

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213736Orig1s000

**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	213736
PDUFA Goal Date	May 29, 2020
OSE RCM #	2019-2009
Reviewer Name	Mei-Yean Chen, Pharm.D.
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Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	March 2, 2020
Subject	Evaluation of Need for a REMS
Established Name	Pemigatinib
Trade Name	Pemazyre
Name of Applicant	Incyte Corporation
Therapeutic Class	A kinase inhibitor
Formulation(s)	Tablets: 4.5 mg, 9 mg, and 13.5 mg
Dosing Regimen	Oral tablet once daily, recommended dose is 13.5 mg for 14 days, followed by 7 days off

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Pemazyre (pemigatinib) is necessary to ensure the benefits outweigh its risks. Incyte Corporation submitted a New Drug Application (NDA) 213736 for pemigatinib with the proposed indication for the treatment of adults with previously treated, locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement as detected by an FDA-approved test. Pemigatinib is under a priority review based on overall response rate and duration of response. The risks associated with pemigatinib include ocular toxicity, hyperphosphatemia, and embryo-fetal toxicity. The applicant did not submit a proposed REMS or risk management plan with this application.

Division of Risk Management (DRM) and the Division of Oncology 3 (DO3) have determined that a REMS is not needed to ensure the benefits of pemigatinib outweigh its risks. Second-line chemotherapies in cholangiocarcinoma have shown limited efficacy, with overall response rates (ORR) no higher than 9.5%. There are currently no available target therapies approved to treat locally advanced or metastatic cholangiocarcinoma. In the clinical trial, pemigatinib demonstrated a 36% ORR with a 3% complete response and 33% partial response. If approved, the labeling will communicate risks of ocular toxicity, hyperphosphatemia, and embryo-fetal toxicity in Section 5 Warnings and Precautions, as well as instructions on how to withhold, reduce dose, and discontinue therapy in Section 2 Dosage and Administration. If approved, this indication will be under accelerated approval and continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Pemazyre (pemigatinib) is necessary to ensure the benefits outweigh its risks. Incyte Corporation submitted a New Drug Application (NDA) 213736 for pemigatinib with the proposed indication for the treatment of adults with previously treated, locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement as detected by an FDA-approved test. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. This application is under review in the Division of Oncology 3 (DO3). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Pemigatinib, a new molecular entity (NME)^a, is a kinase inhibitor proposed for the treatment of adults with previously treated, locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or

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

rearrangement as detected by an FDA-approved test. FGFRs play an important role in tumor cell proliferation and survival, migration and angiogenesis. Activating fusions, rearrangements, and gene amplifications in FGFRs are closely correlated with the development of various cancers. Pemigatinib is an oral inhibitor of FGFR 1-3, and in preclinical studies, demonstrated selective pharmacologic activity against cancer cells with these FGFR alterations. Pemigatinib is available as 4.5 mg, 9 mg, and 13.5 mg tablets. The recommended dose is 13.5 mg oral once daily for 14 days followed by 7 days off. Treatment is to be continued until disease progression or unacceptable toxicity occurs. Pemigatinib is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 213736 relevant to this review:

- 03/12/2018: Orphan designation for the treatment of cholangiocarcinoma granted
- 02/13/2019: Breakthrough therapy designation granted, for the treatment of previously treated, advanced/metastatic or unresectable cholangiocarcinoma with an FGFR2 fusion.
- 09/30/2019: NDA 213736 submission received
- 01/09/2020: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for pemigatinib.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Cholangiocarcinoma, a bile duct cancer, is from the epithelial cells of the intrahepatic and extrahepatic bile ducts. Biliary tract cancers were originally divided into cancers of the gallbladder, the extrahepatic ducts, and the ampulla of Vater, while intrahepatic tumors of the bile system were categorized as primary liver cancers. More recently, the term cholangiocarcinoma has been referred to bile duct cancers from the intrahepatic, perihilar, or extrahepatic biliary tree, exclusive of the gallbladder or ampulla of Vater.

Cholangiocarcinoma (CCA) accounts for about 3% of all gastrointestinal malignancies. They are very rare in the United States (US), but they are highly lethal^b because most are locally advanced at diagnosis.¹ The incidence in the U S is 1-2 cases per 100,000 population.^c The incidence of intrahepatic CCA has been rising over the past two decades in Europe, North America, Asian, and Australia, while rates of

^b 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.*

^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.*

extrahepatic CCA are declining internationally. The typical patient with CCA is between 50 and 70 years of age and the incidence in men is higher than in women. More than 90% of CCA are adenocarcinomas and the remaining cases are squamous cell carcinoma.

Extrahepatic CCA becomes symptomatic when the tumor obstructs the biliary drainage system. Biliary obstruction symptoms include jaundice, pruritis, clay-colored stools, dark urine, abdominal pain, weight loss, and fever. The presentation of intrahepatic CCA (about 15%-20% of all CCA) may be different. Patients are less likely to be jaundiced, and often remain asymptomatic until advanced stages of the disease. Patients with intrahepatic CCA may present with dull right upper quadrant pain, weight loss, and elevated alkaline phosphatase.² The prognosis of patients with locally unresectable or recurrent CCA is usually measured in months with rapid decline with symptoms of progressive biliary obstruction.

The FGFR pathway includes a family of 22 polypeptide ligands and four receptor tyrosine kinases, which regulate diverse physiologic processes. FGFR signaling is activated through mutations, chromosomal translocations, and amplifications in a variety of cancers, including squamous non-small cell lung cancers, head and neck squamous cell carcinomas, breast cancers, urothelial carcinomas, and intrahepatic CCA. Approximately 10%-20% of intrahepatic CCA are positive for FGFR fusions.³

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The role of systemic chemotherapy is evolving in management of advanced CCA. But no single chemotherapy drug or combination regimen consistently shrink tumor, forestall recurrent obstruction, or extends survival beyond eight to 15 months.⁴ For most patients, the recommended first line chemotherapy is gemcitabine plus cisplatin rather than gemcitabine alone or a non-gemcitabine-based regimen.⁴ The optimal second line chemotherapy to treat advanced CCA is not established. The suggested regimens include; folinic acid/fluorouracil and oxaliplatin, capecitabine plus irinotecan and, capecitabine plus oxaliplatin.⁴ Second-line chemotherapies in CCA have shown limited efficacy, with an overall survival of 6.2 to 7.2 months and ORR are approximately 9.5%.⁵

There are currently no available target therapies to FGFR2 fusion or rearrangement to treat locally advanced or metastatic CCA.

4 Benefit Assessment

The registrational trial to evaluate the efficacy of pemigatinib was FIGHT-202 (NCT02924376), a multicenter, open-label, single-arm trial. The trial included 107 patients with locally, advanced, unresectable or metastatic CCA who progressed on or after at least one prior therapy and who had an FGFR2 fusion or rearrangement, as determined by a clinical trial assay performed at a central laboratory. Pemigatinib was given as a 13.5 mg tablet orally once daily for 14 consecutive days, followed by 7 days off. This dosing of pemigatinib was continued until disease progression or unacceptable toxicity^d. The median duration of therapy was 181 days (range: 7-730 days). The major efficacy outcome measures were ORR and duration of response (DoR), as determined by an independent review committee (IRC).⁶

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

The median age in FIGHT-202 was 56 years (26-77 years), 61% of patients were female, 74% were white, and 95% had a baseline Eastern Cooperative Oncology Group performance status of 0 or 1. Eighty-six percent of patients had FGFR2 fusions and 14% had FGFR2 rearrangements. Ninety-eight percent of patients had intrahepatic CCA. All patients had received at least 1 prior line of systemic therapy, 27% had 2 prior lines of therapy, and 12% had 3 or more prior lines of therapy. Ninety-six percent of patients has received prior platinum-based treatment including 76% with prior gemcitabine/cisplatin. Efficacy results are shown in Table 1^{6,e}.

Table 1 Efficacy Results in FIGHT-202

Efficacy Parameter	Pemigatinib, N=107
ORR (95% confidence interval [CI])	36% (27, 45)
Complete response	2.8%
Partial response	33%
Median DoR (months) (95% CI)	9.1 (6.0, 14.5)
Patients with DoR≥6 months, n(%)	24 (63%)
Patients with DoR≥12 months, n(%)	7 (18%)

5 Risk Assessment

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The safety of pemigatinib was evaluated in study FIGHT-202.⁷ One hundred forty-six patients with previously treated, locally, advanced, or metastatic CCA were included in the safety analysis. There were 7 deaths reported including 2 due to hepatobiliary disorders (1 to bile duct obstruction, 1 to cholangitis), 1 to sepsis, 2 to failure to thrive, and 1 to pleural effusion. These deaths were considered not related to treatment per medical safety officer presented in the midcycle meeting.⁷

All risks^f associated with pemigatinib listed below are currently included in the draft labeling⁶ in Warnings and Precautions.

5.1 OCULAR TOXICITY

^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.*

^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.*

- **Retinal Pigment Epithelial Detachment (RPED)**

RPED may be caused by pemigatinib which may manifest symptoms such as blurred vision, visual floaters, or photopsia. In the clinical trials, routine monitoring to detect asymptomatic RPED, such as optical coherence tomography (OCT), was not performed; therefore, the incidence of asymptomatic RPED associated with pemigatinib is unknown.

There was 6% of patients (n=466) reported to have RPED, including grade 3-4 RPED in 0.6% of patients. RPED caused dose interruption in 1.7% of patients, and dose reduction and permanent discontinuation in 0.4% and 0.4% of patients, respectively.

If pemigatinib is approved, labeling will include that a comprehensive ophthalmological examination should be conducted before initiation of pemigatinib, and OCT should be performed every 2 months for the first 6 months and then every 3 months. An ophthalmologic evaluation to be referred urgently if patients show visual symptoms.

- **Dry Eye**

Dry eye occurred in 27% of patients including grade 3-4 in 0.6% of patients. Labeling will include that all patients should receive dry eye prophylaxis with ocular demulcents as needed.

5.2 HYPERPHOSPHATEMIA

Pemigatinib increases serum phosphate levels because of FGFR inhibition. During the clinical trial, hyperphosphatemia was observed in 92% of patients treated with pemigatinib. The median time to onset of hyperphosphatemia was 8 days from initiation of pemigatinib therapy. Twenty-nine percent of patients required phosphate lowering treatment.

If approved, labeling will state to monitor for hyperphosphatemia and start a low phosphate diet when serum phosphate level is > 5.5 mg/dL. Withhold the dose and initiate phosphate lowering treatment when the level is > 7 mg/dL. Section 2 Dosage and Administration will provide recommendations when to withhold, reduce the dose, or discontinue pemigatinib treatment.

5.3 EMBRYO-FETAL TOXICITY

Pemigatinib can cause fetal harm when administered to a pregnant woman based on findings in an animal study and its mechanism of action. The draft label states to advise pregnant women of the potential risk to a fetus and to use effective contraception during therapy and for one week after the last dose. Males with female partners of reproductive potential should be advised to use effective contraception during therapy and for one week after the last dose.

6 Expected Post market Use

If approved, it is expected that oncologists will be the likely health care providers to prescribe pemigatinib in both inpatient and outpatient settings.

7 Risk Management Activities Proposed by the Applicant

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

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of pemigatinib on the basis of the efficacy and safety information currently available.⁷ If approved, it will be under accelerated approval based on overall response rate and duration of response, continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. DRM and DO3 agree that a REMS is not necessary to ensure the benefits of pemigatinib outweigh its risks.

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for pemigatinib, this reviewer considered were the patient population size, seriousness of the disease, the expected benefit of the drug, the expected duration of treatment, and the seriousness of known or potential adverse reactions.

Cholangiocarcinoma accounts for about 3% of all gastrointestinal malignancies, but it is highly lethal because most are advanced at the time of diagnosis. The prognosis of patients with locally unresectable or recurrent CCA is usually measured within months with patients experiencing a rapid decline due to progressive biliary obstruction. First-line therapy for locally, advanced, or metastatic CCA is the chemotherapy combination of gemcitabine and cisplatin. Second-line chemotherapies in CCA have shown limited efficacy, with ORR no higher than 9.5%. Currently, there are no therapies approved for CAA that target FGFR. In the clinical trial, pemigatinib demonstrated 36% ORR with 3% of complete response and 33% of partial response.

Molecularly targeted agents have become as an important systemic therapy for a wide range of cancers. Many of these agents are associated with distinct adverse effect profiles. FGFR inhibitors appear to have a similar type of ocular toxicities to that seen with the MEK inhibitors, possibly because the FGFR pathway intersects with the MEK pathway.⁸ Erdafitinib (Balversa), an FGFR inhibitor, was approved under accelerated approval in April 2019 to treat locally advanced or metastatic urothelial carcinoma. Ocular disorders (central serous retinopathy/RPED), hyperphosphatemia, and embryo-fetal toxicity are included in Warnings and Precautions of erdafitinib labeling.⁹ Pemigatinib is an FGFR inhibitor, and if approved, the labeling will communicate risks of ocular toxicity, hyperphosphatemia, and embryo-fetal toxicity in Section 5 Warnings and Precautions, as well as instructions how to withhold, reduce dose, and discontinue therapy in Section 2 Dosage and Administration. The risks of pemigatinib will be communicated through labeling, oncologists should be familiar with the management of these distinct adverse effects.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for pemigatinib to ensure the benefits outweigh the risks. 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 so that this recommendation can be reevaluated.

10 Appendices

10.1 REFERENCES

- ¹ Lowe, RC. and Anderson, CD “Epidemiology, pathogenesis, and classification of cholangiocarcinoma” www.uptodate.com, accessed 10/08/2019
- ² Lowe, RC Anderson, CD et al “Clinical manifestations and diagnosis of cholangiocarcinoma” www.uptodate.com, accessed 10/08/2019
- ³ Goyal L, Saha SK et al “Polyclonal secondary FGFR2 mutations drive acquired resistance to FGFR inhibition in patients with FGFR2 fusion-positive cholangiocarcinoma” Cancer discovery, March 2017, volume7, Issue 3
- ⁴ Stuart KE. “Systemic therapy for advanced cholangiocarcinoma” www.uptodate.com, accessed 10/08/2019
- ⁵ Vogel, A. Sahai, V. et al FIGHT-202: a phase 2 study of pemigatinib in patients with previously treated locally advanced or metastatic cholangiocarcinoma (CCA) <https://oncologypro.esmo.org/meeting-resources/esmo-2019-congress/FIGHT-202-a-phase-2-study-of-pemigatinib-in-patients-pts-with-previously-treated-locally-advanced-or-metastatic-cholangiocarcinoma-CCA> Accessed 12/02/2019
- ⁶ Pemigatinib NDA 213736 draft prescribing information 03/02/2020
- ⁷ Marcus L., Horiba N., and Chatterjee, S. clinical review for pemigatinib NDA 213736 midcycle presentation, 12/19/2019
- ⁸ Francis JH, Habib LA, et al “Clinical and morphologic characteristics of MEK inhibitor-associated retinopathy: Differences from central serous chorioretinopathy. Ophthalmology 2017, 124 (12): 1788. Epub 2017 Jul 12.
- ⁹ Erdafitinib prescribing information www.Drugs@FDA, accessed 02/19/2020

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