CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217564Orig1s000

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	217564
PDUFA Goal Date	November 30, 2023
OSE RCM #	2023-4349; 2023-4351
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Deputy Director	Laura Zendel, Pharm.D.
Review Completion Date	November 7, 2023
Subject	Evaluation of the need for a REMS
Established Name	Fruquintinib
Trade Name	Fruzaqla
Name of Applicant	Hutchmed Ltd.
Therapeutic Class	Kinase inhibitor
Formulation(s)	1mg and 5mg capsules
Dosing Regimen	5 mg orally once daily, for the first 21 days of each 28-day cycle

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Fruzaqla (fruquintinib) is necessary to ensure the benefits outweigh its risks. Hutchmed Ltd. submitted a New Drug Application (NDA) 217564 for fruquintinib with the proposed indication for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor (VEGF) therapy, and, if *RAS* wild-type, an anti-epidermal growth factor receptor (EGFR) therapy. The serious risks associated with the use of fruquintinib are hypertension, hemorrhagic events, infection, gastrointestinal perforation, hepatotoxicity, proteinuria, palmar-plantar erythrodysesthesia (PPE), posterior reversible encephalopathy syndrome (PRES), impaired wound healing, allergic reactions, and embryo-fetal toxicity. The Applicant did not submit a REMS or risk management plan with this application.

The Division of Risk Management (DRM) and the Division of Oncology 3 (DO3) have determined that a REMS is not necessary to ensure the benefits of fruquintinib outweigh its risks. Based on the efficacy and safety information currently available, the clinical reviewer stated that fruquintinib shows clinically meaningful benefit and recommends approval of fruquintinib as a kinase inhibitor indicated for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if RAS wild-type, an anti-EGFR therapy. The review team concluded that the treatment with fruquintinib demonstrated a statistically significant, clinically meaningful prolongation of overall survival (OS) and progression-free survival (PFS) in both FRESCO and FRESCO-2 studies. The safety profile is similar to another kinase inhibitor approved for a similar indication, which do not require a REMS. If approved, labeling will be like the currently approved kinase inhibitor, regorafenib (Stivarga). Management of the adverse events of fruquintinib will be communicated in Warnings and Precautions, Patient Counseling Information, and the Patient Package Insert (PPI).

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a REMS for Fruzaqla (fruquintinib) is necessary to ensure the benefits outweigh its risks. Hutchmed Ltd. submitted a New Drug Application (NDA) 217564 for fruquintinib with the proposed indication for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor (VEGF) therapy, and, if *RAS* wild-type, an anti-epidermal growth factor receptor (EGFR) therapy.[1] This application is under review in the Division of Oncology 3 (DO3). The applicant did not submit a REMS or risk management plan with this application.

2 Background

2.1 Product Information

Fruquintinib is a new molecular entity (NME) NDA type 505(b)(1) pathway application.[a] It is a kinase inhibitor of VEGFR-1, -2, and -3. In vitro studies showed fruquintinib inhibited VEGF-mediated endothelial cell proliferation and tubular formation. In vitro and in vivo studies showed fruquintinib inhibited VEGF-induced VEGFR-2 phosphorylation. In vivo studies showed fruquintinib inhibited tumor growth in a tumor xenograft mouse model of colon cancer.[1] Fruquintinib is proposed to be supplied as 1 mg and 5 mg capsules. The recommended dosage of fruquintinib is 5 mg orally once daily, with or without food for the first 21 days of each 28-day cycle until disease progression or unacceptable toxicity.[b,1] Fruquintinib was granted fast track designations on June 15, 2020 for multiple indications. Fruquintinib has been marketed in China as Elunate since September 4, 2018.[2]

2.2 Regulatory History

The following is a summary of the regulatory history for fruquintinib (NDA 217564) relevant to this review:

- 08/25/2016: Investigational New Drug (IND) 131038 submission for fruquintinib received.
- 06/15/2020: Fast track designation granted for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if RAS wild-type, an anti-EGFR therapy.
- 03/30/2023: NDA 217564 submission for fruquintinib with the proposed indication for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if *RAS* wild-type, an anti-EGFR therapy, received.
- 07/13/2023: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant at the Post Mid-cycle meeting that no safety issues have been identified for fruquintinib that would require a REMS.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Colorectal cancer (CRC) is a major global health issue and is the third most common malignancy diagnosed in both men and women and the second most common cause of cancer-related deaths worldwide.[3] The expected number of new cases of CRC in the United States in 2023 is 153,020[c], with

[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.*

[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.*

52,550 expected deaths due to the disease[d].[4] Five-year survival for patients diagnosed with CRC is approximately 65%.[5] Of new colorectal cancer diagnoses, 20% of patients have metastatic disease at presentation and another 25% who present with localized disease will later develop metastases. The prognosis of metastatic CRC is poor; among people diagnosed with metastatic colorectal cancer, approximately 70% to 75% of patients survive beyond 1 year, 30% to 35% beyond 3 years, and fewer than 20% beyond 5 years from diagnosis.[6,d]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The primary treatment for unresectable metastatic CRC is systemic therapy including cytotoxic chemotherapy, biologic therapy, immunotherapy, and their combinations.[6] Evaluating treatment options is complex because of the heterogeneity of the patient population, including different molecular subtypes.[7] Established first and second-line systemic treatments for patients with mCRC include cytotoxic chemotherapy with fluoropyrimidine-, oxaliplatin-, and irinotecan-based-regimens. These can be administered with or without anti-angiogenic biologic agents (anti-VEGF or anti-VEGFR-2), such as bevacizumab, aflibercept, or ramucirumab; or, for patients with rat sarcoma (RAS) wild-type tumors, anti-EGFR therapy, such as cetuximab or panitumumab. Fluoropyrimidines, either intravenous fluorouracil or oral capecitabine, have been first-line conventional chemotherapy for metastatic CRC for more than 50 years, and more recently, targeted therapies have been developed for specific molecular subtypes and primary tumor sidedness.[6,7] Chemotherapy and anti–EGFR therapy is recommended for microsatellite stable or proficient mismatch repair left-sided treatment-naive RAS wild-type mCRC; chemotherapy and anti–VEGF therapy is recommended for microsatellite stable or proficient mismatch repair RAS wild-type right-sided mCRC. In patients with high frequency microsatellite instability (MSI-H)/mismatch repair (MMR)-deficient tumors, nivolumab, nivolumab plus ipilimumab, and pembrolizumab are considered.[8] A kinase inhibitor, encorafenib[9] plus cetuximab is recommended for patients with previously treated B-Raf proto-oncogene (BRAF) V600E–mutant mCRC that has progressed after at least one previous line of therapy. Subsequent treatment options include trifluridine/tipiracil or a kinase inhibitor, regorafenib[10].[6,7] Regorafenib has a boxed warning for hepatotoxicity, but a REMS was not required for approval of these kinase inhibitors. Cytoreductive surgery plus systemic chemotherapy may be recommended for selected patients with colorectal peritoneal metastases. Stereotactic body radiation therapy may be recommended following systemic therapy for patients with oligometastases of the liver who are not considered candidates for resection. Perioperative chemotherapy or surgery alone is offered to patients with mCRC who are candidates for potentially curative resection of liver metastases.[7] Please refer DO3's Multi-disciplinary Review and Evaluation for fruquintinib for a detailed clinical review on treatment armamentarium relevant to the proposed indication.[11] After failure of standard therapies, there is currently no standard-of-care, and patients who are well enough to receive additional therapy are either considered for treatment in an available clinical trial or are rechallenged with previously prescribed agents. Despite recent advances for the treatment of mCRC, most newer therapies, such as immunotherapy and BRAF inhibitors, benefit only select populations.[2] There is a need for therapeutic strategies with new alternative modalities that encompass a better tolerated treatment option in heavily treatment-experienced patients with mCRC.

[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.*

4 Benefit Assessment

The efficacy and safety of fruquintinib were established in two multicenter, randomized, double-blind, placebo-controlled studies (FRESCO & FRESCO-2).

4.1 FRESCO STUDY

FRESCO Study (NCT02314819) was a multicenter, randomized, double-blind, placebo-controlled study conducted in China that enrolled 416 patients with metastatic colorectal cancer who had disease progression during or after prior treatment with fluoropyrimidine-, oxaliplatin, or irinotecan-based chemotherapy. Patients older than 75 years of age, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥ 2, left ventricular ejection fraction ≤ 50%, systolic blood pressure >140 mm Hg or diastolic blood pressure > 90 mm Hg, urine protein ≥ 1 g/24h, or brain metastases were ineligible. Randomization was stratified by prior use of VEGF inhibitors (yes vs. no) and *KRAS* status (wild type vs. mutant). Patients were randomized (2:1) to receive fruquintinib 5 mg orally once daily (N=278) for the first 21 days of each 28-day cycle plus best supportive care (BSC) or placebo (N=138) plus BSC. Patients received either fruquintinib or placebo until disease progression or unacceptable toxicity. The study population characteristics were median age of 56 years (range: 23 to 75), with 19% ≥ 65 years of age; 61% male; 100% Asian; 27% had an ECOG PS of 0 and 73% had an ECOG PS of 1 (73%), and 44% had *KRAS*- mutant tumors. All patients received prior treatment with fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapy; 30% of patients received prior anti-VEGF therapy, and 14% received prior anti-EGFR therapy.[1]

4.2 FRESCO-2 STUDY

FRESCO-2 (NCT04322539) was an international, multicenter, randomized, double-blind, placebo-controlled study that enrolled 691 patients with metastatic colorectal cancer who had disease progression during or after prior treatment with fluoropyrimidine-, oxaliplatin-, irinotecan-based chemotherapy, an anti-VEGF biological therapy, if *RAS* wild type, an anti-EGFR biological therapy, and trifluridine/tipiracil, regorafenib, or both. Patients with an ECOG PS ≥2, left ventricular fraction ≤ 50%, systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, urine protein ≥ 1 g/24h, or untreated brain metastases were ineligible. Randomization was stratified by prior use of trifluridine/tipiracil or regorafenib (trifluridine/tipiracil vs. regorafenib vs. trifluridine/tipiracil and regorafenib), *RAS* status (wild type vs. mutant), and duration of metastatic disease (≤18 months vs. 18 months). Patients were randomized (2:1) to receive fruquintinib 5 mg orally once daily (N=461) for the first 21 days of each 28-day cycle plus BSC or placebo (N=230) plus BSC. Patients received either fruquintinib or placebo until disease progression or unacceptable toxicity. The study population characteristics were median age of 64 years (range: 25 to 86), with 47% ≥ 65 years of age; 56% male; 81% White, 9% Asian, 2.9% Black or African American, and 0.7% Native Hawaiian/Pacific Islander; 43% had an ECOG PS of 0 and 57% had an ECOG PS of 1, and 63% had *RAS*-mutant tumors. Eighteen percent of the patients were enrolled in North America, 72% in Europe, and 10% in Asia Pacific (Japan and Australia) region. All patients received prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy; 96% received prior anti-VEGF therapy, 39% received prior anti-EGFR therapy, 91% received trifluridine/tipiracil, 48% received regorafenib, and 39% received both trifluridine/tipiracil and regorafenib.[1]

The major efficacy outcome measure for both studies were overall survival (OS) and an additional efficacy outcome measure was progression-free survival (PFS) according to RECIST v1.1. The efficacy results are summarized in Table 1.[1,11,e]

Table 1: Efficacy Results from FRESCO and FRESCO-2 Studies [1,11,e]

	FRESCO		FRESCO-2	
Endpoint	**FRUZAQLA + BSC N=278**	**Placebo + BSC N=138**	**FRUZAQLA + BSC N=461**	**Placebo + BSC N=230**
OS				
Number of patients with event (%)	188 (68%)	109 (79%)	317 (69%)	173 (75%)
Median in months (95% CI)	9.3 (8.2, 10.5)	6.6 (5.9, 8.1)	7.4 (6.7, 8.2)	4.8 (4.0, 5.8)
Hazard Ratio[a] (95% CI)	0.65 (0.51, 0.83)		0.66 (0.55, 0.80)	
P-Value[b]	<0.001		<0.001	
PFS				
Number of patients with event (%)	235 (85%)	125 (91%)	392 (85%)	213 (93%)
Median in months (95% CI)	3.7 (3.7,4.63	1.8 (1.8, 1.8)	3.7 (3.5, 3.8)	1.8 (1.8, 1.9)
Hazard Ratio[a] (95% CI)	0.26 (0.21, 0.34)		0.32 (0.27, 0.39)	
P-Value[b]	<0.001		<0.001	

Abbreviations: CI=confidence interval; HR=hazard ratio; N=number of patients; OS=overall survival; PFS=progression-free survival
[a]The HR and its 95% CI were estimated using stratified Cox's proportional hazards model (accounting for the stratification factors), in which treatment group is the only covariate in the model.
[b]*P*-Value (2-sided) was calculated using the stratified log-rank test to account for the stratification factors.

The addition of fruquintinib to BSC resulted in a statistically significant improvement in OS and PFS compared to placebo plus BSC (see Table 1).[1,e] The clinical reviewer stated that in the FRESCO study, a statistically significant, clinically meaningful prolongation of overall survival was observed in patients randomized to receive fruquintinib; median overall survival was 9.3 months in the fruquintinib arm (95% CI: 8.2, 10.5) compared to 6.6 months in the placebo arm (95% CI: 5.9, 8.1), with a hazard ratio of 0.65 (95% CI: 0.51, 0.83; p < 0.001). Similarly, in the FRESCO-2 study, a statistically significant, clinically

[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*

meaningful prolongation of overall survival was observed in patients randomized to receive fruquintinib; median overall survival was 7.4 months in the fruquintinib arm (95% CI: 6.7, 8.2) compared to 4.8 months in the placebo arm (95% CI: 4.8, 5.8), with a hazard ratio of 0.66 (95% CI: 0.55, 0.80; p < 0.001). The clinical reviewer also stated that in the FRESCO study, a statistically significant, clinically meaningful prolongation of PFS was observed in patients randomized to fruquintinib; median PFS was 3.71 months in the fruquintinib arm (95% CI: 3.65, 4.63) compared with 1.84 months in the placebo arm (95% CI: 1.81, 1.84), with a hazard ratio of 0.26 (95% CI: 0.21, 0.34; p < 0.001). Similarly, in the FRESCO-2 study, a statistically significant, clinically meaningful prolongation of PFS was observed in patients randomized to receive fruquintinib; median PFS was 3.7 months in the fruquintinib arm (95% CI: 3.5, 38) compared with 1.8 months in the placebo arm (95% CI: 1.8, 1.9), with a hazard ratio of 0.321 (95% CI: 0.267, 0.386; p < 0.001).[11,e]

The clinical reviewer stated that the observed improvement in survival in the overall population with a HR of 0.66 in FRESCO-2 and 0.65 in FRESCO is statistically robust and clinically meaningful.[11,e]

5 Risk Assessment & Safe-Use Conditions

The following section is a summary of relevant safety information to date for fruquintinib. The safety of fruquintinib was evaluated in in two multicenter, randomized, double-blind, placebo-controlled studies (FRESCO & FRESCO-2) (see Section 4: Benefit Assessment). The median duration of therapy with fruquintinib in FRESCO & FRESCO-2 were 3.68 months (range 0.3 to 22.1 months) and 3 months (range (b) (4) months), respectively.[1]

The pooled safety population (n=911) reflects the exposure to fruquintinib as a single-agent in 911 patients with mCRC who were enrolled in three randomized, placebo-controlled studies (FRESCO-2, FRESCO and 2012-013-00CH1) (N=781); three open-label studies (2009-013-00CH1, 2012-013-00CH3 and 2015-013-00US1) (N=124); and an open-label lead-in cohort of FRESCO-2 (N=6), which reflects the data for Warnings and Precautions. Among the 911 patients who received fruquintinib, 23% were exposed for 6 months or longer and 3.5% were exposed for greater than one year. The most common adverse reactions (incidence ≥ 20%) that occurred in pooled monotherapy studies were hypertension, palmar-plantar erythrodysesthesia (PPE), proteinuria, dysphonia, abdominal pain, diarrhea, and asthenia.[1]

Deaths

Out of a total 911 patients in the pooled safety population, 627 patients (68.8%) died. The most frequent primary cause of death was disease progression (59.5%). Other causes of death were AE (2.6%), unknown (5.8%), other (0.1%), and missing (0.8%). A total of 129 patients (14.2%) died during the treatment period. The most frequent primary cause of death was disease progression (11.0%). Other causes of death were AE (2.2%), unknown (0.8%), and missing (0.2%). AEs leading to death that occurred in more than 2 patients (≥ 0.3%) were: Pneumonia (0.4%), death (0.3%), and hemoptysis (0.3%).[2] In the Study FRESCO, fatal adverse reactions occurred in 7 (2.5%) patients who received fruquintinib including cerebral infarction (n=1), gastrointestinal hemorrhage (n=1), hemoptysis (n=1), bacterial infection (n=1), lung/lower respiratory infection (n=2), and multiple organ dysfunction (n=1).[1] Fatal adverse reactions occurred in 14 (3.1%) patients who received fruquintinib. In the Study FRESCO-2, fatal adverse reactions occurring in ≥ 2 patients include pneumonia (n=3), sepsis/septic shock (n=2), and hepatic failure/encephalopathy (n=2).[1]

Serious Adverse Reactions

In the Study FRESCO, serious adverse reactions occurred in 15% of patients treated with fruquintinib. Serious adverse reactions in >2% of patients included intestinal obstruction (2.9%) and hemorrhage (2.2%). Adverse reactions leading to treatment discontinuation occurred in 15% of patients who received fruquintinib. Adverse reactions leading to treatment discontinuations of fruquintinib in ≥ 1% were intestinal obstruction, proteinuria and hepatic function abnormalities. Adverse reactions leading to dose interruptions occurred in 35% of patients treated with fruquintinib. Adverse reactions leading to dose interruptions of fruquintinib in ≥ 2% of patients were PPE, proteinuria, platelet count decreased, ALT increased, hypertension, and diarrhea. Dose reductions of fruquintinib due to an adverse reaction occurred in 24% of patients. Adverse reactions leading to dose reduction of fruquintinib in ≥ 2% of patients were PPE, proteinuria, and hypertension.[1]

In the Study FRESCO-2, serious adverse reactions occurred in 38% of patients treated with fruquintinib. Serious adverse reactions in > 2% of patients treated with fruquintinib include hemorrhage (2.2%) and gastrointestinal perforation (2.0%). Adverse reactions leading to treatment discontinuation occurred in 20% of patients treated with fruquintinib. Adverse reactions leading to treatment discontinuations of fruquintinib in ≥ 1% of patients were asthenia and gastrointestinal perforation. Adverse reactions leading to dose interruptions occurred in 47% of patients treated with fruquintinib. Adverse reactions leading to dose interruptions of fruquintinib in ≥ 2% of patients fruquintinib were palmar-plantar erythrodysesthesia, proteinuria, asthenia, abdominal pain, hypertension, vomiting and diarrhea. Adverse reactions leading to dose reductions occurred in 24% of patients treated with fruquintinib. Adverse reactions leading to dose redactions of fruquintinib in ≥ 2% of patients were PPE, hypertension and asthenia.[1]

Similar to another kinase inhibitor, regorafenib (Stivarga)[10], if approved, labeling will include the following risks in the Warnings and Precautions section.

5.1 HYPERTENSION

In the pooled safety population (n=911), hypertension occurred in 450 (49%) patients with mCRC treated with fruquintinib, including Grade 3-4 events in 19%, and hypertensive crisis in three patients (0.3%). The median time to first onset of hypertension was 14 days from first dose of fruquintinib. Labeling instructs not to initiate fruquintinib unless blood pressure is adequately controlled. Labeling also instructs to monitor patients' blood pressure weekly the first month, at least monthly thereafter and as clinically indicated, and to initiate or adjust anti-hypertensive therapy as appropriate. Monitoring and dosage modifications for toxicities to address the safety issues with fruquintinib will also be included in the Dosage and Administration section of the label.[1]

5.2 HEMORRHAGIC EVENTS

In 911 patients with mCRC treated with fruquintinib, 6% of patients experienced a gastrointestinal hemorrhage, including 13 patients (1%) with a Grade ≥3 event including 2 patients with fatal hemorrhages. Labeling instructs to permanently discontinue fruquintinib in patients with severe or life-threatening hemorrhage, and to monitor the International Normalized Ratio (INR) levels in patients receiving anticoagulants. Monitoring and dosage modifications for toxicities to address the safety issues with fruquintinib will also be included in the Dosage and Administration section of the label.[1]

5.3 INFECTIONS

In 781 patients treated with fruquintinib across three randomized, placebo-controlled trials, the overall incidence of infections was higher (18% vs. 12%) including for fatal infections (1% vs. 0.3%) in the fruquintinib-treated patients with mCRC as compared to the placebo arms (n=391). In the pooled safety population of 911 patients with mCRC treated with fruquintinib, the most common infections were urinary tract infections (6.8%), upper respiratory tract infections (3.2%) and pneumonia (2.5%); fatal infections included pneumonia (0.4%), sepsis (0.2%), bacterial infection (0.1%), lower respiratory tract infection (0.1%) and septic shock (0.1%).Labeling instructs to withhold fruquintinib for Grade 3 or 4 infections, or worsening infection of any grade, and resume fruquintinib at the same dose when the infection has resolved.[1]

5.4 GASTROINTESTINAL PERFORATION

In 911 patients with mCRC treated with fruquintinib, 12 patients (1.3%) experienced a Grade ≥3 gastrointestinal perforation, including one fatal event. Labeling instructs to permanently discontinue Fruquintinib in patients who develop gastrointestinal perforation or fistula.[1]

5.5 HEPATOTOXICITY

In the pooled safety population of 911 patients with mCRC treated with fruquintinib, 48% experienced increased ALT or AST, including Grade ≥3 events in 5%, and fatal events in 0.2%. Median time to first onset of elevated liver enzymes was 29 days from first dose of fruquintinib. Labeling instructs to monitor for liver function tests (ALT, AST, and bilirubin) before initiation and periodically throughout treatment with fruquintinib. Monitoring and dosage modifications for toxicities depending on the severity and persistence of hepatotoxicity as manifested by elevated liver function tests to address the safety issues with fruquintinib will also be included in the Dosage and Administration section of the label.[1]

5.6 PROTEINURIA

In 911 patients with mCRC treated with fruquintinib, 36% experienced proteinuria and 2.5% of patients experienced Grade ≥3 events. Median time to first onset of proteinuria was 22 days from first dose of fruquintinib. Labeling instructs to monitor for proteinuria before initiation and periodically throughout treatment with fruquintinib. For proteinuria ≥2g/24 hours, labeling instructs to withhold fruquintinib until improvement to ≤Grade 1 proteinuria, resume fruquintinib at a reduced dose, and discontinue fruquintinib in patients who develop nephrotic syndrome. Monitoring and dosage modifications for toxicities to address the safety issues with fruquintinib will also be included in the Dosage and Administration section of the label.[1]

5.7 PALMAR-PLANTAR ERYTHRODYSESTHESIA (PPE)

In 911 patients with mCRC treated with fruquintinib, PPE occurred in 35%, including 8% with Grade 3 events. Median time to first onset of PPE was 19 days from first dose of fruquintinib. Labeling instructs to discontinue fruquintinib for severe and persistent skin reactions. Monitoring and dosage modifications for toxicities to address the safety issues with fruquintinib will also be included in the Dosage and Administration section of the label.[1]

5.8 Posterior Reversible Encephalopathy Syndrome (PRES)

In 911 patients with mCRC treated with fruquintinib, PRES occurred in one patient. Labeling instructs to perform an evaluation for PRES in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function, and to discontinue fruquintinib in patients who develop PRES.[1]

5.9 Impaired Wound Healing

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. In 911 patients with mCRC treated with fruquintinib, 1 patient experienced a Grade 2 event of wound dehiscence. Labeling instructs not to administer fruquintinib for at least 2 weeks prior to major surgery, and also not to administer fruquintinib for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of fruquintinib after resolution of wound healing complications has not been established.[1]

5.10 Arterial Thromboembolic Events

In 911 patients with mCRC treated with fruquintinib, 7 patients (0.8%) experienced an arterial thromboembolic event; additionally, fruquintinib studies excluded patients with clinically significant cardiovascular disease, uncontrolled hypertension, or with thromboembolic events within the prior 6 months. Labeling recommends for a careful consideration should be made before the initiation of fruquintinib in patients with a recent history of thromboembolic events. In patients who develop arterial thromboembolism discontinue fruquintinib.[1]

5.11 Allergic Reactions to FD&C Yellow No. 5 (Tartrazine) and No. 6 (Sunset Yellow FCF)

Fruquintinib 1 mg capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity. Fruquintinib 1 mg contains FD&C Yellow No. 6 (sunset yellow FCF), which may cause allergic reactions.[1]

5.12 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal data, fruquintinib can cause fetal harm when administered to a pregnant woman. In an embryo-fetal developmental study in rats, embryotoxic and teratogenic effects were observed at exposures below the clinical exposure. Oral administration of fruquintinib to pregnant rats during the period of organogenesis resulted in fetal external (edema and head and tail abnormalities), visceral, and skeletal malformations at doses approximately 0.2 times the recommended clinical dose of 5mg based on body surface area (BSA). Labeling instructs healthcare providers to advise pregnant women of the potential risk to a fetus. Besides being communicated in the Warnings and Precautions section of the label, recommended guidance to use effective contraception during treatment with fruquintinib and for 2 weeks after the last dose for females of childbearing potential and males with female partners of childbearing potential, will be communicated in the Use in Specific Populations section of the label.[1]

6 Expected Postmarket Use

Similar to other kinase inhibitors, such as encorafenib (Braftovi)[9] and regorafenib (Stivarga)[10], if approved, fruquintinib will be administered in both inpatient and outpatient settings. It is expected that oncologists, familiar with the management of toxicities such as hypertension, hemorrhagic events, infection, gastrointestinal perforation, hepatotoxicity, proteinuria, PPE, PRES, impaired wound healing, allergic reactions, and embryo-fetal toxicity, will be the likely prescribers of fruquintinib.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not submit any risk management activities for fruquintinib beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for fruquintinib, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the likely prescribing population.

Fruquintinib is a kinase inhibitor, with the proposed indication for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if RAS wild-type, an anti-EGFR therapy. CRC is the third most common malignancy diagnosed in both men and women and the second most common cause of cancer-related deaths worldwide. The primary treatment for unresectable metastatic CRC is systemic therapy, and evaluating treatment options is complex because of the heterogeneity of the patient population, including different molecular subtypes. After failure of standard therapies, there is currently no standard-of-care, and patients who are well enough to receive additional therapy are either considered for treatment in an available clinical trial or are rechallenged with previously prescribed agents. Despite recent advances for the treatment of mCRC, most newer therapies, such as immunotherapy and BRAF inhibitors, benefit only select populations. There is a need for therapeutic strategies with new alternative modalities that encompass a better tolerated treatment option in heavily treatment-experienced patients with mCRC. Based on the efficacy and safety information currently available, the clinical reviewer stated that fruquintinib shows clinically meaningful benefit and recommends approval of fruquintinib as a kinase inhibitor indicated for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if RAS wild-type, an anti-EGFR therapy.[1,11]

DRM and DO3 have determined that if approved, a REMS is not necessary to ensure the benefits of fruquintinib outweigh its risks. Fruquintinib appeared efficacious in its primary outcome of OS and secondary outcome of PFS, and its risks can be communicated and managed through labeling.[1,11] The clinical reviewer stated that the treatment with fruquintinib demonstrated a statistically significant, clinically meaningful prolongation of OS and PFS in both FRESCO and FRESCO-2 studies.[11] The most concerning adverse reactions observed with the use of fruquintinib are risks for hypertension, hemorrhagic events, infection, gastrointestinal perforation, hepatotoxicity, proteinuria, PPE, PRES, impaired wound healing, allergic reactions, and embryo-fetal toxicity, which are the same as in the

currently approved kinase inhibitor, regorafenib (Stivarga)[10]. It is expected that oncologists, familiar with the management of these toxicities, will be the likely prescribers of fruquintinib. The review team concluded that the adverse reaction profile observed in patients receiving fruquintinib is consistent with the adverse reaction profile of other agents in the same pharmacological class and the disease setting. The risks of fruquintinib are acceptable considering the life-threatening nature of mCRC.[11] Regorafenib has a boxed warning for hepatotoxicity, but a REMS was not required for approval of these kinase inhibitors. At the time of this review, none of the risks identified for fruquintinib will receive a boxed warning in the label.[1] If fruquintinib is approved, similar to the other approved kinase inhibitors, Warnings and Precautions in the labeling will be used to communicate the safety issues and management of toxicities associated with fruquintinib, as well as information to be included in Patient Counseling Information, and in the PPI. Additionally, as minorities were underrepresented in the studies, the Agency is planning to issue a post-marketing commitment (PMC) study to conduct a clinical study to further characterize any potential differences in the clinical effects of fruquintinib, including pharmacokinetics (PK), activity and safety in these populations.[12]

9 Conclusion & Recommendations

DRM has determined that a REMS is not necessary to ensure the benefits outweigh the risks of fruquintinib for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if RAS wild-type, an anti-EGFR therapy. The management of the risks associated with fruquintinib treatment will 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 References

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[9] Braftovi. Prescribing Information (last updated 02/2022).

[10] Stivarga. Prescribing Information (last updated 12/2020).

[11] Division of Oncology 3 (DO3). Multi-disciplinary Review and Evaluation (draft) for fruquintinib, NDA 217564, dated October 31, 2023.

[12] Late-Cycle Meeting Minutes for fruquintinib, NDA 217564, dated September 27, 2023. [Reference ID: 5251946]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed September 29, 2023.

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