years, 6 – 11 years, 12 – 17 years, ≥ 18 years). Include patient narratives and additional outcomes measures (such as clinical outcomes assessments) to support the assessment of clinical benefit in the study report. The distribution of race and ethnicity in the patient population studied should be sufficiently reflective of the U.S. patient population to support generalizability of results to U.S. patients with PROS.

Draft Protocol Submission:	07/2022
Final Protocol and Analysis Plan Submission:	10/2022
Trial Completion:	02/2027
Final Report Submission:	08/2027

Submit clinical protocols to your IND 143387 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 subjects 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 (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.

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 identify an unexpected serious risk of long-term adverse effects of alpelisib on growth and development in pediatric patients; to assess known serious risks of severe hypersensitivity, severe cutaneous adverse reactions and pneumonitis in patients with PROS; and to identify an unexpected serious risk of carcinogenicity with the chronic use of alpelisib.

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.

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

4260-2 Conduct comprehensive safety analyses from clinical studies that further characterize the potential serious risk of long-term adverse effects of alpelisib on growth and development, including an assessment of growth plate abnormalities and development of teeth in a sufficient number of pediatric patients. Monitor patients for growth and development using age-appropriate screening tools. Include evaluations of growth as measured by height, weight, height velocity and height standard deviation scores, age at adrenarche if applicable, age at menarche if applicable (females) and Tanner stage. Monitor patients until discontinuation of study treatment or a minimum of 5 years from start of treatment, whichever occurs first.

The timetable you submitted on April 5, 2022, states that you will conduct this study according to the following schedule:

Final Protocol Submission (Analysis Plan):	05/2023
Study Completion:	03/2030
Final Report Submission:	09/2030

Submit the datasets with the final report.

4260-3 Conduct comprehensive safety analyses from ongoing trials to further assess the serious risks of alpelisib, including severe hypersensitivity, severe cutaneous adverse reactions and pneumonitis, in patients with PROS over a sufficient period of follow-up time to characterize these risks. The analysis should include appropriate monitoring and risk mitigation strategies.

The timetable you submitted on April 5, 2022, states that you will conduct this study according to the following schedule:

Final Protocol Submission (Analysis Plan):	05/2023
Study Completion:	03/2030
Final Report Submission:	09/2030

4260-4 Conduct a carcinogenicity study in rats to evaluate the potential for carcinogenicity. A carcinogenicity protocol for a Special Protocol Assessment (SPA) was submitted and reviewed by the FDA prior to initiating the study.

The timetable you submitted on April 5, 2022, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2022
Study Completion:	06/2023
Final Report Submission:	05/2024

4260-5 Conduct a carcinogenicity study in mice to evaluate the potential for carcinogenicity. Submit a carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

The timetable you submitted on April 5, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	05/2025
Final Protocol Submission:	09/2025
Study Completion:	08/2026
Final Report Submission:	07/2027

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 clinical protocol(s) to your IND 143387 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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4260-6 Conduct a study using a higher starting dose of alpelisib (i.e., 125 mg) in addition to the 50 mg once daily starting dose in pediatric patients 6 to 17 years of age to evaluate the pharmacokinetics, safety, and clinical outcomes (including confirmed objective response rate and duration of response) for dose optimization in this patient population.

The timetable you submitted on April 5, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 07/2022

[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.

Final Protocol Submission:	10/2022
Study Completion:	02/2027
Final Report Submission:	08/2027

4260-7 Conduct an analysis from EPIK-P3, an ongoing single-arm study, to further describe the long-term outcomes of patients receiving alpelisib for the treatment of severe manifestations of PROS. Evaluate a sufficient number of patients over a sufficient period of time to better characterize clinical response over time, and include case narratives describing additional patient outcome measures (such as clinical outcomes assessments) to support assessment of benefit of alpelisib in this patient population.

The timetable you submitted on April 5, 2022, states that you will conduct this study according to the following schedule:

Interim Report Submission	09/2026
Study Completion:	03/2028
Final Report Submission:	09/2028

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 143387 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment 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/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

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 Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

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]

[4] https://www.fda.gov/media/128163/download.

REPORTING REQUIREMENTS

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

If you have any questions, call Maritsa Stephenson, PharmD, Regulatory Health Project Manager, at 301-796-1760.

Sincerely,

{See appended electronic signature page}

Julia Beaver, M.D.
Deputy Director (acting),
Office of Oncologic Diseases
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- 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/

JULIA A BEAVER
04/07/2022 10:53:42 AM