Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	215039
Target Action Date	April 5, 2022
OSE RCM #	2021-1508;2021-1510
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Associate Director for REMS	Laura Zendel, Pharm.D.
Design and Evaluation	
Review Completion Date	April 01, 2022
Subject	Review to determine if a REMS is necessary
Established Name	Alpelisib
Trade Name	Vijoice
Name of Applicant	Novartis Pharmaceuticals Corp.
Therapeutic Class	Kinase inhibitor
Formulation(s)	50 mg, 125 mg, and 200 mg tablets
Dosing Regimen	The recommended dosage of alpelisib in adult patients is 250 mg orally, once daily. The recommended initial dosage of alpelisib in pediatric patients is 50 mg orally, once daily.

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Vijoice (alpelisib) is necessary to ensure the benefits outweigh its risks. Novartis Pharmaceuticals Corp. submitted a New Drug Application (NDA) 215039 for alpelisib with the proposed indication for the treatment of adult and pediatric patients aged 2 years and older with PIK3CA-Related Overgrowth Spectrum (PROS). Alpelisib was approved by the US Food and Drug Administration (FDA) on May 24, 2019, under the established name of Piqray® (NDA 212526) to be used in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (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. The serious risks associated with the use of alpelisib are severe hypersensitivity reactions, severe cutaneous adverse reactions (SCARs), hyperglycemia, pneumonitis, diarrhea and embryo-fetal toxicity. The Applicant did not submit a REMS or risk management plan with this application.

The Division of Risk Management (DRM) and the Division of Oncology Disease 2 (DO2) have determined that a REMS is not necessary to ensure the benefits of alpelisib outweigh its risks. PROS is a group of rare disorders that cause overgrowth of parts of the body, due to mutations in the *PIK3CA* gene. The severity of PROS is highly variable, ranging from localized overgrowth, for example of a digit, to severe, extensive, and life-threatening overgrowth affecting major vessels and/or critical organs. Currently, there are no FDA-approved therapies for the treatment of PROS. Therefore, there remains a clear medical need to develop new therapies for the treatment of this serious and life-threatening rare disease. Alpelisib appeared efficacious in its primary outcome of response, and its risks can be communicated and managed through labeling. Based on the efficacy and safety information currently available, the clinical reviewer stated that alpelisib shows clinically meaningful benefit and recommends approval of alpelisib using the accelerated approval pathway for the treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PROS, who require systemic therapy. Although not all of the toxicities observed with alpelisib in the oncology setting were observed in the safety population for PROS, if approved, labeling will be similar to the currently approved product, Piqray, including risk messaging in Warnings and Precautions, Patient Counseling Information, and a Patient Package insert will be used to communicate the safety issues and management of toxicities associated with alpelisib. The review team concluded the observed safety profile is acceptable when assessed in the context of the treatment of this rare and serious disease.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a REMS for Vijoice (alpelisib) is necessary to ensure the benefits outweigh its risks. Novartis Pharmaceuticals Corp. submitted a New Drug Application (NDA) 215039 for alpelisib with the proposed indication[1] for the treatment of adult and pediatric patients aged 2 years and older with PIK3CA-Related Overgrowth Spectrum (PROS). This application is under review in the Division of Oncology Disease 2 (DO2). The Applicant did not submit a REMS with this application.

2 Background

2.1 PRODUCT INFORMATION

Alpelisib is a non-new molecular entity (Non-NME) NDA type 505(b)(1) pathway application.[a] Alpelisib was approved by the US Food and Drug Administration (FDA) on May 24, 2019 under the established name of Piqray®[2] (NDA 212526) to be used in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (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. It is an inhibitor of phosphatidylinositol-3-kinase (PI3K) with inhibitory activity predominantly against PI3Kα.[1] Gain-of-function mutations in the gene encoding the catalytic α-subunit of PI3K (PIK3CA) lead to activation of PI3Kα and Akt-signaling, cellular transformation and the generation of tumors in in vitro and in vivo models. Activating mutations in PIK3CA have been found to induce a spectrum of overgrowths and malformations comprising a wide group of clinically recognizable disorders commonly known as PROS. In a mouse model of congenital lipomatosis with overgrowth, vascular malformations, epidermal nevi, and skeletal/scoliosis/spinal abnormalities (CLOVES), a phenotype of PROS, alpelisib inhibition of the PI3K pathway resulted in the prevention and improved phenotypes (e.g., scoliosis, muscle hypertrophy and vessel malformation) and withdrawal of alpelisib resulted in recurrence.[1]

Alpelisib is proposed to be supplied as 50 mg, 125 mg, and 200 mg tablets. The recommended dosage of alpelisib in adult patients is 250 mg orally, once daily, until disease progression or unacceptable toxicity. The recommended initial dosage of alpelisib in pediatric patients is 50 mg orally, once daily, until disease progression or unacceptable toxicity.[b,1] Alpelisib for the treatment of PROS is currently not approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for alpelisib (NDA 215039) relevant to this review:

- 09/11/2019 Investigation New Drug IND 143387 submission for alpelisib received.
- 11/13/2019: Breakthrough Therapy Designation granted
- 11/18/2019: Orphan Drug Designation granted
- 10/06/2021: NDA 215039 submission for alpelisib with the proposed indication for the treatment of adult and pediatric patients aged 2 years and older with PROS, received.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

PROS is a group of rare disorders that cause overgrowth of parts of the body, due to mutations in the *PIK3CA* gene.[3] PROS is considered as a group of rare diseases with diverse phenotypes, including (but not limited to): fibroadipose hyperplasia or overgrowth (FAO), hemihyperplasia multiple lipomatosis (HHML), CLOVES syndrome, macrodactyly, fibroadipose infiltrating lipomatosis/facial infiltrative lipomatosis, megalencephaly–capillary malformation polymicrogyria (MCAP), dysplastic megalencephaly (DMEG), capillary malformation of the lower lip, lymphatic malformation of the face and neck, asymmetry with partial/generalized overgrowth (CLAPO), lipomatosis of nerve (LON),and Klippel-Trenaunay syndrome (KTS).[4,5] Signs and symptoms of PROS depend on the specific disorder present. Depending on the disorder, they can include having a larger-than-normal brain (megalencephaly), low muscle tone (hypotonia), seizures, intellectual disability, changes in the blood vessels, and overgrowth of one area of the body (focal overgrowth) or of multiple areas of the body (segmental overgrowth), with normal growth elsewhere.[6] Since the prevalence of PROS is difficult to estimate because of its rarity, variation in ascertainment, the broad phenotypic spectrum, and the occurrence of atypical or mild phenotypes leading to misdiagnosis, the Applicant compiled data from NIH Genetics Home Reference and Orphanet to assess the prevalence. The estimated prevalence of the following five combined PROS conditions is about 14 per 1,000,000: MCAP syndrome, hemihyperplasia multiple lipomatosis, macrodactyly, fibroadipose hyperplasia, and KTS. Based on the most current US population estimate of 332,582,420 (US Census Bureau, August 2021), the summation results in less than 4,700 patients with PROS in the United States.[7,c] The severity of PROS is highly variable, ranging from localized overgrowth, for example of a digit, to severe, extensive, and life-threatening overgrowth affecting major vessels and/or critical organ.[8,d] PROS may be conceived of as a highly anatomically variable admixture of overgrown tissues, with vasculature (capillaries, veins and lymphatics) and adipose tissue often most dramatically affected macroscopically. Many other tissues and organs, including bone, brain, peripheral nerves, liver, skeletal and cardiac muscle, may also be affected.[8]

3.2 Description of Current Treatment Options

Current treatment relies on supportive care, which is comprised of surgical debulking, amputations, orthopedic procedures to limit growth, and blocking of overgrowth vessels (sclerotherapy, endovascular occlusive procedure). In one study of 35 patients (median age, 7 years), 83% underwent surgical interventions for their overgrowth, many with multiple surgeries including 43% with amputations of affected limbs and or digits.[9]

Sirolimus emerged as a therapeutic option for complex vascular anomalies in 2011.[10] Since then, sirolimus has been described as an effective treatment for KTS, GLA, CLAPO, and has been shown to stabilize disease severity and diminish symptoms in PROS. A recent open-label trial supports sirolimus'

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

ability to modestly reduce tissue growth at overgrown sites. However, this study also reported a significant adverse effect profile with 72% reporting an adverse effect, which included infection (41%), followed by blood or lymphatic disorders (21%), 37% grade 3 or 4, which included neutropenia, interstitial pneumonitis, and sirolimus hypersensitivity syndrome, and 18% withdrawing from treatment.[5,11] There are no FDA-approved therapies for the treatment of PROS.[3,7] Therefore, there remains a clear medical need to develop new therapies for the treatment of this serious and life-threatening rare disease, PROS.

4 Benefit Assessment

The efficacy of alpelisib was evaluated in study EPIK-P1 (NCT04285723), a single arm study in patients 2 years of age and older with PROS who received alpelisib as part of an expanded access program for compassionate use.[1] Eligible patients had clinical manifestations of PROS that were assessed by the treating physician as severe or life-threatening and necessitating systemic treatment and had documented evidence of mutation in the PIK3CA gene as determined by a local laboratory. Patients were enrolled across seven sites in five countries (France, Spain, US, Ireland and Australia). Patients received alpelisib based on age at dosages ranging from 50 mg to 250 mg orally once daily. A total of 37 patients were identified with at least one target lesion identified on imaging performed within 24 weeks prior to receipt of the first dose of alpelisib. The median age of patients was 14 years (range: 2 to 38); 22% of patients were 2 to 5 years, 22% were 6 to 11 years, 27% were 12 to 17 years, and 30% were ≥ 18 years; 57% were female 11% were White and race was not reported for 89%. Ninety-two percent of patients had congenital overgrowth and 8% had early childhood-onset. Patients had heterogeneous manifestations of PROS, including CLOVES (81%), MCAP (8%), KTS (2.7%), Facial Infiltrating Lipomatosis (FIL; 8%), and Other (5%). Five percent (5%) of patients had concurrent manifestations of CLOVES and MCAP.[1]

At the time of this review, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant efficacy information to date for alpelisib. Efficacy was based upon the proportion of patients with radiological response at Week 24 as determined by blinded independent central review (BICR), defined as a ≥ 20% reduction from baseline in the sum of measurable target lesion volume (1 to 3 lesions) confirmed by at least one subsequent imaging assessment, in the absence of a ≥ 20% increase from baseline in any target lesion, progression of non-target lesions, or appearance of a new lesion. An additional efficacy outcome measure was duration of response (DOR), defined as the time from the first documented response to the date of the first documented disease progression or death due to any cause. The efficacy results are summarized in Table 1.[1,7,12,e] The median DOR was not estimable as no events (i.e., progressions or deaths) were observed at the cut-off date.[7] Alpelisib appeared efficacious in its primary outcome of response and the clinical reviewer stated that alpelisib shows clinically meaningful benefit, and recommends approval.[1,7,12] Given the rarity of PROS and lack of an approved or standard systemic treatment, the review team did not consider a randomized trial as necessary to demonstrate efficacy in the population. The review team noted that response rate and DOR are considered early clinical endpoints considered reasonably likely to predict clinical benefit. Additional data, including data on response rate and DOR obtained from a larger study are needed to confirm the clinical benefit in the indicated population.[7]

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition*

Table 12: Efficacy Results at Week 24 in EPIK-P1[1,7,12 ,e]

Efficacy Parameters	Pediatric Patients N = 26	Adult Patients N = 11	All Patients N = 37
Response[a,b]			
Responders, n (%) 95% CI	7 (27) (12, 48)	3 (27) (6, 61)	10 (27) (14, 44)
Duration of response (DOR)			
Median in months (range)	NR (2.8+, 29.7+)	NR (0.9+, 42.9+)	NR (0.9+, 42.9+)
% ≥ 6-months	5 (71)	2 (67)	7 (70)
% ≥ 12-months	5 (71)	1 (33)	6 (60)

Abbreviations: +: censored observation
[a] Confirmed response as determined by independent central radiology review (ICRR).
[b] Patients without any response assessment at Week 24 were considered non-responders.

5 Risk Assessment & Safe-Use Conditions

The safety profile of alpelisib (Piqray) has been characterized during the development of treatment for postmenopausal women, and men, with HR-positive, HER2-negative, advanced/locally advanced or metastatic breast cancer with a PIK3CA mutation under NDA 212526.[13] The pivotal clinical Study BYL719C2301 (SOLAR-1) provided the safety data of treatment combination of alpelisib (Piqray) 300 mg q.d. with fulvestrant 500 mg i.m compared with patients receiving combination of placebo and fulvestrant.[13]

At the time of this review, labeling negotiations were ongoing with the applicant. The following section is a summary of relevant safety information to date for alpelisib. The safety of alpelisib for use in PROS was evaluated in EPIK-P1 (see Section 4: Benefit Assessment). Among patients who received alpelisib, 95% were exposed for 6 months or longer and 79% were exposed for greater than one year.[1] The most common adverse reactions (Grades 1 to 4, incidence ≥ 10%) were diarrhea (16%), stomatitis (16%) and hyperglycemia (12%).[1] There were no deaths in the study population in EPIK-P1.[12]

Serious Adverse Events (SAE)

Serious adverse reactions occurred in 12% (n=21) of patients who received alpelisib. Serious adverse reactions occurring in two or more patients included dehydration (n=2) and cellulitis (n=2). Dosage interruption of alpelisib due to an adverse reaction occurred in 11% of patients. Adverse reactions which required dosage interruption in two or more patients included dizziness (n=2) and vomiting (n = 2). Dose reductions of alpelisib due to an adverse reaction occurred in 3.5% of patients. Adverse reactions which required dose reduction included alopecia and soft tissue infection.[1,12]

The following serious adverse events are associated with alpelisib and if approved, similar to alpelisib (Piqray)[2], these risks will be described in the Warnings and Precautions section of the label.

5.1 SEVERE HYPERSENSITIVITY AND SEVERE CUTANEOUS ADVERSE REACTIONS (SCARS)

Although no severe hypersensitivity reactions or severe cutaneous adverse reactions (SCARs) occurred in the clinical trial, they are a known risk for this product. The labeling will indicate that severe hypersensitivity reactions including anaphylaxis and anaphylactic shock and SCARs, including Stevens-Johnson syndrome (SJS), erythema multiforme (EM), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), have occurred in adult patients treated with alpelisib in the oncology setting[13,14] , and may occur in patients treated with alpelisib in the setting for PROS. Labeling will instruct that if signs or symptoms of SCARs occur, interrupt alpelisib until the etiology of the reaction has been determined. Labeling will also recommend a consultation with a dermatologist and that if a SCAR is confirmed, permanently discontinue alpelisib. If a SCAR is not confirmed, alpelisib may require dose modifications, topical corticosteroids, or oral antihistamine treatment, will be included in the Warnings and Precautions section of the label.

5.2 HYPERGLYCEMIA

In the EPIK-P1 study, Grade 1 or 2 hyperglycemia was reported in 12% of patients treated with alpelisib. Severe hyperglycemia, including fatal cases associated with hyperglycemic hyperosmolar non-ketotic syndrome (HHNKS) or ketoacidosis, has occurred in adult patients treated with alpelisib in the oncology setting[13,14] and may occur in patients treated with PROS. If alpelisib is approved, the labeling will include recommendations to perform fasting plasma glucose (FPG), HbA1c, and optimize blood glucose before initiating alpelisib as well as to monitor FPG at least once every week for the first 2 weeks, then at least once every 4 weeks. Additionally, it is advised to monitor HbA1c every 3 months, as well as when clinically indicated. Labeling will also communicate to closely monitor patients with diabetes by checking FPG at least twice weekly until FPG decreases to normal levels. During therapy with anti-diabetic medication, continue monitoring FPG at least once a week for 8 weeks, followed by once every 2 weeks. Instructions for dose modification and management for hyperglycemia will be communicated in the Dosage and Administration section of the label.[1]

5.3 PNEUMONITIS

Pneumonitis is a class effect with PI3K/mTOR inhibition. No cases of rash or pneumonitis were reported in EPIK-P1.[7] Severe pneumonitis, including acute interstitial pneumonitis and interstitial lung disease, has occurred in adult patients treated with alpelisib in the oncology setting[13,14] and may occur in patients treated with alpelisib in the treatment of PROS. Monitoring and dosage modifications for toxicities to address the safety issues with alpelisib will be included in the Dosage and Administration section of the label.[1]

5.4 DIARRHEA

In the EPIK-P1 study, 16% of patients experienced Grade 1 diarrhea during treatment with alpelisib. Labeling instructs to interrupt, reduce the dose or permanently discontinue alpelisib based on severity. Labeling will include dose modifications in the Dosage and Administration section of the label.[1]

5.5 EMBRYO-FETAL TOXICITY

Based on its mechanism of action and findings from animal data, alpelisib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of alpelisib to pregnant animals during organogenesis caused adverse developmental outcomes, including embryo-fetal mortality (post-implantation loss), reduced fetal weights, and increased incidences of fetal malformations at doses that were approximately equivalent to the recommended pediatric and adult doses.[1] The clinical trial protocol included precautions to exclude patients who did not apply highly effective contraception during the treatment with alpelisib.[15] The safety population included patients aged 2-38 years of age, however there was no exposure of alpelisib in pregnant and lactating women in EPIK-P1.[7] If approved, healthcare providers should advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with alpelisib and for at least one week after the last dose.[1]

6 Expected Postmarket Use

According to the currently proposed indication, if approved, alpelisib will be used in both inpatient and outpatient settings and patients may be followed by a multi-disciplinary team that may include a neurologist, cardiologist, nephrologist, and an orthopedist.[3]

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for alpelisib beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for alpelisib, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the likely prescribing population.

The Applicant proposes aplelisib for the treatment of adult and pediatric patients 2 years of age and older with PROS. PROS is a group of rare disorders that cause overgrowth of parts of the body, due to mutations in the *PIK3CA* gene. PROS may be severe resulting in extensive, and life-threatening overgrowth affecting major vessels and critical organs. Current treatment relies on supportive care, which is comprised of surgical debulking, amputations, orthopedic procedures to limit growth, and blocking of overgrowth vessels such as sclerotherapy, endovascular occlusive procedure. Currently, there are no FDA-approved therapies for the treatment of PROS. Therefore, there remains a clear medical need to develop new therapies for the treatment of this serious and life-threatening rare disease, PROS.

Alpelisib appeared efficacious in its primary outcome of response, which is defined by achieving at least 20% reduction from baseline in the sum of measurable target lesion volume, and its risks can be communicated and managed through labeling.[1,7,12]The clinical reviewer stated that alpelisib shows clinically meaningful benefit, and recommends approval of alpelisib for the treatment of adult and

pediatric patients 2 years of age and older with severe manifestations of PROS, who require systemic therapy.[1,7,12]

DRM and DO2 have determined that if approved, a REMS is not necessary to ensure the benefits of alpelisib outweigh its risks. The safety profile of alpelisib (Piqray) has been characterized during the development of treatment for postmenopausal women, and men, with HR-positive, HER2-negative, advanced/locally advanced or metastatic breast cancer with a PIK3CA mutation under NDA 212526.[13] No newly identified or emerging safety issues were observed in the clinical trial setting for PROS that have not been already seen with alpelisib in the oncology setting. The dose used for the treatment of cancer is higher than the proposed dosing regimen for PROS.[2] The SAEs seen in the clinical trials for PROS were less severe than those seen in the oncology indication, however, the same risks will be included in the Warnings and Precautions section of the label to communicate the potential for these risks. If approved, the warnings and precautions section of the labeling will include information on the following risks: severe hypersensitivity reactions, SCARs, hyperglycemia, pneumonitis, diarrhea and embryo-fetal toxicity. None of the risks rose to the level of a boxed warning.

Based on its mechanism of action and findings from animal data, alpelisib can cause fetal harm when administered to a pregnant woman. Due to the younger patient population treated for PROS, the embryo-fetal toxicity risk is more concerning than in the oncology indication. DO2 determined based on the available data that the risk of embryo-fetal toxicity did not rise to the level of a boxed warning.[1] The recommended guidance as per the label will be to use effective contraception for females of reproductive potential and males with female partners of reproductive potential during treatment with alpelisib and for at least one week after the last dose. In addition to the warnings and precautions, embryofetal toxicity risk mitigation recommendations will be communicated in the Use in Specific Populations section of the label and included in a Patient Package Insert, but pregnancy or use in females of reproductive potential will not be listed as a contraindication.

At the time this review was completed, labeling negotiations were still ongoing with the Applicant. If alpelisib is approved for the treatment of severe manifestations of PROS, the Warnings and Precautions in the labeling will be used to communicate the safety issues and management of toxicities associated with alpelisib, as well as information to be included in Patient Counseling Information, and a PPI. Patients with severe manifestations of PROS are likely to be followed by a multi-disciplinary team that may include a neurologist, cardiologist, nephrologist, and an orthopedist. The risks identified are risks that these providers can manage without additional risk mitigation measures. The review team concluded that alpelisib has a favorable benefit-risk profile for the treatment of adult and pediatric 2 years of age and older with severe manifestations of PROS who require systemic therapy.[7]

To better characterize safety in this patient population affected by PROS, the Agency has issued four post-marketing required (PMR) studies, which include conducting a multiregional clinical trial to verify and describe the clinical benefit of alpelisib, through more precise estimation of confirmed objective response rate and mature response duration, conducting an integrated safety analysis 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, conducting a carcinogenicity study in rats and mice, and one post-marketing commitment (PMC), which includes conducting a study using a higher starting dose of alpelisib (i.e., 125 mg) 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.[16]

9 Conclusion & Recommendations

DRM has determined that a REMS is not necessary to ensure the benefits outweigh the risks of alpelisib for the treatment of adult and pediatric patients aged 2 years and older with severe manifestations of PROS. The management of the risks associated with alpelisib treatment will be communicated through labeling. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 References

[1] Draft Prescribing Information for alpelisib as currently edited by the FDA, last updated March 29, 2022.

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[15] Novartis Pharmaceuticals Corp. Clinical Study Report Appendix 16.1.1, v1.0. Protocols and protocol amendments, dated September 20, 2021.

[16] PMR/PMC document (proposed by FDA) for alpelisib -NDA 215039, dated March 4, 2022. [Reference ID: 4947679]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed March 16, 2022.

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