CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214801Orig1s000

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	214801
PDUFA Goal Date	September 30, 2022
OSE RCM #	2021-1537
Reviewer Name	Bob Pratt, Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Associate Director for REMS Design and Evaluation	Laura Zendel, Pharm.D., BCPS
Review Completion Date	August 26, 2022
Subject	Evaluation of Need for a REMS
Established Name	Futibatinib
Trade Name	Lytgobi
Name of Applicant	Taiho Oncology, Inc.
Therapeutic Class	Fibroblast Growth Factor Receptor Inhibitor
Formulation(s)	4 mg tablets
Dosing Regimen	20 mg (five 4-mg tablets) taken orally once daily until disease progression or unacceptable toxicity occurs

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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 Lytgobi (futibatinib) is necessary to ensure the benefits outweigh its risks. Taiho Oncology, Inc. submitted a New Drug Application (NDA) 214801 for futibatinib with the proposed indication for the treatment of patients with previously treated locally advanced or metastatic cholangiocarcinoma harboring fibroblast growth factor receptor 2 (FGFR2) gene rearrangements, including gene fusions (b) (4) The serious risks associated with futibatinib include ocular toxicity, hyperphosphatemia and soft tissue mineralization, and embryo-fetal toxicity. The Applicant did not submit a proposed REMS or risk management plan.

DRM and the Division of Oncology 3 (DO3) agree that a REMS is not necessary to ensure the benefits of futibatinib outweigh its risks. The efficacy of futibatinib was supported by Study TAS-120-101 Phase 2, in which patients treated with futibatinib had an overall response rate of 42% with a median duration of response of 10 months. DO3 recommends accelerated approval based on the currently available data. The serious risks associated with futibatinib of ocular toxicity, hyperphosphatemia and soft tissue mineralization, and embryo-fetal toxicity will be communicated in the warnings and precautions section of the label. The likely prescribers will be oncologists who should have experience managing the serious adverse events associated with futibatinib.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Lytgobi (futibatinib) is necessary to ensure the benefits outweigh its risks. Taiho Oncology, Inc., submitted a New Drug Application (NDA) 214801 for futibatinib with the proposed indication for the treatment of patients with previously treated locally advanced or metastatic cholangiocarcinoma harboring fibroblast growth factor receptor (FGFR) 2 gene rearrangements, including gene fusions (b) (4) This application is under review in the Division of Oncology 3 (DO3). The Applicant did not submit a proposed REMS or risk management plan.

2 Background

2.1 PRODUCT INFORMATION

Lytgobi (futibatinib), an NME, is a kinase inhibitor of fibroblast growth factor receptor (FGFR) 1-4 that inhibits fibroblast growth factor (FGF) receptor signaling. The interaction between FGFR and fibroblast growth factors plays a critical role in a wide range of normal cellular functions, including differentiation, proliferation, migration, and apoptosis that help maintain tissue homeostasis. Dysregulated FGFR signaling promotes the malignant transformation of cells.[1] Futibatinib is proposed for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangement (b) (4) Futibatinib is supplied as 4 mg tablets in blister cards. The proposed dosing regimen is futibatinib 20 mg (five 4 mg tablets) taken

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

orally once daily until disease progression or unacceptable toxicity occurs.[b] Futibatinib is not currently approved in any jurisdiction. Futibatinib was designated as an orphan product and received fast track and breakthrough therapy designations. If approved, the indication will be approved under accelerated approval based on overall response rate (ORR) and duration of response.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for futibatinib NDA 214801 relevant to this review:

- 05/23/2018: Orphan product designation granted
- 08/20/2018: Fast Track designation granted
- 02/11/2021: Breakthrough Therapy designation granted
- 01/31/2022: Final submission of NDA 214801 rolling review for the treatment of patients with previously treated locally advanced or metastatic cholangiocarcinoma harboring fibroblast growth factor receptor (FGFR) 2 gene rearrangements, including gene fusions (b) (4) (b) (4) received
- 05/10/2022: The Mid-Cycle Communication meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the review to date, FDA has not identified major safety concerns that would require a REMS to ensure safe use in the indicated population.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Cholangiocarcinomas (bile duct cancers) arise from the epithelial cells of the intrahepatic and extrahepatic bile ducts. Although these cancers are rare in the United States, they are highly lethal because most are locally advanced at presentation. Data from an analysis of the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program from 2001 to 2015 suggest an incidence of 1.26 cases of cholangiocarcinoma per 100,000 people per year, and that two-thirds of cases are intrahepatic.[1,c] The prognosis of patients with Stage III or IV cholangiocarcinoma is extremely poor, with 5-year survival rates of 10% and 0% respectively, and a median overall survival (OS) of 8 to 12 months.[d,2]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

There is no single standard of care regimen that consistently leads to objective tumor shrinkage, forestalls recurrent biliary obstruction, or extends survival beyond 8 to 15 months in patients with advanced cholangiocarcinoma. Depending on the patient's performance status, bilirubin levels, and comorbidities,

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

first-line regimens include gemcitabine alone or in combination with cisplatin, leucovorin and fluorouracil, a fluoropyrimidine plus oxaliplatin, and capecitabine monotherapy, among others. The choice of second-line therapies depends on the prior failed regimen and includes FOLFOX (folinic acid, fluorouracil and oxaliplatin), capecitabine plus oxaliplatin, irinotecan with or without bevacizumab, and other regimens.[3]

FGFR2 gene alterations are involved in the pathogenesis of cholangiocarcinoma, and approximately 9 to 16 percent of patients with cholangiocarcinoma (15 to 20 percent of intrahepatic tumors) harbor FGFR2 alterations.[3] Pemazyre (pemigatinib) and Truseltiq (infigratinib) are oral kinase inhibitors that target FGFR1-3 and were approved by the FDA in 2020 and 2021, respectively, for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement as detected by an FDA-approved test. Neither drug has a boxed warning in its label nor required a REMS for approval. The serious risks associated with these drugs include ocular toxicity, hyperphosphatemia and soft tissue mineralization, and embryo-fetal toxicity.[4,5]

4 Benefit Assessment

The pivotal trial supporting this application for efficacy and safety consisted of the Phase 2 portion of an open label, multicenter, single arm study (Study TAS-120-101, NCT02052778) to assess the single-agent efficacy of futibatinib in patients with locally advanced or metastatic intrahepatic cholangiocarcinoma (iCCA) with FGFR2 gene fusions or other rearrangements, and who have failed one or more lines of prior systemic therapy. The primary endpoint was ORR as assessed by an independent review committee according to the Response Evaluation Criteria in Solid Tumors (RECIST). Secondary endpoints included duration of response as well as other endpoints. Patients (N=103) received futibatinib 20 mg orally daily for 21 consecutive days (21-day cycles) continuously until disease progression or unacceptable toxicity. The futibatinib treatment group had an ORR of 42% (95% CI, 32% to 52%) with a median duration of response of 9.7 months (95% CI, 7.6 to 17.1). The review team recommends accelerated approval based on the efficacy information currently available.[e,6]

5 Risk Assessment & Safe-Use Conditions

The focus of the risk assessment is on the serious adverse events (SAEs) associated with futibatinib in the 103 patients treated in the Phase 2 portion of Study TAS-120-101.[f]

The serious risks[g] associated with futibatinib, which include ocular toxicity, hyperphosphatemia and soft tissue mineralization, and embryo-fetal toxicity are summarized in the sections below.

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[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.*

[g] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that

5.1 SERIOUS AND SEVERE ADVERSE EVENTS

At least one serious adverse event was experienced by 39 (38%) patients. Serious adverse event preferred terms reported for more than 2 patients (1.9%) were pyrexia (n=4, 3.9%), ascites, upper gastrointestinal hemorrhage, and bile duct obstruction (n=3, 2.9% each). Grade 3/4 severe adverse events occurred in 79 (77%) patients. The most frequently reported severe events by preferred term having an incidence >5% were hyperphosphatemia (n=31, 30%), hyponatremia (n=11, 11%), aspartate aminotransaminase increased (n=10, 10%), fatigue (n=8, 8%), stomatitis (n=6, 6%), and alanine aminotransferase increased (n=6, 6%). Seven patients died on-treatment and within 30 days of the last dose date.[7,8]

Reviewer comment: The draft integrated review states that for all seven patients who died within 30 days of receiving the last treatment dose, the cause of death was disease progression.[6]

5.2 ADVERSE EVENTS OF SPECIAL INTEREST

5.2.1 Ocular Toxicity

In Phase 2 of Study TAS-120-101, eight (8%) patients had adverse events in the category of retinal disorders. Preferred terms were subretinal fluid (3 patients, 3%), chorioretinopathy (2 patients, 2%), detachment of retinal pigment epithelium, maculopathy, and serious retinal detachment (1 patient, 1% each).[7] Section 5.1 of the draft labeling states that among 318 patients who received futibatinib in the pooled safety population[h] where ophthalmologic monitoring did not routinely include optical coherence tomography (OCT), retinal pigment epithelium detachment occurred in 9% of patients. The proposed label recommends performing a comprehensive ophthalmological examination, including OCT of the macula, prior to initiation of therapy, at 6 weeks, and every 3 months thereafter. For onset of visual symptoms, patients are to be referred for ophthalmologic evaluation urgently, with follow-up every 3 weeks until resolution or discontinuation of futibatinib. Section 5.1 of the draft labeling also states that dry eye occurred in 15% of patients in the safety population. The proposed label recommends treating patients with ocular demulcents as needed. If approved, these risks will be communicated in the warnings and precautions section of the label.[9]

5.2.2 Hyperphosphatemia and Soft Tissue Mineralization

In Phase 2 of Study TAS-120-101, adverse events in the category of hyperphosphatemia were reported for 94 (91%) patients. Thirty-two (31%) patients had Grade 3 events, defined as serum phosphate >7 mg/dL irrespective of symptoms. Eighty (85%) of 94 patients with hyperphosphatemia used phosphate lowering medications.[7,i] Section 5.2 of the draft labeling states that futibatinib can cause hyperphosphatemia

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may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

[h] The pooled safety population (n=318) includes studies of patients with cholangiocarcinoma and with other advanced solid tumors.

[i] The majority of cancer patients treated with fibroblast growth factor receptor (FGFR) inhibitors develop hyperphosphatemia. This class effect is due to inhibition of fibroblast growth factor 23 (FGF23) signaling, which normally maintains systemic phosphate balance by stimulating urinary phosphate excretion. Blockade of FGF23 signaling enhances phosphate reabsorption in the proximal tubule, potentially resulting in hyperphosphatemia.

leading to soft tissue mineralization, calcinosis, nonuremic calciphylaxis, and vascular calcification. The proposed label recommends monitoring for hyperphosphatemia throughout treatment and to initiate a low phosphate diet and phosphate lowering therapy when serum phosphate level is ≥5.5 mg/dL. For serum phosphate levels >7 mg/dL, initiate or intensify phosphate lowering therapy and dose reduce, withhold, or permanently discontinue futibatinib based on duration and severity of hyperphosphatemia. If approved, this risk will be communicated in the warnings and precautions section of the label.[9]

5.2.3 Embryo-Fetal Toxicity

Futibatinib may cause fetal harm based on animal studies and the mechanism of action of the drug. The proposed label states to advise pregnant women of the potential risk to the fetus and to advise female patients of reproductive potential as well as males with female partners of reproductive potential to use effective contraception during treatment with futibatinib and for one week after the last dose. If approved, this risk will be communicated in the warnings and precautions section of the label.[9]

6 Expected Postmarket Use

If approved, futibatinib will likely be used in both inpatient and outpatient settings. The likely prescribers will be oncologists.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not submit a proposed REMS or risk management plan and proposed that the risks will be managed by the product labeling.

8 Discussion of Need for a REMS

The FDA review team recommends approval of futibatinib based on the efficacy and safety information currently available.[6] The indication will be approved under accelerated approval based on ORR and duration of response. Futibatinib is a kinase inhibitor and is an additional treatment option for adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangements. The efficacy of futibatinib was supported by Study TAS-120-101 Phase 2, in which patients treated with futibatinib had an overall response rate of 42% with a median duration of response of 10 months. The serious risks associated with futibatinib of ocular toxicity, hyperphosphatemia and soft tissue mineralization, and embryo-fetal toxicity will be communicated in the warnings and precautions section of the label.

Cholangiocarcinoma, which may be classified as intrahepatic or extrahepatic, involves tumors originating in the epithelium of the bile duct. Although these cancers are rare in the United States, they are highly lethal because most are locally advanced at presentation. The prognosis of patients with Stage III or IV

[Stubbs J, Yu A. Overview of the causes and treatment of hyperphosphatemia. In: Goldfarb S, Lam A, eds. UpToDate. Waltham, MA: UpToDate; 2022]

cholangiocarcinoma is extremely poor, with 5-year survival rates of 10% and 0% respectively, and a median overall survival (OS) of 8 to 12 months. The likely prescribers will be oncologists who should have experience monitoring for and managing the serious risks reported with futibatinib. Based on the efficacy and safety associated with futibatinib for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangements, DRM and DO3 agree that a REMS is not necessary to ensure that the benefits outweigh the risks.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable. Therefore, a REMS is not necessary for futibatinib 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; this recommendation can be reevaluated.

10 Appendices

10.1 REFERENCES

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/s/

ROBERT G PRATT
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LAURA A ZENDEL on behalf of NAOMI S BOSTON
08/26/2022 04:16:59 PM

LAURA A ZENDEL
08/26/2022 04:17:06 PM