CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212526Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
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	212526
PDUFA Goal Date	August 19, 2019
OSE RCM #	2018-2331
Reviewer Name(s)	Mei-Yean Chen, Pharm.D.
Team Leader	Elizabeth Everhart, RN, MSN, ACNP
Division Director	Cynthia, LaCivita, Pharm.D.
Review Completion Date	April 25, 2019
Subject	Evaluation of Need for a REMS
Established Name	Alpelisib
Trade Name	Piqray
Name of Applicant	Novartis
Therapeutic Class	An alpha-specific class I phosphatidylinositol-3-kinase (PI3K) inhibitor
Formulation(s)	Tablets: 50 mg, 150 mg, and 200 mg
Dosing Regimen	300 mg orally once daily in combination with fulvestrant.

Table of Contents

EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) alpelisib is necessary to ensure the benefits outweigh its risks. Novartis submitted a New Drug Application (NDA) 212526 for alpelisib with the proposed indication: in combination with fulvestran, for the treatment of postmenopausal women, and men, with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-), phosphatidylinositol-3-kinase (PIK3)-mutated advanced or metatstatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen. The serious risks associated with alpelisib include severe hypersenisitivity (e.g, anaphylaxis and anaphylactic shock), severe cutaneous reactions, hyperglycemia, pneumonitis, diarrhea, and embryo-fetal toxicity. The applicant did not submit a proposed REMS or risk management plan with this application. If approved, the prescribing information of alpelisib will convery these risks in the Warnings and Precautions section of the label, and will include management recommendations in the Dosage and Administration section of the label; labeling will also include a Patient Package Insert. DRISK and the Division of Oncolgoy Product 1 (DOP1) agree that a REMS is not needed to ensure the benefits of alpelisib outweigh its risks.

1 Introduction

This review by DRISK evaluates whether a REMS for the new molecular entity (NME), alpelisib is necessary to ensure the benefits outweigh its risks. Novartis submitted a NDA 212526 for alpelisib with the proposed indication, in combination with fulvestran, for the treatment of postmenopausal women, and men, with hormone HR+, HER2-,PIK3 mutated advanced or metatstatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen. This application is under review in DOP1. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 Product Information

Alpelisib, an NME[a], is an alpha-specific Class I PI3K inhibitor proposed, in combination with fulvestran, for the the treatment of postmenopausal women, and men, with HR+, HER2-, PIK3 catalytic α-subunit (PIK3CA) -mutated advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen. Class I PI3K lipid kinases are key components of the PI3K signaling pathway. In vivo, alpelisib inhibits the PI3K pathway and also provides dose-dependent tumor growth inhibition in relevant tumor xenograft models, including models of breast cancer. PI3K inhibiton by alpelisib has been demonstrated to induce an increase in endocrine receptor (ER)

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

transcription in breast cancer cells, sensitizing these cells to ER inhibition by fulvestrant therapy. The combination of alpelisib and fulvestrant showed increased anti-tumor activity than either therapy alone in xenograft models from ER+, PI3KCA mutated breast cancer lines[1].

Alpelisib is proposed as 300 mg (two of 150 mg tablets) taken orally, once daily. The recommended dose of fulvestrant is 500 mg intamuscular (IM) on days 1 and 15 of a 28 day cycle and on day 1 every 28 days there after. Alpelisib is not currently approved in any jurisdiction.

2.2 Regulatory History

The following is a summary of the regulatory history for NDA 212526 relevant to this review:

- 10/16/2018: A pre-NDA meeting was held between the Agency and the applicant.
- 12/19/2018: NDA 212526 submission received.
- 02/04/2019: A Post Mid-cycle meeting was held between the Agency and the Applicant. The Agency informed the Applicant that based on the currently available data, there are currently no safety issues that require a REMS for alpelisib.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

The number of new cases of breast cancer in female is 126 per 100,000 women per year in the United States (US) with an estimation of new cases in 2018 at 266,120[2]; in 2018, it is estimated to be the cause of 40,920[b] Deaths. In men, breast cancer is a rare condition constituting <1% of all breast cancer diagnoses. Adavnced breast cancer is serious and life-threatening.[c] Metastatic breast cancer is the most advanced stage of the disease and the 5-year survival rate is about 25%.[3]

3.2 Description of Current Treatment Options

Patients with ER positive metastatic breast cancer often respond to endocrine therapy (ET) alone or in combination with targeted agents that can reduce tumor burden and symptoms with generally fewer side effects than chemotherapy. Several clinical trials in the last decade have demonstrated that the addition of targeted agents that work in different ways other than through ER interference can enhance the benefit seen with ET alone.[4] The approved targeted agents include mechanistic target of rapamycin (mTOR) or cycline-dependent kinase (CDK) 4/6 inhibitors. Appendix 2[3] is the summary of these targeted agents. There is no approved therapy specific for PIK3CA mutation advanced breast cancer.

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

[c] 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.*

Sequential ET or combination regimens with targeted agents (mTOR or CDK 4/6 inhibitors) are the currently preferred treatment for patients with HR+, HER2- advanced breast cancer. However, these current therapies may become ineffective due to endocrine resistance.

PIK3CA mutations are present in 1/3 of all breast cancers. Up to 45% of patients with HR+, HER2- have PIK3CA mutations.[5] The PI3K signaling pathway regulates cell growth, survival, and angiogenesis. Mutations in components of the PI3K pathway are frequently observed in estrogen receptor (ER)-positive breast cancer. Patients with PIK3CA mutations have a poorer outcome than patients with no mutation. This may be due to PIK3CA mutations being associated with resistance to ET.[5] The testing for PIK3A mutations is not routinely performed in current clinical practice. Novartis submitted a companion diagnostic (CDx), Qiagen therascreen PIK3CA RGQ (Tissue) PCR kit to the Center of Devices and Radiological Health (CDRH) for approval. This kit was used during clinical trail SOLAR-1 enrollment. Plasma (baseline) samples were also collected from randomized patients and banked for retrospective analysis. Qiagen also is developing a CDx for PIK3CA mutation determination in plasma (ctDNA) samples.

4 Benefit Assessment

In the mid-cycle meeting,[5] the medical officers concluded that the progression free survival (PFS) benefit was statistically significant and clinically meaningful in the indicated population (PIK3CA mutant). Overall Survival (OS) results are not yet mature, but favor the alpelisib arm.[d]

The SOLAR-1 (NCT2437318) trial was a randomized, double-blind, plcebo controlled study to evaluate the efficacy of alpelisib. Alpelisib, with or without fulvestrant, was given to patients with HR+, HER2- locally advanced breast cancer whose disease had progressed or recurred on or after an aromatase inhibitor (AI) based treatment (with or without CDK4/6 kinase inhibitor). A total of 572 advanced breast cancer patients were enrolled into 2 cohorts, 341 patients enrolled with PIK3CA mutation and 231 patients enrolled without PIK3CA mutation. Patients received either alpelisib 300 mg plus fulvestrant (n=284) or placebo plus fulvestrant (n=287). Fulvestrant 50 mg was given IM on cycle 1 day 1 and 15, and then at day 1 of each 28-day cycle during treatment phase.

Of the 341 patients with a PIK3CA mutation, 336 (99%) patients had one or more PIK3CA mutations confirmed in tumor tissue using the FDA approved *therascreen* PIK3CA RGQ PCR Kit; 8 patients did not have specimen available for testing with the kit. Of the remaining 328 patients with PIK3CA mutations confirmed in tumor tissue, 179 patients (55%) had PIK3CA mutations identified in plasma specimen. And 149 patients (45%) did not have PIK3CA mutations identified in plasma specimen. The median age of patients was 63 years (range 25 to 92). Most patients were women (99.8%) and most patients were white (66%), followed by Asian (22%), other/unknown (10%), black or African American (1.4%), and American Indian or Alaskan Native (<1%). The majority of patients (98%) received prior hormonal thearapy as the last therapy (48% metastatic setting, 52% adjuvant setting).

[d] 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.*

The major efficacy outcome was PFS in the cohort with a PIK3CA mutation per Response Evaluation Criteria in Solid Tumors (RECIST vl.1). Additional efficacy outcome measures were overall response rate (ORR) and overall survival (OS) in the cohort with a PIK3CA mutation. Table 1 presents efficacy results for the cohort with a PIK3CA mutation in tumor tissue.

Table 1 Efficacy results in SOLAR-1 (PIK3CA positive cohort, Investigartor Assessment)[1]

	Alpelisib+ fluvestrant	Placebo+ fulvestrant
Progression free survival	N=169	N=172
# of PFS events - n (%)	103 (61%)	129 (75%)
Median PFS months (95% CI)	11.0 (7.5, 14.5)	5.7 (3.7, 7.4)
P-value	0.0013	
Overall Response Rate	N=126	N=136
ORR (95% CI)	35.7 (27.4, 44.7)	16.2 (10.4, 23.5)

5 Risk Assessment[e] & Safe-Use Conditions

The SOLAR-1 trial evaluated the safety of apelisib in 572 patients with HR+, HER2-, locally advanced breast cancer. There were no deaths due to adverse events of treatment.[5] There were 78 deaths in alpelisib+fulvestrant arm (n=284) with 74 deaths due to progressive disease and 4 deaths due to other reasons. Two of the deaths occurred within 30 days after last dose, one was due to cardiopulmonary disease, the other was due to secondary primary cancer. The other 2 deaths occurred beyond 30 days after last dose were decided not related to the drug treatment. There were 92 deaths in placebo+fluvestrant arm (n=287) with 79 deaths due to progressive disease and 12 deaths due to other reasons.[5] Four of these deaths occurred within 30 days after last dose, 1 was due to GI bleed, 1 was due to pulmonary nodular amyloidosis, 1 was due to septic shock, and the last one was due to an unknown reason. The other 8 deaths occurred beyond 30 days after last dose were decided not related to the drug treatment.

The followings are the serious adverse events reported in the trial; if approved, these risks will be described in the Warnings and Precautions section of the label.[1]

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

5.1 SEVERE HYPERSENSITIVITY

Severe hypersensitivity reactions, which included anaphylaxis and anaphylactic shock, were reported in patients treated with alpelisib. The incidence of grade 3 and 4 hypersensitivity reactions occurred in (b) (4)% of patients treated with alpelisib. The hypersensitivity reactions were manifested by symptoms including dyspnea, flushing, rash, fever, or tachycardia. The prescribing information will advise healthcare providers (HCPs) to inform patients of the signs and symtpoms of severe hypersensitivity reactions if alpelisib is approved.

5.2 SEVERE CUTANEOUS REACTIONS

Patients receiving alpelisb experienced severe cutaneous reactons, including Stevens-Johnson Syndrome (SJS) and Erythema Mulfiforme (EM). SJS and EM were reported in (b) (4)% and 1.1% of patients, respectively.

Labeling will communicate that alpelisbi therapy should not be started in patients with a history of SJS, EM, or toxic epidermal necrolysis (TEN). The prescribing information will also state that treatment with alpelisib should be interrupted tif signs or symptoms of severe cutaneous reactions are present, and held until the etiology of the reactions is determined. If SJS, TEN, or EM is confirmed, alpelisib should be permanently discontinued. Labeling will include recommendations for dose modifications and the management of the cutaneous reactions including the need for steroid administration.

5.3 HYPERGLYCEMIA

Hyperglycemia was reported in 65% of patients treated with alpelisib. Grade 3 (fasting plasma glucose [FPG]> 250-500 mg/dL) and grade 4 (FPG ≥500 mg/dL) hyperglycemia was reported in 33%, and 3.9% of patients, respectively. Ketoacidosis was reported in (b) (4)% of patients treated with alpelisib. PI3K-alpha is important for insulin signaling and PI3K-alpha inhibition results in insulin resistance.[6] Hyperglycemia is an on-target effect linked to the activity of alpelisib.

If alpelisib is approved, the labeling will include recommendations to perform 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, HCPs will be 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 if alpelisib is approved.

5.4 PNEUMONITIS

Severe pneumonitis was reported in 1.8% of patients treated with alpelisib. Labeling will indicate to interrupt alpelisib immediately and evaluate patients that have new or worsening respiratory symptoms or are suspected to have developed pneumonitis. Alpelisib should be permanently discontinued in patients with confirmed pneumonitis. HCPs should inform patients to report new or worsening respiratory symptoms immediately.

5.5 DIARRHEA

Diarrhea, including severe diarrhea with sequelae of dehydration and acute kidney injury, was reported in (b) (4)% of patients treated with alpelisib. (b) (4), and 7% of patients experienced grade 3 diarrhea.

In 164 patients that experienced diarrhea, anti-diarrheal medications (e.g., loperamide) were required to manage symptoms in 63% of these patients;2.8% of patients permanently discontinued alpelisib due to diarrhea. Labeling will include dose modifications in the Dosage and Administration section of the label. Patients should be instructed to start antidiarrheal therapy and increase oral fluids and notify their healthcare provider should diarrhea occur with alpelisib treatment.

5.6 EMBRYO-FETAL TOXICITY

Based on findings in animals, as well as its mechanism of action, apelisib can cause fetal harm when administered to a pregnant woman. If alpelisib is approved, HCPs should advise pregnant women and females of reproductive potential to use effective contraception during treatment with alpelisib and for 1 week after the last dose. Additionally, male patients with female partners of reproductive potential to use condoms and effective contraception during therapy with alpelisib and for 1 week after the last dose.

6 Expected Postmarket Use

It is expected that oncologists will be the likely HCPs who prescribe alpelisib in both inpatient and outpatient settings.

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

The clinical reviewer recommends approval of alpelisib on the basis of the efficacy and safety information currently available. In the US, there were an estimated 266,120 new cases[2] in 2018 and an estimated number of deaths of 40,920. Advanced breast cancer is serious and life-threatening. Metastatic breast cancer is the most advanced stage of the disease and the 5-year survival rate is about 25%.

The SOLAR-1 (NCT2437318) trial was a randomized, double-blind, plcebo controlled study to evaluate the efficacy of alpelisib. Alpelisib, with or without fulvestrant, was demonstrated to have statistically significant and clinically meaningful PFS benefit in the indicated population (PIK3CA mutant). Overall survival results are immature, but favor the alpelisib arm.

The major concerning risks of alpelisib are severe hypersensitivity, severe cutaneous reactions, hyperglycemia, pneumonitis, diarrhea, and embryo-fetal toxicity. These risks will be communicated in the Warnings and Precautions section of the labeling. The Dosage and Administration section of the label will include recommendations on how to manage these risks. A Patient Package Insert will be included in labeling as a resourse to inform patients of the risks of alpelisib.

Metastatic breast cancer is a serious and life threatening disease. The likely prescirbers of alpelisib are oncologists who should have experience with managing these adverse events with other products that are used to treat cancer, and more specifically breast cancer. Although there are risks associated with alpelisib, based on the clinically meaningful benefit demonstrated with alpelisib, a REMS is not needed to ensure the benefits out weigh the risks. These risks will be communicated thorugh labeling.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for alpelisib to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

[1] Draft prescribing information for alpelsib as of 04/11/2019

[2] Cancer Stat Facts: female breast cancer, www.cancer.gov, accessed 1/31/2019

[3] Prowell T, Narayan P, medical officers, Draft Alpelisib multi-disciplinary review and evaluation

[4] Ma C, Treatment approach to metastatic HR+, HER2- breast cancer: endocrine therapy and target agents, www.UpToDate.com, accessed 01/28/2019

[5] Prowell T, Narayan P. medical officers, slide presentation in internal mid-cycle meeting, 01/28/2019

[6] Juric D, Liquid biopsies predict alpelisib benefit in breast cancer, 2018 San Antonio Breast Cancer Symposium (Abstract GS3-08)

Appendix 2 Summary of Treatment Options Relevant to Proposed Indications.

Product	Indication	Dosing	Warnings & Precaustions
Everolimus (Afinitor): mTOR inhibitor 2012	Tx of postmenopausal womem with advanced HR+, HER2- breast cancer in combination with exemestane after failure of tx with letrozole or anastrozole	10 mg once daily orally	Non-infectious pneumonitis, infections, severe hypersensitivity, angioedema, stomatitis, renal failure, impaired would healing, metabolic disorders, myelosuppression, and embryo-fetal toxicity
Palbociclib (Ibrance) CDK 4/6 inhibitor, 2015	Tx of HR+, HER2- advanced or met. Breast cancer in combination with 1) an aromatase inhibitor as initial ET in postmenopaulsa women; or 2)fulvestrant in women with dx progression following ET	125 mg orally for 21 days then 7 days off	Neutropenia and embryo-fetal toxicity
Ribociclib (Kisqali) CDK 4/6 inhibitor, 2017	A co-packaged product containing ribociclib and letrozole, is indicated as initial ET for Tx of postmenopausal women with HR+, HER2- advanced or met. Breast cancer	600 mg orally for 21 days then 7 days off; letrozole 2.5 mg daily	QT prolongation, hepatobiliary toxicity, neutropenia, and embryo-fetal toxicity
Abemaciclib (Verzenio) CDK 4/6 inhibitor, 2017	In combination with an aromatase inhibitor as initial ET for Tx of postmenopausal women with HR+, HER2- advanced or met. breast ca; or with fulvestrant for pts with dx progression following ET; as monotherapy for tx of adult pts with dx progression following ET & prior chemotherapy	150 mg orally twice daily in combination therapy; 200 mg orally twice daily in mono-therapy	Diarrhea, neutropenia, hepatotoxicity, venous thromboembolism, and embryo-fetal toxicity

---

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/

MEI-YEAN T CHEN
04/25/2019 01:55:32 PM

ELIZABETH E EVERHART
04/25/2019 01:58:25 PM
I concur.

CYNTHIA L LACIVITA
04/25/2019 04:58:09 PM