RXADVANCE
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NEW DRUG APPROVAL

Brand Name	Pemazyre™
Generic Name	pemigatinib
Drug Manufacturer	Incyte Corporation

New Drug Approval

FDA Approval Date: April 17, 2020
Review Designation: Orphan
Type of Review: New Drug Application 213736

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Cholangiocarcinoma is a group of cancers that begin in the bile ducts. Bile ducts are branched tubes that connect the liver and gallbladder to the small intestine. They carry bile, which is a fluid that helps the body digest fats that are in food. Bile is made in the liver and stored in the gallbladder before being released in the small intestine after a person eats. Cholangiocarcinoma is classified by its location in relation to the liver. Intrahepatic cholangiocarcinoma begins in the small bile ducts within the liver. This is the least common form of the disease, accounting for less than 10 percent of all cases. Perihilar cholangiocarcinoma (also known as a Klatskin tumor) begins in an area called the hilum, where the right and left major bile ducts join and leave the liver. It is the most common form of the disease, accounting for more than half of all cases. The remaining cases are classified as distal cholangiocarcinomas, which begin in bile ducts outside the liver. The perihilar and distal forms of the disease, which both occur outside the liver, are sometimes grouped together and called extrahepatic cholangiocarcinoma.The three types of cholangiocarcinoma do not usually cause any symptoms in their early stages, and this cancer is usually not diagnosed until it has already spread beyond the bile ducts to other tissues. Symptoms often result when bile ducts become blocked by the tumor. The most common symptom is jaundice, in which the skin and whites of the eyes turn yellow. Other symptoms can include extreme tiredness (fatigue), itching, dark-colored urine, loss of appetite, unintentional weight loss, abdominal pain, and light-colored and greasy stools. These symptoms are described as "nonspecific" because they can be features of many different diseases.

Cholangiocarcinoma (CCA) is a heterogeneous disease arising from a complex interaction between host-specific genetic background and multiple risk factors. Globally, CCA incidence rates exhibit geographical variation, with much higher incidence in parts of the Eastern world compared to the West. These differences are likely to reflect differences in geographical risk factors as well as genetic determinants. Of note, over the past few decades, the incidence rates of CCA appear to change and subtypes of CCA appear to show distinct epidemiological trends. These trends need to be interpreted with caution given the issues of diagnosis, recording and coding of subtypes of CCA. Epidemiological evidences suggest that in general population some risk factors are less frequent but associated with a higher CCA risk, while others are more common but associated with a lower risk. Moreover, while some risk factors are shared by intrahepatic and both extrahepatic forms, others seem more specific for one of the two forms. Currently some pathological conditions have been clearly associated with CCA development, and other conditions are emerging; however, while their impact in increasing CCA risk as single etiological factors has been provided in many studies, less is known when two or more risk factors co-occur in the same patient. Moreover, despite the advancements in the knowledge of CCA aetiology, in Western countries about 50% of cases are still diagnosed without any identifiable risk factor. It is therefore conceivable that other still undefined etiologic factors are responsible for the recent increase of CCA (especially iCCA) incidence worldwide.

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Efficacy

FIGHT-202 (NCT02924376), a multicenter open-label single-arm trial, evaluated the efficacy of PEMAZYRE in 107 patients with locally advanced unresectable or metastatic cholangiocarcinoma whose disease had progressed on or after at least 1 prior therapy and who had an FGFR2 gene fusion or non-fusion rearrangement, as determined by a clinical trial assay performed at a central laboratory. Qualifying in-frame fusions and other rearrangements were predicted to have a breakpoint within intron 17/exon 18 of the FGFR2 gene leaving the FGFR2 kinase domain intact.Patients received Pemazyre in 21-day cycles at a dosage of 13.5 mg orally once daily for 14 consecutive days, followed by 7 days off therapy. Pemazyre was administered until disease progression or unacceptable toxicity. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DoR) as determined by an independent review committee (IRC) according to RECIST v1.1.

The median age was 56 years (range: 26 to 77 years), 61% were female, 74% were White, and 95% had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (42%) or 1 (53%). Ninety-eight percent of patients had intrahepatic cholangiocarcinoma. Eighty-six percent of patients had in-frame FGFR2 gene fusions and the most commonly identified FGFR2 fusion was FGFR2-BICC1 (34%). Fourteen percent of patients had other FGFR2 rearrangements that could not be confidently predicted to be in-frame fusions, including rearrangements without an identifiable partner gene. 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 had received prior platinum-based therapy including 76% with prior gemcitabine/cisplatin.The median time to response was 2.7 months (range 0.7 – 6.9 months).

Efficacy Parameter	**PEMAZYRE N = 107**
ORR (95% 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%)

Table 1: Efficacy Results in FIGHT-202

* The 95% confidence interval (CI) was calculated using the Brookmeyer and Crowley's method.
Note: Data are from IRC per RECIST v1.1, and complete and partial responses are confirmed.

Safety

ADVERSE EVENTS

The most common adverse reactions (incidence ≥ 20%) are hyperphosphatemia, alopecia, diarrhea, nail toxicity, fatigue, dysgeusia, nausea, constipation, stomatitis, dry eye, dry mouth, decreased appetite, vomiting, arthralgia, abdominal pain, hypophosphatemia, back pain, and dry skin

WARNINGS & PRECAUTIONS

- Pemazyre can cause retinal pigment epithelial detachment. Perform ophthalmological examination including optical coherence tomography (OCT) prior to initiation of therapy, every 2 months for the first 6 months of treatment and every 3 months thereafter, and urgently at any time for visual symptoms.
- Hyperphosphatemia: Increases in phosphate levels are a pharmacodynamic effect of Pemazyre. Monitor for hyperphosphatemia and withhold, reduce the dose, or permanently discontinue based on duration and severity of hyperphosphatemia.
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of reproductive potential of the potential risk to the fetus and use effective contraception.

CONTRAINDICATIONS

None

Clinical Pharmacology

MECHANISMS OF ACTION

Pemigatinib is a small molecule kinase inhibitor that targets FGFR1, 2 and 3 with IC50 values of less than 2 nM. Pemigatinib also inhibited FGFR4 in vitro at a concentration approximately 100 times higher than those that inhibit FGFR1, 2, and 3. Pemigatinib inhibited FGFR1-3 phosphorylation and signaling and decreased cell viability in cancer cell lines with activating FGFR amplifications and fusions that resulted in constitutive activation of FGFR signaling. Constitutive FGFR signaling can support the proliferation and survival of malignant cells. Pemigatinib exhibited anti-tumor activity in mouse xenograft models of human tumors with FGFR1, FGFR2, or FGFR3 alterations resulting in constitutive FGFR activation including a patient-derived xenograft model of cholangiocarcinoma that expressed an oncogenic FGFR2- Transformer-2 beta homolog (TRA2b) fusion protein.

Dose & Administration

ADULTS

13.5 mg orally once daily for 14 consecutive days followed by 7 days off therapy in 21-day cycles. Continue treatment until disease progression or unacceptable toxicity occurs.

PEDIATRICS

The safety and effectiveness of Pemazyre have not been established in pediatric patients.

GERIATRICS

In FIGHT-202, 32% of patients were 65 years and older, and 8% of patients were 75 years and older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

RENAL IMPAIRMENT

The recommended dose of Pemazyre has not been established for patients with severe renal impairment (GFR <30mL/min).

HEPATIC IMPAIRMENT

The recommended dose of Pemazyre has not been established for patients with severe hepatic impairment (total bilirubin >3 × ULN with any AST).

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

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Tablets 4.5 mg, 9 mg, and 13.5 mg.