CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218466Orig1s000

CLINICAL REVIEW(S)

Clinical Review Memo

Application Type (NDA/BLA)	NDA
Application Number(s)/ Supplement number	NDA 218466, NDA 215039 supplement 2
Received Date	June 29, 2023
PDUFA Goal Date	April 29, 2024
Review Completion Date	April 20, 2024
Division/Office	Division of Oncology 2
Clinical Reviewer	Sonia Singh
Team Leader	Diana Bradford
Associate Director for Labeling	Barbara Scepura
Deputy Division Director	Nicole Drezner
Product: Established Name (Trade name)	Alpelisib (VIJOICE)
Formulation	Granules
Applicant	Novartis
Recommended Regulatory Action	Approval

1. Executive Summary

Alpelisib (VIJOICE) is an oral kinase inhibitor targeting phosphatidylinositol-3-kinase (PI3K) with activity predominantly against PI3K alpha. It is currently approved as film-coated tablets (FCTs) in strengths of 50 mg, 125 and 200 mg for oral use.

The Applicant submitted NDA 218466 (a Type 3 NDA) on June 29, 2023, and NDA 215039/supplement 2, which cross-references NDA 218466, on September 15, 2023 for a new 50 mg granule dosage form that was developed as an alternative to the 50 mg FCT. The indication for the granule is unchanged from that approved for use with the commercial tablet formulation.

The granules can be administered orally, either with the contents of the packet poured directly onto the tongue and swallowed with water, or the granules can be administered in a beverage (water, milk, or apple juice) or soft food (apple sauce or yogurt).

There were no new clinical patient data submitted with this application. The review team determined that based on the overall benefit-risk profile of alpelisib in previously reviewed clinical studies and additional clinical pharmacology studies submitted to NDA 215039, the submitted data meet criteria for approval.

2. Regulatory History

Alpelisib (PIQRAY) was originally approved on May 24, 2019, in combination with fulvestrant for the treatment of postmenopausal women and men with hormone receptor (HR)-positive, HER2-negative, PIK3CA-mutated advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

On April 5, 2022, alpelisib (VIJOICE) was granted accelerated approval 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. The recommended dosage of alpelisib for patients with PROs is as follows: 50 mg taken orally once daily with food for patients 2 to less than 18 years of age, and 250 mg taken orally once daily with food for adult patients.

3. Background and Review of Clinical Data

No additional clinical patient data were submitted in support of this application.

The use of alpelisib 50 mg granules is supported by data from Study CBYL719F12101 (Study F12101), a single-center, randomized, open-label, three-period six-sequence crossover study to evaluate the bioequivalence of the alpelisib granule and FCT dosage forms, both at a single oral dose of 50 mg in healthy adult subjects in the fed state. This study also evaluated the food effect on the alpelisib granule dosage. Refer to the Clinical Pharmacology review team's review dated April 1, 2024, under NDA 218466, for further information.

The overall benefit-risk profile of alpelisib was determined to be favorable during the review of the original NDA 215039, based on previously reviewed clinical studies and additional clinical pharmacology studies. Refer to the original multi-disciplinary review under NDA 215039 (date April 7, 2022) for a description and review of the clinical data in patients with PROS.

4. Labeling changes

The Applicant's proposed label revisions were reviewed and revised by FDA for consistency with 21 Code of Federal Regulations (CFR), labeling guidance and current labeling practices of the Office of Oncologic Diseases. In addition to labeling changes made to reflect the new granule dosage form, the Applicant also proposed minor revisions to align with the latest PIQRAY label which were acceptable. Please refer to the agreed upon label for finalized edits.

The table below summarizes key changes. The italicized text has been newly added to the label. Refer to the Clinical Pharmacology review for additional details regarding label changes.

Table 1: Key Changes to Alpelisib (VIJOICE) Label

Label Section	Applicant Proposal	FDA Revision / Agreed Text
HIGHLIGHTS Product Title	VIJOICE® (alpelisib) (b) (4)	VIJOICE® (alpelisib) oral granules Text revised for consistency with the draft guidance: Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry
HIGLIGHTS Dosage Form	(b) (4)	Oral Granules: 50 mg (3)
HIGHLIGHTS Drug Interactions	•CYP3A4 Inducers: Avoid coadministration of VIJOICE with a strong CYP3A4 inducer. *Consider an alternative concomitant drug with no or minimal potential to induce CYP3A4.* (7.1)	FDA agreed with the proposal.
DOSAGE AND ADMINISTRATION	2.2 (b) (4) The Applicant proposed administration instructions for both tablet and oral granules.	2.2 VIJOICE Dosage Form Overview New section was included to provide details to assist healthcare providers (HCPs) in determining with dosage form to order for their patient. 2.3 VIJOICE Administration Overview New section was included to provide general administration information that applies to both dosage forms. 2.4 VIJOICE Preparation and Administration Instructions New section included to provide specific information for each dosage form.

DRUG INTERACTIONS	CYP3A4 Inducers Avoid coadministration of VIJOICE with strong CYP3A4 inducers *and consider an alternative concomitant drug with no or minimal potential to induce CYP3A4.*	FDA agreed with the proposal
DESCRIPTION	*VIJOICE granules are supplied for oral administration with one strength that contains 50 mg of alpelisib. The granules also contain hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, and sodium starch glycolate.*	FDA agreed with the proposal.
PHARMACOKINETICS	(b) (4)	Text revised for brevity and moved below *Effect of Food*:
		Revised to state: "No clinically relevant differences in alpelisib C_{max} and AUC were observed following administration of a single 50 mg dose of VIJOICE as granules or tablets taken with a LFLC meal."
	Metabolism Alpelisib is primarily metabolized by chemical and enzymatic hydrolysis *to form its metabolite BZG791 and*	Revision for consistency with PIQRAY labeling. FDA agreed with the proposal.

	followed by CYP3A4 mediated hydroxylation.	
	Effect of CYP3A4 Inducers on Alpelisib: Coadministration of repeat doses of rifampin (a strong CYP3A4 inducer) with a single 300 mg dose of alpelisib decreased alpelisib Cmax by 38% and AUC by 57%, respectively. *Coadministration of rifampin with repeat doses of 300 mg alpelisib decreased alpelisib Cmax by 59% and AUC by 74%, respectively.* *Model-Informed Approaches* *Coadministration of repeat doses of ketoconazole (a strong CYP3A4 inhibitor) with a single 300 mg dose of alpelisib is expected to increase alpelisib AUC by 37% or less.* *Coadministration of repeat doses of efavirenz (a moderate CYP3A4 inducer) with a single 300 mg dose of alpelisib is expected to decrease alpelisib AUC by 30% or less.*	Revision for consistency with PIQRAY labeling. FDA agreed with the proposal.
HOW SUPPLIED/STORAGE AND HANDLING	New table proposed: *Table 14: VIJOICE Oral Granules*	FDA agreed with the proposal.
PATIENT COUNSELING INFORMATION	Minor revisions to describe oral granule administration.	FDA agreed with the proposal.

5. Financial Disclosures

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 5		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant) ☒ Not applicable given 0 investigators with disclosable financial interests/arrangements
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant) ☒ Not applicable given 0 investigators with disclosable financial interests/arrangements
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) ☒ Not applicable given 0 investigators with disclosable financial interests/arrangements

6. Recommended Regulatory Action
   The clinical review team recommends approval of NDA 218466 and NDA 215039 supplement 2 as summarized in this review and upon satisfactory review from other FDA disciplines.

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/

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