CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219249Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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	219249
PDUFA Goal Date	November 27, 2024
Nexus TTT #	2024-9035
Reviewer Name(s)	Celeste Will, PharmD, MPH
Team Leader	Naomi Boston, PharmD
Associate Division Director	Laura Zendel, PharmD
Review Completion Date	October 9, 2024
Subject	Evaluation of Need for a REMS
Established Name	inavolisib
Trade Name	Itovebi
Name of Applicant	Genentech, Inc.
Therapeutic Class	kinase inhibitor
Formulation(s)	Film-coated tablets
Dosing Regimen	9 mg orally once daily

Table of Contents

EXECUTIVE SUMMARY 3

1. Introduction 3

2. Background 4

2.1. Product Information 4

2.2. Regulatory History 5

3. Therapeutic Context and Treatment Options 5

3.1. Description of the Medical Condition 5

3.2. Description of Current Treatment Options 6

4. Benefit Assessment 6

5. Risk Assessment & Safe-Use Conditions 8

5.1. Hyperglycemia 9

5.2. Stomatitis 10

5.3. Diarrhea 10

5.4. Embryo-Fetal Toxicity 10

6. Expected Postmarket Use 11

7. Risk Management Activities Proposed by the Applicant 11

8. Discussion of Need for a REMS 11

9. Conclusion & Recommendations 12

10. Appendices 12

10.1. References 12

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Itovebi (inavolisib) is necessary to ensure the benefits outweigh its risks. Genentech, Inc. submitted a New Drug Application (NDA 219249) for [redacted] (b) (4) The FDA approved indication will be: in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, *PIK3CA*-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy.[1] The risks associated with inavolisib include hyperglycemia, stomatitis, diarrhea, and embryo-fetal toxicity.[1] The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and the Division of Oncology 1 (DO1) determined a REMS is not needed to ensure the benefits of inavolisib outweigh its risks. The efficacy of inavolisib is supported by the INAVO120 study in which the primary efficacy endpoint was met with a statistically significant and clinically meaningful improvement in investigator-assessed progression free survival (PFS).[2] The addition of inavolisib to the standard of care regimen of palbociclib and fulvestrant reduced the risk of disease progression or death by 57% and more than doubled the median PFS (15.0 months in the Inavo+Palbo+Fulv arm vs. 7.3 months Pbo+Palbo+Fulv arm).[2] Patient-reported outcomes showed that adding inavolisib to palbociclib and fulvestrant extends time without clinically meaningful worsening of pain severity without contributing additional burden to patients' day-to-day function and overall quality of life.[2] The clinical reviewer concluded the risk-benefit of inavolisib is favorable for this population with a serious, life-threatening disease.[2] The risks of hyperglycemia, stomatitis, diarrhea, and embryo-fetal toxicity will be addressed in the warnings and precautions section of the label.[2] The likely prescribers will be oncologists who are expected to have experience monitoring, identifying, and managing the adverse events that may occur with inavolisib.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Itovebi (inavolisib) is necessary to ensure the benefits outweigh its risks. Genentech, Inc. submitted a New Drug Application (NDA) 219249 for inavolisib with the proposed indication: [redacted] (b) (4) The FDA approved indication will be: in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, *PIK3CA*-mutated, hormone receptor (HR)-positive, human

epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy.[1] This application is under review in the Division of Oncology 1 (DO1). The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Inavolisib, a new molecular entity[a], is a kinase inhibitor of the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) catalytic subunit alpha isoform protein (p110α; encoded by the PIK3CA gene).[1] In vivo, inavolisib reduced tumor growth in *PIK3CA*-mutated, estrogen receptor (ER)-positive, breast cancer xenograft models.[1] The combination of inavolisib with palbociclib and fulvestrant increased tumor growth inhibition compared to each treatment alone.[1]

Therefore, inavolisib will be indicated in combination with palbociclib and fulvestrant.[1] Palbociclib is FDA approved for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor (AI) as initial endocrine-based therapy or fulvestrant in patients with disease progression following endocrine therapy.[3] Fulvestrant is FDA approved for the treatment of HR-positive, HER2-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy, HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy, HR-positive, HER2-negative advanced or metastatic breast cancer in postmenopausal women in combination with ribociclib, as initial endocrine based therapy or following disease progression on endocrine therapy, HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy.[4]

Inavolisib is proposed to be supplied as 3 mg and 9 mg tablets.[1] The proposed dosing regimen 9 mg taken orally once daily, with or without food, until disease progression or unacceptable toxicity.[b,1] Dose reductions may be needed for adverse reactions. The first dose reduction is 6 mg once daily and the second dose reduction is 3 mg once daily.[1] Inavolisib should be permanently discontinued if patients are unable to tolerate the second dose reduction.[1] The recommended dose of palbociclib is 125 mg taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a cycle of 28 days.[1] (b) (4) Inavolisib is not currently approved in any jurisdiction.[5]

[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.*

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 219249 relevant to this review:

- 04/25/2002: NDA 021344 approved for fulvestrant, indicated for the treatment or the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.[4]
- 02/03/2015: NDA 207103 approved for palbociclib, indicated in combination with letrozole for the treatment of postmenopausal women with ER-positive, HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. This indication is approved under accelerated approval based on PFS. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.[3]
- 03/27/2024: NDA 219249 submission received with the proposed indication for the treatment (b) (4) [redacted][5]
- 05/20/2024: Breakthrough Therapy Designation granted.[2]
- 7/09/2024: Sponsor midcycle meeting. The Applicant was informed that the stomatitis/ (b) (4) [redacted] and diarrhea safety concerns are under review for appropriate labeling. There is currently no need for a REMS.[6]

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Breast cancer is the most common cancer and is second only to lung cancer as a cause of cancer death in American women.[6] About 313,510 new cases of breast cancer are expected to be diagnosed and 42,780 people are expected to die of breast cancer in 2024.[7] According to the National Cancer Institute's SEER database, the 5-year relative survival rate for patients locally advanced and metastatic breast cancer breast cancer was 29.2%.[8] HR-positive, HER2-negative breast cancer is the most common subtype accounting for approximately 70% of all breast cancers.[c,8] Other less prevalent breast cancer subtypes include, HR-/HER2-, HR+/HER2+, HR-/HER2+.[8] Within the HR-positive, HER2-negative subtype, one of the commonly mutated genes is PIK3CA which relates to tumorigenesis, progression, and therapeutic resistance.[9] The estimated prevalence of the of the PIK3CA mutation with HR+ breast cancer is 40%.[9] PIK3CA mutations are a negative prognostic factor and it has been estimated that patients with HR+,

[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.*

HER2– mBC whose tumors harbor one or more PIK3CA mutations exhibit approximately 2 months shorter progression-free survival (PFS) and 8 months shorter overall survival (OS).[d,2]

3.2. Description of Current Treatment Options

The goals of breast cancer treatment are to prolong survival and improve quality of life.[10] In patients with new metastatic disease, a biopsy of a metastatic lesion should be done to confirm estrogen receptor (ER), progesterone receptor (PR), and HER2 status.[11] The following mutations should also be assessed: PIK3CA, AKT1, PTEN, and ESR1 in tumor tissue and/or blood for eligibility for AKT inhibitor, PI3K inhibitor, and elacestrant, respectively.[11]

Initial therapy for patients with HR +/HER2 – metastatic breast cancer is typically cyclin-dependent kinase (CDK) 4/6 inhibitor (palbociclib, abemaciclib, or ribociclib) in combination with an aromatase inhibitor (AI).[11] Another acceptable option is single agent fulvestrant or anastrozole or fulvestrant in combination with an AI.[11] For premenopausal women treated with endocrine therapy, concurrent ovarian suppression or ablation is suggested and imperative for premenopausal patients receiving AIs.[11]

Subsequent treatment for patients who have previously experienced progression on an AI and CDK 4/6 inhibitor includes combination of fulvestrant with capivasertib for those harboring alterations in PIK3CA, AKT1, or PTEN.[11] For PIK3CA-mutant breast cancer, fulvestrant with the alpha isoform-specific PI3K inhibitor alpelisib is an alternative option.[11] For patients with PIK3CA-wild-type cancers, options include fulvestrant monotherapy or everolimus-based combinations, with a choice between them driven by side-effect profiles if the tumor is PIK3CA-wild-type.[11] For patients with PIK3CA-wild-type cancers, elacestrant is recommended instead of fulvestrant although fulvestrant with or without everolimus is a reasonable alternative if an ESR1 mutation is present.[11]

Chemotherapy may be considered for patients who have progressed on two or more lines of endocrine therapy.[11] However, for patients who are asymptomatic with slowly progressive disease, continuation of endocrine therapy is reasonable and tamoxifen may be an appropriate later-line option.[11]

4. Benefit Assessment

The pivotal trial, INAVO120 (NCT04191499) supporting this application consisted of a Phase 3, randomized, double-blind, placebo-controlled, multi center, global study designed to compare the efficacy, measured by investigator-assessed PFS, and the safety of the triplet combination of inavolisib with palbociclib and fulvestrant (Inavo+Palbo+Fulv) vs. placebo with palbociclib and fulvestrant (Pbo+Palbo+Fulv) in patients with *PIK3CA* mutated, HR+, HER2– locally advanced/ metastatic breast cancer whose disease progressed during treatment or within 12 months of completing adjuvant ET and who had not received prior systemic therapy for locally advanced or metastatic disease.[2] Patient biomarker eligibility (i.e., positive for a study-eligible *PIK3CA* mutation) was determined through testing of blood plasma-derived circulating tumor DNA (ctDNA) with a next-generation sequencing (NGS) assay

[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.*

performed at the Sponsor-designated central laboratory, or through local testing of ctDNA or tumor tissue with an appropriately-validated NGS or polymerase chain reaction assay.[2]

Patients who were positive for a study-eligible PIK3CA mutation were randomly assigned in a 1:1 ratio to one of two treatment arms: Inavo+Palbo+Fulv (n = 161) or Pbo+Palbo+Fulv (n = 161).[2] Patients were required to have a HbA1c less than 6% and fasting blood glucose less than 126 mg/dL.[1] The study excluded patients with Type 1 diabetes mellitus or Type 2 diabetes mellitus requiring ongoing systemic therapy at the start of study treatment.[1] Inavolisib/placebo was administered at 9 mg PO QD on Days 1-28 of each 28-day cycle; palbociclib was administered at 125 mg PO QD on Days 1-21 of each 28-day cycle; fulvestrant was administered at 500 mg by intramuscular injection on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle, or approximately every 4 weeks.[2] Patients received study treatment until unequivocal disease progression as determined by the Investigator, unacceptable toxicity, patient withdrawal of consent, loss to follow-up, death, or study termination.[2]

The primary efficacy endpoint was PFS as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria.[2] Primary efficacy analyses were based on the tumor assessments performed to assess for response every 8 weeks (±7 days) during the first 2 years of study treatment and every 12 weeks (±7 days) thereafter.[2] A retrospective blinded independent central review (BICR) of tumor assessment data was performed to support the primary endpoint of investigator-assessed PFS.[2] Secondary efficacy endpoints include: OS; ORR; BOR rate; DOR for patients with objective response; CBR; time to confirmed deterioration (TTCD) in worst pain severity; TTCD in physical functioning (PF); TTCD in role functioning (RF); and TTCD in Global Health Status/Health-Related Quality of Life (GHS/HRQoL). ORR, BOR, DOR, and CBR were based on tumor assessment by the investigator.[2]

The primary efficacy endpoint was met with a statistically significant and clinically meaningful improvement in investigator-assessed PFS.[2] Among the 161 patients randomized to the Inavo + Palbo + Fulv arm, 82 patients (50.9% of patients) experienced an event over a median of 15 months (95% confidence interval 11.3, 20.5) compared to the 164 patients randomized to the Pbo + Palbo + Fulv arm, in which 113 patients (68.9% of patients) experienced an event over a median of 7.3 months (95% confidence interval 5.6, 9.3).[2] The hazard ratio is 0.43 (0.32, 0.59) with a log-rank p-value of < 0.0001.[2] The addition of inavolisib to the standard of care regimen of palbociclib and fulvestrant reduced the risk of disease progression or death by 57% and more than doubled the median PFS (15.0 months in the Inavo+Palbo+Fulv arm vs. 7.3 months Pbo+Palbo+Fulv arm).[e,2] Patient-reported outcomes showed that adding inavolisib to palbociclib and fulvestrant extends time without clinically meaningful worsening of pain severity and without contributing additional burden to patients' day-to-day function and overall quality of life.[2]

[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.*

5. Risk Assessment & Safe-Use Conditions

The following section is a summary of relevant safety information to date for inavolisib. The safety database includes 351 individuals exposed to the study drug, inavolisib for the indication under review.[2] However, FDA safety analyses were based primarily on data from the phase 3 INAVO120 (WO41554) Trial.[2] Results from the GO39374 Trial are considered supportive.[2] Pooling across the studies was not considered appropriate due to differences in the patient population, treatment regimens, the range of inavolisib dose levels, and the differences in AE grading criteria for these two studies.[2]

Among the 162 patients who received inavolisib as part of the triplet combination of Inavo+Palbo+Fulv, the median treatment duration was 9.2 months with a standard deviation of 12.1 (9.6).[2] The median relative dose intensity of inavolisib in the Inavo+Palbo+Fulv arm was 95.8%. In addition, the median relative dose intensity of palbociclib and fulvestrant was similar between the two treatment arms of the INAVO120 Trial; therefore, the triplet combination therapy including inavolisib did not have a significant impact on the ability to administer full dose palbociclib+fulvestrant.[2] The most notable increase in adverse events were observed in hyperglycemia, stomatitis, and diarrhea, including severe cases.[2] Therefore, hyperglycemia, stomatitis and diarrhea will be labeled under warnings and precautions in the prescribing information to better inform physicians and to provide guidance for dose modifications.[2] These adverse events were managed with dose interruptions and dose reductions in most cases.[2] The clinical reviewer notes that the safe use of inavolisib with palbociclib plus fulvestrant can be communicated with labeling.[2]

Deaths

Fatal adverse reactions occurred in 3.7% of patients who received inavolisib with palbociclib and fulvestrant, including (0.6% each) acute coronary syndrome, cerebral hemorrhage, cerebrovascular accident, COVID-19 infection, and gastrointestinal hemorrhage.[1] It was determined that none of these deaths were related to the study drug.[2]

Serious Adverse Events (SAE)

Serious adverse reactions occurred in 24% of patients who received inavolisib with palbociclib and fulvestrant. Serious adverse reactions in ≥ 1% of patients included anemia (1.9%), diarrhea (1.2%), and urinary tract infection (1.2%).[1] A numerically higher proportion of patients experienced SAEs in the Inavo+Palbo+Fulv arm compared with the Pbo+Palbo+Fulv arm (24.1% vs. 10.5%, respectively).[f,2] The clinical reviewer noted the highest incidence of SAEs on the inavolisib treatment arm occurred in the System Organ Class (SOC) of Infections and Infestations (6.8%), followed by Gastrointestinal disorders (4.3%) and Blood and Lymphatic disorders (4.3%).[2] In addition, most of the infections were assessed by the investigator as not related to any study drug.[2] Patients on the inavolisib arm were on treatment for a longer duration (compared to the placebo arm) with potential concomitant neutropenia, which may

[f] 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.*

have led a higher rate of infections.[2] However, it is not known if inavolisib may have exacerbated the risk of infection.[2]

5.1. Hyperglycemia

PI3K inhibitors inhibit PI3K in host tissues which impairs the intracellular action of insulin and induces insulin resistance.[12] As a result, PI3K inhibitor driven insulin resistance causes hyperglycemia.[12] Increased fasting glucose occurred in 85% of patients treated with inavolisib, including 22% of patients with Grade 2 (FPG > 160 to 250 mg/dL), 12% with Grade 3 (FPG > 250 to 500 mg/dL), and 0.6% with Grade 4 (FPG > 500 mg/dL) events.[1]

In INAVO120, 46% (74/162) of patients who received inavolisib were treated with oral anti-hyperglycemic medications and 7% (11/162) were treated with insulin to manage increased fasting glucose.[1] In patients who experienced increased fasting glucose of > 160 mg/dL, 96% (52/54) had an improvement in fasting glucose of at least one grade level with a median time to improvement from the first event of 8 days (range: 2 to 43 days).[1]

Among patients with hyperglycemia, the median time to first onset was 7 days (range: 2 to 955 days).[1] Hyperglycemia led to dose interruption in 28%, to dose reduction in 2.5%, and to discontinuation of inavolisib in 1.2% of patients.[1]

The safety of inavolisib in patients with Type 1 diabetes mellitus, or Type 2 diabetes mellitus requiring ongoing anti-hyperglycemic treatment has not been studied, since these patients were excluded from the clinical trial.[1] Recommendations for management of hyperglycemia are to test fasting glucose levels (FPG or FBG), HbA1C levels, and optimize fasting glucose before initiating treatment with inavolisib.[1] If a patient experiences hyperglycemia after initiating treatment with inavolisib, healthcare providers should monitor or have the patient self-monitor FPG or FBG once every 3 days for the first week (Day 1 to 7), then once every week for the next 3 weeks (Day 8 to 28), then once every 2 weeks for the next 8 weeks, then once every 4 weeks thereafter, and as clinically indicated.[1] Healthcare providers should monitor HbA1C every 3 months and as clinically indicated.[1] Hyperglycemia can be managed with anti-hyperglycemic medications as clinically indicated and fasting glucose levels should continue to be monitored during treatment with anti-hyperglycemic medication.[1] Patients with a history of well-controlled Type 2 diabetes mellitus may require intensified anti-hyperglycemic treatment and close monitoring of fasting glucose levels.[1]

Labeling will also recommend that healthcare providers consider consultation with another healthcare professional experienced in the treatment of hyperglycemia and initiation of fasting glucose monitoring at home for patients who have risk factors for hyperglycemia or who experience hyperglycemia.[1] Patients should be advised of the signs and symptoms of hyperglycemia and counseled on lifestyle changes.[1]

Based on the severity of the hyperglycemia, inavolisib may require dose interruption, reduction, or discontinuation.[1] Of note, another FDA-approved kinase inhibitor indicated in combination with fulvestrant for the treatment of adults with hormone receptor (HR)-positive, human epidermal growth

factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer, alpelisib, also has risk for hyperglycemia that is included in the warnings and precautions section of the alpelisib prescribing information.[13] The alpelisib prescribing information states that Grade 3 (FPG > 250 to 500 mg/dL) and Grade 4 (FPG > 500 mg/dL) hyperglycemia was reported in 33% and 3.9% of patients, respectively.[13] As noted above, hyperglycemia is expected due to the mechanism of action of these products in PI3K inhibition.

5.2. Stomatitis

Stomatitis occurred in 51% of patients treated with inavolisib in combination with palbociclib and fulvestrant; including Grade 3 events in 6% of patients.[1] The median time to first onset was 13 days (range: 1 to 610 days).[1] Stomatitis led to interruption of inavolisib in 10%, dose reduction in 3.7%, and discontinuation of inavolisib in 0.6% of patients.[1]

In patients who received inavolisib in combination with palbociclib and fulvestrant, 38% used a mouthwash containing corticosteroid for management of stomatitis.[1]

Recommendations for management of stomatitis are to monitor patients for signs and symptoms of stomatitis.[1] Withhold, reduce dose, or permanently discontinue inavolisib based on severity.[1]

5.3. Diarrhea

Severe diarrhea, associated with dehydration or acute kidney injury, can occur in patients treated with inavolisib.[1] Diarrhea occurred in 48% of patients treated with inavolisib in combination with palbociclib and fulvestrant; including Grade 3 events in 3.7% of patients.[1] The median time to first onset was 15 days (range: 2 to 602 days).[1] Anti-diarrheal medicines were used in 28% (46/162) of patients who received inavolisib in combination with palbociclib and fulvestrant to manage symptoms.[1] Dose interruptions were required in 7% of patients, and dose reductions occurred in 1.2%.[1]

Recommendations for management of diarrhea are to monitor patients for signs and symptoms of diarrhea.[1] Patients should be advised to increase oral fluids and start antidiarrheal treatment at the first sign of diarrhea while taking inavolisib. Withhold, reduce dose, or permanently discontinue inavolisib based on severity.[1]

5.4. Embryo-Fetal Toxicity

Based on findings in animals and its mechanism of action, inavolisib can cause fetal harm when administered to a pregnant woman.[1] However, inavolisib is not contraindicated in pregnancy.[1] In an animal reproduction study, oral administration of inavolisib to pregnant rats during the period of organogenesis caused adverse developmental outcomes, including embryo-fetal mortality, structural abnormalities, and alterations to growth at maternal exposures approximately equivalent to the human exposure based on area under the curve (AUC) at the recommended dose of 9 mg/day.[1]

Labeling will include recommendations for management of embryo-fetal toxicity. Healthcare providers should advise pregnant women and females of reproductive potential of the potential risk to a fetus.[1] Females of reproductive potential should use effective non-hormonal contraception during treatment with inavolisib and for 1 week after the last dose.[1] Male patients with female partners of reproductive potential should use effective contraception during treatment with inavolisib and for 1 week after the last dose.[1]

6. Expected Postmarket Use

If approved, inavolisib will primarily be used in outpatient settings, self-administered by patients or administered from patients' caregivers or inpatient settings depending on the disease progression. We expect this product will be dispensed from either inpatient our outpatient pharmacy settings. The likely prescribers will be oncologists who a specialized in the treatment and management of breast cancer and their associated therapies.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities beyond labeling and routine pharmacovigilance.

8. Discussion of Need for a REMS

The review team recommends regular approval of inavolisib on the basis of the efficacy and safety information currently available.

Breast cancer is the most common cancer and is second only to lung cancer as a cause of cancer death in American women.[6] HR positive, HER2 negative breast cancer is the most common subtype accounting for approximately 70% of all breast cancers.[8] Within HR+ breast cancers, the prevalence of the of the PIK3CA mutation is 40%.[9] PIK3CA mutations are a negative prognostic factor and it has been estimated that patients PIK3CA mutations exhibit approximately 2 months shorter PFS and 8 months shorter OS.[2]

The goals of treatment are to prolong survival and improve quality of life.[10] A CDK 4/6 inhibitor in combination with endocrine therapy with either fulvestrant or an aromatase inhibitor are considered standard of care for first or second line treatment for HR positive/HER2 negative metastatic breast cancer.[14,15] However, currently there are no FDA approved treatments specifically for first line treatment of patients with PIK3CA mutated locally advanced or metastatic HR positive, HER2 negative breast cancer considered to have endocrine resistant disease.[2]

Inavolisib is a kinase inhibitor of the PI3K catalytic subunit alpha isoform protein (p110α; encoded by the PIK3CA gene) proposed to be used in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, *PIK3CA*-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy.[1] The efficacy of inavolisib is supported by the INAVO120 study in which the primary efficacy endpoint was met with a statistically significant and clinically meaningful improvement in investigator-assessed PFS.[2]

The addition of inavolisib to the standard of care regimen of palbociclib and fulvestrant reduced the risk of disease progression or death by 57% and more than doubled the median PFS (15.0 months in the Inavo+Palbo+Fulv arm vs. 7.3 months Pbo+Palbo+Fulv arm).[2] Patient-reported outcomes showed that adding inavolisib to palbociclib and fulvestrant extends time without clinically meaningful worsening of pain severity without contributing additional burden to patients' day-to-day function and overall quality of life.[2]

The serious risks associated with inavolisib include hyperglycemia, stomatitis, diarrhea, and embryo-fetal toxicity.[1] These risks will be addressed in the warnings and precautions section of the label.[1] None of the adverse events of inavolisib rise to the level of a boxed warning at this time. The likely prescribers are oncologists who are expected to have experience managing the adverse events reported with inavolisib. The adverse event profile does not contain any new or unusual risks that oncologists treating this population would be unfamiliar with or require additional information. Based on the efficacy and risks associated with inavolisib for treatment of adult patients with PIK3CA mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of adjuvant therapy in combination with palbociclib and fulvestrant, this reviewer's recommendation is that a REMS is not necessary to ensure the benefits outweigh the risks.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable in this life-threatening condition therefore, a REMS is not necessary for inavolisib to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. The management of the risks associated with inavolisib can be communicated through labeling. Please notify DRM 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 inavolisib as currently edited by FDA. 2024.
2. Draft NDA/BLA Multi-disciplinary Review and Evaluation for Itovebi (inavolisib) NDA 219249. 2024.
3. Ibrance [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Updated September 6, 2023. Accessed August 15, 2024.
4. Faslodex [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Updated January 19, 2021. Accessed August 15, 2024.
5. Genentech I. Clinical Overview. 2024.
6. FDA Midcycle Communication. Division of Oncology 1 (DO1).
7. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. Jan-Feb 2024;74(1):12-49. doi:10.3322/caac.21820
8. Cancer Stat Facts: Female Breast Cancer Subtypes. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Accessed August 23, 2024. https://seer.cancer.gov/statfacts/html/breast-subtypes.html

9. Fillbrunn M, Signorovitch J, Andre F, et al. PIK3CA mutation status, progression and survival in advanced HR + /HER2- breast cancer: a meta-analysis of published clinical trials. *BMC Cancer*. Sep 21 2022;22(1):1002. doi:10.1186/s12885-022-10078-5
10. Schott AF. Endocrine therapy resistant, hormone receptor-positive, HER2-negative advanced breast cancer. 2024. Accessed August 23, 2024. https://www.uptodate.com/contents/endocrine-therapy-resistant-hormone-receptor-positive-her2-negative-advanced-breast-cancer?search=PIK3CA+mutated%2C+hormone+receptor+%28HR%29-positive%2C+human+epidermal+growth+factor+receptor+2+%28HER2%29-negative%2C+locally+advanced+or+metastatic+breast+cancer&source=search_result&selectedTitle=2%7E150&usage_type=default&display_rank=2
11. Ma CX, Spaano, J. A.,. Treatment for hormone receptor-positive, HER2-negative advanced breast cancer. 2024. Accessed August 26, 2024. https://www.uptodate.com/contents/treatment-for-hormone-receptor-positive-her2-negative-advanced-breast-cancer?search=PIK3CA%20mutated%2C%20hormone%20receptor%20%28HR%29-positive%2C%20human%20epidermal%20growth%20factor%20receptor%202%20%28HER2%29-negative%2C%20locally%20advanced%20or%20metastatic%20breast%20cancer&topicRef=83848&source=see_link#H264716193
12. Weintraub MA, Liu D, DeMatteo R, Goncalves MD, Flory J. Sodium-Glucose Cotransporter-2 Inhibitors for Hyperglycemia in Phosphoinositide 3-kinase Pathway Inhibition. *Res Sq*. Mar 21 2023;doi:10.21203/rs.3.rs-2655905/v1
13. Piqray [Prescribing Information]. DailyMed. National Library of Medicine. Updated July 18, 2024. Accessed August 28, 2024. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b20b4e18-7a4b-4500-a08f-06c6dab0ee5b
14. FDA Midcycle Meeting. Division of Oncology 1 (DO1).
15. <NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer Version 47.2024 — July 3, 2024>.

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/

CELESTE A WILL
10/09/2024 12:20:15 PM

NAOMI S BOSTON
10/09/2024 01:08:53 PM

LAURA A ZENDEL
10/09/2024 02:00:53 PM