# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 214622Orig1s000

# 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)

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| Application Type | NDA |
| Application Number | 214622 |
| PDUFA Goal Date | May 29, 2021 |
| OSE RCM # | 2020-1808, 2020-1810 |
| | |
| Reviewer Name(s) | Brad Moriyama, Pharm.D., BCCCP |
| Team Leader | Naomi Boston, Pharm.D. |
| Deputy Division Director | Doris Auth, Pharm.D. |
| Review Completion Date | May 19, 2021 |
| Subject | Evaluation of Need for a REMS |
| | |
| Established Name | infigratinib |
| Trade Name | Truseltiq |
| Name of Applicant | QED Therapeutics |
| Therapeutic Class | kinase inhibitor |
| Formulation(s) | 25 mg, 100 mg capsules |
| Dosing Regimen | infigratinib 125 mg orally once daily for 21 consecutive days followed by 7 days off therapy, in 28-day cycles. |

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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 Truseltiq (infigratinib) is necessary to ensure the benefits outweigh its risks. QED Therapeutics submitted a New Drug Application (NDA) 214622 for infigratinib with the proposed indication for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test. The serious risks associated with infigratinib 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 infigratinib outweigh its risks. The efficacy of infigratinib was supported by study CBGJ398X2204 cohort 1, in which the infigratinib group had an overall response rate of 23% with a median duration of response of 5 months. D03 recommends accelerated approval based on the currently available data. The serious risks associated with infigratinib 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 reported with infigratinib.

# 1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Truseltiq (infigratinib) is necessary to ensure the benefits outweigh its risks. QED Therapeutics submitted a New Drug Application (NDA) 214622 for infigratinib with the proposed indication for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test.[1] 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

Truseltiq (infigratinib), an NME, is a kinase inhibitor, proposed for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangement as detected by an FDA-approved test. Infigratinib is supplied as 25 mg and 100 mg capsules. The proposed dosing regimen is infigratinib 125 mg orally once daily for 21 consecutive days followed by 7 days off therapy, in 28-day cycles.[b] Infigratinib is not currently approved in any

[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.*

jurisdiction. Infigratinib was designated as an orphan product and received fast track designation. 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 infigratinib NDA 214622 relevant to this review:

- 09/10/2019: Fast track designation granted
- 09/11/2019: Orphan drug designation granted
- 09/29/2020: NDA 214622 submission for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangement as detected by an FDA-approved test received
- 01/28/2021: 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 infigratinib

## 3 Therapeutic Context and Treatment Options

### 3.1 DESCRIPTION OF THE MEDICAL CONDITION

Cholangiocarcinoma, which may be classified as intrahepatic or extrahepatic, involves tumors originating in the epithelium of the bile duct.[2] Approximately 8000 patients are diagnosed with cholangiocarcinoma in the United States each year.[3,4,c] The five year survival of advanced/metastatic cholangiocarcinoma is less than 10%.[4,5,d]

### 3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Current guidelines from the National Comprehensive Cancer Network (NCCN) for biliary tract cancers list gemcitabine and cisplatin in the "Preferred Regimens" section for primary treatment of unresectable and metastatic disease.[2] For subsequent line therapy for biliary tract cancers if disease progression, the NCCN guidelines list FOLFOX (fluorouracil/leucovorin and oxaliplatin) in the "Preferred Regimens" section. Mutations in FGFR2 fusions have been reported in 13% to 14% of intrahepatic cholangiocarcinomas.[2] Recently, pemigatinib (Pemazyre), a kinase inhibitor, was approved by the FDA in 2020 for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangement as detected by an FDA-approved test.[6] Pemigatinib does not have boxed warning in its label or have required a REMS for approval. The serious

[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.*

risks associated with pemigatinib include ocular toxicity, hyperphosphatemia and soft tissue mineralization, and embryo-fetal toxicity.

# 4 Benefit Assessment

The pivotal trial NCT 02150967 (CBGJ398X2204) supporting this application for efficacy and safety consisted of a Phase 2, multicenter, open-label, single arm trial which in cohort 1 evaluated infigratinib in patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or rearrangement as determined for enrollment by local or central testing.[1,4,7] Patients (N=108) received infigratinib 125 mg orally daily for 21 consecutive days followed by 7 days off therapy, in 28-day cycles. The primary endpoints were ORR and duration of response. The infigratinib treatment group had an ORR of 23% (95% CI 16% to 32%) with a median duration of response of 5 months (95% CI 3.7 to 9.3). The FDA clinical reviewer recommended accelerated approval based on the currently available data.[e]

# 5 Risk Assessment & Safe-Use Conditions

The safety of infigratinib was evaluated in study NCT 02150967 (CBGJ398X2204).[1,4,7,f] In the safety population from Study CBGJ398X2204 in patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangement, 108 patients received infigratinib. However, the safety population for the serious risk in section 5.1 to section 5.3 below included 351 patients in studies CBGJ398X2204, CBGJ398X2101, CBGJ398X2201, and CBGJ398XUS04. Discontinuation due to an adverse event occurred in 15% of the infigratinib group. Common adverse reactions reported with infigratinib included nail toxicity, stomatitis, dry eye, fatigue, alopecia, palmar-plantar erythrodysesthesia syndrome, arthralgia, dysgeusia, constipation, abdominal pain, dry mouth, eyelash changes, diarrhea, dry skin, decreased appetite, vision blurred, and vomiting.

The serious risks[g] associated with infigratinib 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 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.

### 5.1 OCULAR TOXICITY

Section 5.1 of the draft labeling states that retinal pigment epithelial detachment (RPED), which may cause symptoms such as blurred vision, has been reported with infigratinib. Retinal pigment epithelial detachment, including patients with asymptomatic RPED, occurred in 11% of patients receiving infigratinib in clinical trials. The proposed label recommends to perform a comprehensive ophthalmic examination including optical coherence tomography prior to initiation of infigratinib, at 1 month, at 3 months, and then every 3 months thereafter during treatment. It recommends to refer patients for ophthalmic evaluation urgently for onset of visual symptoms, and follow-up every 3 weeks until resolution or discontinuation of infigratinib. Section 5.1 of the draft labeling also states that dry eye occurred in 29% of patients receiving infigratinib in clinical trials. The proposed label recommends to treat patients with ocular demulcents as needed. If approved, these risks will be communicated in the warnings and precautions section of the label.

### 5.2 HYPERPHOSPHATEMIA AND SOFT TISSUE MINERALIZATION

Section 5.2 of the draft labeling states that hyperphosphatemia, which may lead to soft tissue mineralization, cutaneous calcinosis, non-uremic calciphylaxis, vascular calcification, and myocardial calcification, has been reported with infigratinib. Hyperphosphatemia occurred in 82% of patients receiving infigratinib in clinical trials. The proposed label recommends to monitor for hyperphosphatemia throughout treatment. It recommends to initiate phosphate lowering therapy when serum phosphate level is > 5.5 mg/dL and for serum phosphate level > 7.5 mg/dL to withhold infigratinib and initiate phosphate lowering therapy. It also recommends to withhold, dose reduce, or permanently discontinue infigratinib based on duration and severity of hyperphosphatemia. If approved, this risk will be communicated in the warnings and precautions section of the label.

### 5.3 EMBRYO-FETAL TOXICITY

Infigratinib may cause fetal harm based on animal studies and the mechanism of action of the drug. The proposed label states to advise patients of the potential risk of embryo-fetal harm. The proposed label recommends in females of reproductive potential to verify pregnancy status before starting infigratinib and that effective contraception be used during treatment and for 1 month after the final dose. In addition, in males with a female partner of reproductive potential it is recommended that effective contraception be used during treatment and for 1 month after the final dose. If approved, this risk will be communicated in the warnings and precautions section of the label.

## 6 Expected Postmarket Use

If approved, infigratinib will primarily 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 propose any risk management activities for infigratinib beyond routine pharmacovigilance and labeling.

# 8 Discussion of Need for a REMS

The FDA clinical reviewer recommends approval of infigratinib on the basis of the efficacy and safety information currently available. The indication will be approved under accelerated approval based on ORR and duration of response. Infigratinib 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 rearrangement as detected by an FDA-approved test. The efficacy of infigratinib was supported by study CBGJ398X2204 cohort 1, in which the infigratinib group had an ORR of 23% with a median duration of response of 5 months. The serious risks associated with infigratinib 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. Approximately 8000 patients are diagnosed with cholangiocarcinoma in the United States each year. The five year survival of advanced/metastatic cholangiocarcinoma is less than 10%. The likely prescribers will be oncologists who should have experience managing the serious adverse events reported with infigratinib. Based on the efficacy and risks associated with infigratinib for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangement as detected by an FDA-approved test, the DRM and D03 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 infigratinib 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

[1] Proposed prescribing information for infigratinib as currently edited by FDA, May 5, 2021.

[2] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Hepatobiliary Cancers (version 2.2021 – April 16, 2021). https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf (accessed 2021 April 27).

[3] Key Statistics for Bile Duct Cancer. American Cancer Society. Last revised July 3, 2018. https://www.cancer.org/cancer/bile-duct-cancer/about/key-statistics.html (accessed 2021 April 27)

[4] Infigratinib multi-disciplinary review and evaluation. Accessed May 6, 2021.

[5] Fostea RM, Fontana E, Torga G, Arkenau HT. Recent Progress in the Systemic Treatment of Advanced/Metastatic Cholangiocarcinoma. Cancers (Basel). 2020;12(9):2599.

[6] Pemazyre (pemigatinib) package insert. Wilimington, DE: Incyte Corporation; 2021 February.

[7] Pelosof L, Casak S, Bhattacharjee A, Cheng J. Division of Oncology 3 (DO3). Infigratinib. Mid-Cycle Meeting, clinical and statistics reviewer slides. January 14, 2021.

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