SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

FRUZAQLA® 5 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 5 mg fruquintinib.

Excipient with known effect

Each 5 mg hard capsule contains 0.1829 mg of Allura red AC (E129) colourant.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule

Opaque hard gelatin capsule, size 1 (approximate length 19 mm), with a red cap and a white body imprinted with “HM013” over “5mg” in black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

FRUZAQLA is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, with or without an anti-VEGF therapy, and if RAS wildtype and medically appropriate, an anti-EGFR therapy.

4.2 Posology and method of administration

FRUZAQLA should be initiated by a physician experienced in the administration of anticancer therapy.

Posology
The recommended dose of fruquintinib is 5 mg (one 5 mg capsule) once daily at approximately the same time each day for 21 consecutive days, followed by a 7-day rest period to comprise a complete cycle of 28 days.

Duration of treatment
Treatment with fruquintinib should be continued until disease progression or unacceptable toxicity occurs.

Missed doses or vomiting
If a dose is missed by less than 12 hours, it should be taken, and the next dose should be taken as scheduled.

If a dose is missed by more than 12 hours, it should be skipped, and the next dose should be taken as scheduled.

If a patient vomits after taking a dose, the patient should not repeat the dose on the same day, but resume the usual dosing as scheduled on the following day.

Dose Adjustments for Adverse Reactions
The dose should be modified based on safety and tolerability. Fruquintinib should be permanently discontinued in patients unable to tolerate a dose of 3 mg once daily. The recommended dose reduction schedule for adverse reactions is provided in Table 1.

Table 1: Recommended FRUZAQLA Dose Reduction Schedule

Dose Reduction Schedule	**Dose and Schedule**	**Number and Strength of Capsules**
First dose reduction	4 mg once daily	Four 1 mg capsules once daily
Second dose reduction	3 mg once daily	Three 1 mg capsules once daily

The recommended dose modifications for adverse reactions are provided in Table 2.

Table 2: Recommended Dose Modifications for FRUZAQLA for Adverse Reactions

Adverse Reaction	**Severity[1]**	**Dose Modification**

Hypertension	Grade 3	• Withhold if Grade 3 hypertension persists despite initiation or modification of antihypertensive treatment. • If hypertension recovers to Grade 1 or baseline, resume at a reduced dose as per Table 1. If the patient still experiences Grade 3 hypertension after taking 3 mg daily, permanently discontinue.
	Grade 4	Permanently discontinue.
Haemorrhagic Events	Grade 2	• Withhold until bleeding fully resolves or recovers to Grade 1. • Resume at a reduced dose as per Table 1. If the patient still experiences Grade 2 haemorrhagic events after taking 3 mg daily, permanently discontinue.
	Grade ≥ 3	Permanently discontinue.
Proteinuria	≥ 2 g / 24 hours	• Withhold until proteinuria fully resolves or is < 1 g / 24 hours (Grade 1). • Resume at a reduced dose as per Table 1. If the patient still experiences ≥ 2 g / 24 hours proteinuria after taking 3 mg daily, permanently discontinue. Permanently discontinue for nephrotic syndrome.
Liver Function Test Abnormalities	Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 3 times upper limit of normal (ULN) if baseline was normal, or greater than 3.0 times baseline if baseline was abnormal; or bilirubin greater than 1.5 times ULN if	• Withhold until liver function test abnormality recovers to Grade 1 or baseline. • Resume at a reduced dose as per Table 1. If the patient still experiences Grade 2 or Grade 3 liver function test abnormalities after taking 3 mg daily, permanently discontinue.

	baseline was abnormal	
	ALT or AST greater than 3 times ULN with concurrent total bilirubin greater than 2 times ULN (in the absence of alternative etiologies)	Permanently discontinue.
	AST or ALT greater than 20 times ULN if baseline was normal, or greater than 20 times baseline if baseline was abnormal; or bilirubin greater than 10 times ULN if baseline was normal, or greater than 10 times baseline if baseline was abnormal	Permanently discontinue.
Palmar-plantar Erythrodysesthesia Syndrome (PPES)	Grade 2	• Administer supportive treatment. • Withhold until PPES recovers to Grade 1 or baseline. • Resume at the same dose level.
	Grade 3	• Administer supportive treatment. • Withhold until PPES recovers to Grade 1 or baseline. • Resume at a reduced dose as per Table 1. If the patient still experiences Grade 3 PPES after taking 3 mg daily, permanently discontinue.
Other Adverse Reactions	Grade 3	• Withhold until the reaction recovers to Grade 1 or baseline. • Resume at a reduced dose as per Table 1. If the patient still experiences Grade 3 other adverse reactions after taking 3 mg daily, permanently discontinue.
	Grade 4	Discontinue. Consider resuming at a reduced dose as per Table 1 if the toxicity recovers to Grade 1 or baseline and the potential

		benefit outweighs the risks.

[1]Graded per national cancer institute common terminology criteria for adverse events. Version 5.0 (NCI CTCAE v5).

Special Populations

Renal Impairment
No dose adjustment is required for patients with mild, moderate, or severe renal impairment (see section 5.2).

Hepatic Impairment
No dose adjustment is required for patients with mild or moderate hepatic impairment (see section 5.2).

FRUZAQLA is not recommended for use in patients with severe hepatic impairment as FRUZAQLA has not been studied in this population.

Elderly Population
No dose adjustment is required in patients aged 65 years or above.

Paediatric Population
The safety and efficacy of FRUZAQLA in children aged 0 to <18 years have not been established. No data are available.

Method of Administration
FRUZAQLA is for oral use.

FRUZAQLA capsules can be taken with or without food and should be swallowed whole.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.

4.4 Special Warnings and Precautions for Use

Hypertension
Hypertension, including hypertensive crisis, has been reported in patients treated with fruquintinib. (see section 4.8). Pre-existing hypertension should be adequately controlled before starting fruquintinib treatment.

Hypertension should be medically managed with antihypertensive medicinal products and adjustment of the fruquintinib dose, if necessary (see section 4.2). Fruquintinib should be permanently discontinued for hypertension that cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis.

Haemorrhagic events

Haemorrhagic events have been reported in patients treated with fruquintinib, including gastrointestinal (GI) tract events (see section 4.8). Serious and sometimes fatal bleeding events have been reported in patients after treatment with fruquintinib.

Monitor haematologic and coagulation profiles more frequently in patients at risk for bleeding, including those treated with anticoagulants or other concomitant medicinal products that increase the risk of bleeding. In the event of severe bleeding requiring immediate medical intervention, fruquintinib should be permanently discontinued (see section 4.2).

Infections
Infections have been reported in in patients treated with fruquintinib, including fatal events (1%) in clinical studies (see section 4.8).

Fruquintinib should be withheld for Grade 3 or 4 infections or worsening of the infection of any grade. Fruquintinib to be resumed at the same dose when infection is resolved.

Gastrointestinal (GI) perforation
GI perforation events, including fatal events, have been reported in patients treated with fruquintinib (see section 4.8).

Symptoms of GI perforation should be periodically monitored during treatment with fruquintinib.

Fruquintinib should be permanently discontinued in patients developing GI perforation.

Hepatotoxicity
Liver function test abnormalities have been reported in patients treated with fruquintinib, including fatal events in clinical studies (see section 4.8).

The liver function test abnormalities should be monitored before initiation and throughout the treatment with fruquintinib. Based on the severity and persistence of liver function abnormalities as manifested by elevated liver function tests, treatment should be withheld, and then reduced or permanently discontinued.

Proteinuria
Proteinuria events have occurred in patients treated with fruquintinib.

Urine protein should be monitored regularly. If urine dipstick proteinuria ≥2 g / 24 hours is detected, dose interruptions, adjustments, or discontinuation may be necessary. Fruquintinib should be permanently discontinued in patients developing nephrotic syndrome (see section 4.2).

Palmar-plantar erythrodysesthesia syndrome (PPES)
PPES is the most frequently reported dermatological adverse reaction (see section 4.8).

If Grade ≥2 skin reactions are detected, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

Posterior reversible encephalopathy syndrome (PRES)

PRES has been reported with the use of fruquintinib (0.1%) (see section 4.8). PRES is a rare neurologic disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, discontinuation of fruquintinib, along with control of hypertension and supportive medical management of other symptoms, are recommended.

Impaired wound healing
No formal studies of the effect of fruquintinib on wound healing have been conducted.

Impaired wound healing has been reported in 1 patient (0.1%) treated with fruquintinib.

Patients are recommended to withhold fruquintinib for at least 2 weeks prior to surgery. Fruquintinib should not be resumed for at least 2 weeks after surgery, as clinically indicated when there is evidence of adequate wound healing.

Arterial thromboembolic events
It is recommended to avoid starting treatment with fruquintinib in patients with a history of thromboembolic events (including deep vein thrombosis and pulmonary embolism) within the past 6 months or if they have a history of stroke and/or transient ischemic attack within the last 12 months. If arterial thrombosis is suspected, fruquintinib should be discontinued immediately.

Aneurysms and artery dissections
The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating fruquintinib, this risk should be carefully considered in patients with a history of risk factors such as hypertension or aneurysm.

Excipients

Fruquintinib 5 mg capsules contain Allura red AC (E129), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro results indicated that fruquintinib was metabolised by CYP and non-CYP enzymes. CYP3A4 was the main enzyme among the CYP isoforms involved in the metabolism of fruquintinib, with minor contributions from CYP2C8, CYP2C9 and CYP2C19. Fruquintinib inhibited P-gp and BCRP in a dose-dependent manner *in vitro* and demonstrated pH-dependent aqueous solubility.

Effects of other medicinal products on the pharmacokinetics of fruquintinib

CYP3A inhibitors
Co-administration of fruquintinib with itraconazole (a strong CYP3A inhibitor) 200 mg twice daily did not result in clinically meaningful changes in the area under the concentration-time curve (AUC) and C_{max} of fruquintinib.

CYP3A inducers
Co-administration of fruquintinib with rifampicin (a strong CYP3A inducer) 600 mg once daily decreased fruquintinib AUC by 65% and decreased fruquintinib C_{max} by 12%. Co-administration of fruquintinib with efavirenz (a moderate CYP3A inducer) 600 mg once daily is predicted to decrease fruquintinib AUC by 32% and fruquintinib C_{max} by 4%. No clinically meaningful differences in the AUC of fruquintinib are predicted when fruquintinib is co-administered with dexamethasone (a weak CYP3A inducer) 8 mg twice daily. The concomitant use of fruquintinib with strong and moderate CYP3A inducers should be avoided.

Gastric acid lowering agents
Co-administration of fruquintinib with rabeprazole (a proton pump inhibitor) 40 mg once daily did not result in clinically meaningful changes in the AUC of fruquintinib.

Effect of fruquintinib on the pharmacokinetics of other medicinal products

Medicinal products that are substrates of P-glycoprotein (P-gp)
Co-administration of a single dose of dabigatran etexilate 150 mg (a P-gp substrate) with a single dose of fruquintinib 5 mg decreased AUC of dabigatran by 9%. Co-administration of a single dose of digoxin (a P-gp substrate) 0.5 mg with multiple doses of fruquintinib is predicted to result in a 6% increase in AUC of digoxin.

Medicinal products that are substrates of breast cancer resistance protein (BCRP)
Co-administration of a single 10 mg dose of rosuvastatin (a BCRP substrate) with a single 5 mg dose of fruquintinib decreased AUC of rosuvastatin by 19%. Co-administration of a single 20 mg dose of rosuvastatin with multiple doses of fruquintinib is predicted to result in a 19% increase in AUC of rosuvastatin (a BCRP substrate).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females
Women of childbearing potential and male patients with female partners of childbearing potential should be advised to use effective contraception during and for at least 2 weeks following the last dose of fruquintinib.

Pregnancy
There are no clinical data available on the use of fruquintinib in pregnant women.

Based on its mechanism of action, fruquintinib has the potential to cause foetal harm. Studies in animals have shown reproductive toxicity, including foetal malformations (see section 5.3). FRUZAQLA should not be used during pregnancy unless the woman's clinical condition requires treatment with this medicinal product and after careful consideration of the benefits for the mother and the risk to the foetus.

If fruquintinib is used during pregnancy or if the patient becomes pregnant while on treatment, the patient must be informed of the potential hazard to the foetus.

Breast-feeding
It is unknown whether FRUZAQLA or its metabolites are excreted in human milk. A risk to newborns/infants cannot be excluded.

Breast-feeding should be discontinued during treatment with FRUZAQLA and for at least 2 weeks after the last dose.

Fertility
There are no data on the effects of fruquintinib on human fertility. Results from animal studies indicate that fruquintinib may impair male and female fertility (see section 5.3).

4.7 Effects on Ability to Drive and Use Machines

Studies to evaluate the effects of fruquintinib on the ability to drive or operate machinery have not been conducted. Fruquintinib may have a minor influence on the ability to drive and use machines. Fatigue may occur following administration of fruquintinib (see section 4.8).

4.8 Undesirable Effects

Summary of the safety profile
The overall safety profile of fruquintinib is based on pooled data from clinical studies with 911 patients with mCRC. Patients were exposed to at least one dose (5 mg) of fruquintinib (5 mg once daily 3 weeks on/1 week off) during a median of 3.68 months. In this patient population, the most common adverse reactions of any grade (incidence ≥ 20%) were hypertension (49.3%), anorexia (35.6%), proteinuria (35.5%), PPES (34.6%), hypothyroidism (32.4%), dysphonia (28.6%), diarrhoea (26.3%), and asthenia (24.5%), the majority of which were of Grades 1 or 2 severity. The most common adverse reactions of Grade 3/4 (incidence ≥ 5%) were hypertension (19.1%) and PPES (8.3%). The most common serious adverse reactions (incidence ≥ 1%) were gastrointestinal haemorrhage (1.5%), pneumonia (1.5%), hypertension (1.5%), and gastrointestinal perforation (1.3%) (see section 4.4).
The frequency of treatment discontinuation due to adverse reactions was 7.6%. The most common adverse reaction leading to treatment discontinuation was proteinuria (1.6%).
The frequency of dose reduction due to adverse reactions was 20.5%. The most common adverse reactions leading to dose reduction were PPES (6.4%), hypertension (3.7%), and proteinuria (3.4%).

Tabulated list of adverse reactions
Adverse reactions reported in clinical studies of fruquintinib are listed in Table 3. These reactions are presented by system organ class and by frequency. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse Reactions Reported in Clinical Studies in Patients with mCRC Treated with Fruquintinib (N=911)

System Organ Class	Frequency Category	Adverse Reactions All Grades

Infections and infestations	Common	Pneumonia Upper respiratory tract infection[1]
Blood and lymphatic system disorders	Very Common	Thrombocytopenia[2]
	Common	Leukopenia[3] Neutropenia[4]
Endocrine disorders	Very Common	Hypothyroidism[5]
Metabolism and Nutrition disorders	Very Common	Anorexia[6]
	Common	Hypokalaemia
Nervous system disorders	Uncommon	Posterior reversible encephalopathy syndrome
Vascular disorders	Very Common	Hypertension[7]
Respiratory, thoracic and mediastinal disorders	Very Common	Dysphonia[8]
	Common	Epistaxis Throat pain[9]
Gastrointestinal disorders	Very Common	Diarrhoea Stomatitis[10]
	Common	Gastrointestinal haemorrhage[11] Gastrointestinal perforation[12] Pancreatic enzymes increased[13] Oral pain[14]
	Uncommon	Pancreatitis[15]
Hepatobiliary disorders	Very Common	Aspartate aminotransferase increased Total bilirubin increased[16] Alanine aminotransferase increased
Skin and subcutaneous tissue disorders	Very Common	Palmar-plantar erythrodysaesthesia syndrome
	Common	Rash[17]
Musculoskeletal and connective tissue disorders	Very Common	Musculoskeletal discomfort[18] Arthralgia
Renal and urinary disorders	Very Common	Proteinuria[19]
General disorders and administrative site conditions	Very Common	Asthenia Fatigue
	Common	Mucosal inflammation

The safety data is based on all patients with mCRC who received at least 1 dose (5 mg) of fruquintinib (5 mg once daily 3 weeks on/1 week off) in the following pooled studies: 2012-013-00CH1; 2013-013-00CH1/ FRESCO; 2019-013-GLOB1/FRESCO-2 including the open-label Japanese safety lead-in cohort; 2009-013-00CH1; 2012 013-00CH3; 2015-013-00US1. MedDRA 25.0.
The following terms represent a group of related events that describe a medical condition rather than a single event:
[1]Upper respiratory tract infection includes nasopharyngitis, pharyngitis, upper respiratory tract infection
[2]Thrombocytopenia includes platelet count decreased and thrombocytopenia
[3]Leukopenia includes leukopenia and white blood cell count decreased
[4]Neutropenia includes neutropenia and neutrophil count decreased
[5]Hypothyroidism includes blood thyroid stimulating hormone increased, hypothyroidism
[6]Anorexia includes appetite decreased and weight loss
[7]Hypertension includes blood pressure diastolic increased, blood pressure increased, diastolic hypertension, hypertension, hypertensive crisis
[8]Dysphonia includes aphonia and dysphonia
[9]Throat pain includes laryngeal discomfort, laryngeal pain, oropharyngeal discomfort, oropharyngeal pain
[10]Stomatitis includes aphthous ulcer, gingival ulceration, mouth ulceration, stomatitis, tongue ulceration
[11]Gastrointestinal haemorrhage includes anal haemorrhage, anastomotic haemorrhage, gastric haemorrhage, gastrointestinal haemorrhage, haematochezia, haemorrhoidal haemorrhage, intestinal haemorrhage, lower gastrointestinal haemorrhage, rectal haemorrhage, upper gastrointestinal haemorrhage
[12]Gastrointestinal perforation includes gastric perforation, gastric ulcer perforation, gastrointestinal perforation, intestinal perforation, large intestine perforation, rectal perforation, small intestinal perforation
[13]Pancreatic enzymes increased includes amylase increased, hyperamylasaemia, hyperlipasaemia, lipase increased
[14]Oral pain includes gingival pain, oral pain, toothache
[15]Pancreatitis includes pancreatitis, pancreatitis acute
[16] Total bilirubin increased includes bilirubin conjugated increased, blood bilirubin increased, blood bilirubin unconjugated increased, hyperbilirubinaemia, jaundice, jaundice cholestatic
[17]Rash includes rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic
[18]Musculoskeletal discomfort includes bone pain, muscle spasms, musculoskeletal chest pain, musculoskeletal pain, neck pain, pain in extremity
[19]Proteinuria includes albuminuria, protein urine present, proteinuria

<u>Description of selected adverse reactions</u>
Data for the following selected adverse reactions are based on patients who received at least 1 dose (5 mg) of fruquintinib (5 mg once daily 3 weeks on/1 week off) across three randomised placebo-controlled studies (2012-013-00CH1; 2013-013-00CH1/ FRESCO; 2019-013-GLOB1/FRESCO-2). The management guidelines for these adverse reactions are described in section 4.4.

Hypertension
Hypertension was reported in 47.4% of patients in the fruquintinib arm and 11.8% in the placebo arm. Approximately half of these events occurred during the first 2 weeks after initiating treatment with fruquintinib. The incidence of Grade ≥3 hypertension events were 18.4% in the fruquintinib arm and 1.3% in the placebo arm. Median time to onset in fruquintinib-treated patients was 15 days (range: 1 day to 7.6 months).

Two patients (0.3%) treated with fruquintinib experienced life-threatening hypertension. The majority of the events recovered or resolved following dose interruption or reduction, which occurred in 3.1% and 3.7% of patients, respectively. In 0.5% of patients treated with fruquintinib, hypertension led to permanent treatment discontinuation.

Haemorrhagic events
Haemorrhagic events were reported in 26.5% of patients in the fruquintinib arm and 14.6% in the placebo arm. Most haemorrhagic events in patients treated with fruquintinib were mild to moderate in severity; the incidence of Grade ≥ 3 haemorrhagic events were 2.0% in the fruquintinib arm and 1.0% in the placebo arm. Median time to onset in fruquintinib treated patients was 23 days (range: 1 day to 9.8 months). Fatal haemorrhagic events were reported in 0.5% of patients in the fruquintinib arm. In 1.2% of patients treated with fruquintinib, haemorrhagic events led to dose discontinuation. The most common haemorrhagic reactions were gastrointestinal haemorrhage (7%) and epistaxis (5.6%). The most frequently reported serious haemorrhagic event was gastrointestinal haemorrhage, which was reported in 1.5% of patients in the fruquintinib arm compared with 0.5% in the placebo arm.

Gastrointestinal (GI) perforation
GI perforation events were reported in 1.5% of patients in the fruquintinib arm, and no events were reported in the placebo arm. Fatal GI perforation was reported in 0.1% of patients treated with fruquintinib. The most common GI perforation event was intestinal perforation (0.8%). In 1.0% of patients treated with fruquintinib, GI perforation events led to dose discontinuation.

Hepatotoxicity
Liver function test abnormalities were reported in 36.4% of the patients on the fruquintinib arm-and 23.5% in the placebo arm. Most hepatobiliary disorders in patients treated with fruquintinib were mild to moderate in severity (incidence of Grade ≥ 3 liver function test abnormalities were 8.8% in the fruquintinib arm and 9.5% in the placebo arm). The most common liver function test abnormality events were AST increase (18.1%), total bilirubin increase (18.3%), and ALT increase (15.5%). Median time to onset in fruquintinib treated patients was 28 days (range: 4 days to 12 months). Serious liver function test abnormalities were reported in 2.3% of patients in the fruquintinib arm and 3.1% in the placebo arm. Fatal liver function test abnormalities were reported in 0.3% of patients in the fruquintinib arm and 0.8% in the placebo arm. Liver function test abnormalities led to dose interruption and reduction in 4.6% and 2.0% of patients, respectively, and to permanent discontinuation in 1.5% of patients.

Proteinuria
Proteinuria was reported in 32.9% of the patients in the fruquintinib arm and 15.1% in the placebo arm. Most of the events in patients treated with fruquintinib were mild to moderate in severity; the incidence of Grade ≥ 3 proteinuria events were 2.8% in the fruquintinib arm and 0.5% in the placebo arm. Median time to onset in fruquintinibtreated patients was 28 days (range: 6 days to 1.3 years). The majority of the events recovered or resolved following dose interruption or reduction. In 1.8% of patients treated with fruquintinib, proteinuria led to permanent treatment discontinuation.

Palmar-plantar erythrodysesthesia syndrome (PPES)
Palmar-plantar erythrodysaesthesia syndrome was reported in 32.7% of patients in the fruquintinib arm and 3.1% in the placebo arm. The incidence of Grade ≥3 PPES

events were 8.5% in the fruquintinib arm and 0.3% in the placebo arm. Median time to onset in fruquintinib-treated patients was 20 days (range: 1 day to 7.4 months). The majority of the events recovered or resolved following dose interruption or reduction, which occurred 6.4% and 6.3%, respectively. In 0.5% of patients treated with fruquintinib, PPES led to permanent treatment discontinuation.

Hypothyroidism
Hypothyroidism was reported in 31.5% of the patients in the fruquintinib arm and 2.8% in the placebo arm. Most of the events in patients treated with fruquintinib were mild to moderate in severity; the incidence of Grade ≥3 hypothyroidism in the fruquintinib arm was low (0.3%). Median time to onset in fruquintinib-treated patients was 56 days (range: 18 days to 1.4 years). No events led to dose reduction or discontinuation.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The highest dose of fruquintinib studied in clinical studies was 6 mg per day.

The effects of fruquintinib overdose are unknown, and there is no known antidote for fruquintinib overdose. In the event of an overdose, interrupt fruquintinib, general supportive measures should be undertaken and observe until clinical stabilisation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EK04

Mechanism of Action and Pharmacodynamic Effects
Fruquintinib is a highly selective small molecule tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR) -1, -2, and -3 with antitumour effects resulting from suppression of tumour angiogenesis and tumour deprivation of nutrients and oxygen.
uquintinib has been shown to inhibit receptor tyrosine kinases, including VEGFR-1, -2, and -3, at therapeutic plasma concentrations. These receptors are implicated in pathologic angiogenesis, tumour growth, and cancer progression. VEGF mediated endothelial cell proliferation and survival were inhibited by fruquintinib *in vitro* and in mouse models. Fruquintinib was shown to inhibit tumour growth and phosphorylation of VEGFR-2 in tumour xenograft mouse models.

Cardiac Electrophysiology

No prolongation of heart rate-corrected QT (QTc) interval (> 10 milliseconds) was observed at the recommended dosage of fruquintinib. A concentration-QT analysis (N=205) showed no evidence of an association between fruquintinib plasma concentrations and changes in QTc interval from baseline.

Clinical efficacy and safety

The efficacy of fruquintinib plus best supportive care (BSC) was evaluated in two randomised, placebo-controlled, double-blind, phase III studies (FRESCO and FRESCO-2) in patients with mCRC previously treated with but not limited to oxaliplatin or irinotecan-based chemotherapies. The clinical efficacy of fruquintinib in the FRESCO and FRESCO-2 studies are described below.

FRESCO Study

The clinical safety and efficacy of fruquintinib were initially evaluated in a randomised, double-blind, placebo-controlled, multicentre phase III study (FRESCO) conducted in China in 416 patients with previously treated mCRC. The primary efficacy endpoint was overall survival (OS). The secondary efficacy endpoints included investigator-assessed progression-free survival (PFS) according to RECIST version 1.1, tumour objective response rate (ORR), disease control rate (DCR), duration of response (DoR), and safety.

In total, 416 patients were randomised (2:1) to receive fruquintinib 5 mg orally once daily (N=278) plus BSC or placebo orally once daily (N=138) (hereafter referenced as fruquintinib and placebo respectively) plus BSC, for 21 days on therapy followed by 7 days off therapy in a 28-day treatment cycle.

Among the 416 randomised patients, the median age was 56 years (range: 23 to 75), with 19% ≥ 65 years of age. 61.3% of patients were male, all were Asian (100%), and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (27%) and 1 (73%). Tumour *RAS* mutation was reported in 44% of patients at study entry.

In addition to treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, 30% of patients received prior anti-VEGF therapy, and 14% received prior anti-EGFR therapy.

The addition of fruquintinib to BSC resulted in a statistically significant improvement in OS and PFS compared to placebo plus BSC (see Table 4, Figure 1).

FRESCO-2 Study

The clinical safety and efficacy of fruquintinib were evaluated in a global, randomised, double-blind, placebo-controlled, multicentre, phase III study (FRESCO-2) in 691 patients with previously-treated mCRC. Patients were stratified according to prior therapy (trifluridine/tipiracil [52.2%] vs. regorafenib [8.4%] vs. both [39.4%]), RAS mutational status (wild-type [36.9%] vs. [63.1%] mutant) and duration of metastatic disease (≤ 18 months [7.2%] vs. > 18 months [92.8%]).
The primary endpoint was OS. The key secondary endpoint was PFS. Other secondary endpoints included tumour objective response rate (ORR), disease control rate (DCR), duration of response (DoR), and safety.

In total, 691 patients were randomised (2:1) to receive fruquintinib 5 mg orally once daily (N=461) plus BSC or placebo orally once daily (N=230) (hereafter referenced as fruquintinib and placebo respectively) plus BSC, for 21 days on therapy followed by 7 days off therapy in a 28-day treatment cycle.

Among the 691 randomised patients, the median age was 64 years (range: 25 to 86), with 47% ≥ 65 years of age. 55.7% of patients were male, 80.9% were White, and had an ECOG performance status of 0 (43.1%) or 1 (56.9%). Tumour *RAS* mutation was reported in 63.1% of patients at study entry.

In addition to treatment with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, 96.4% of patients received prior anti-VEGF therapy, 38.8% received prior anti-EGFR therapy, 52.2 % received trifluridine/tipiracil, and 8.4% received regorafenib, and 39.4% received both trifluridine/tipiracil and regorafenib.

The addition of fruquintinib to BSC resulted in a statistically significant improvement in OS and PFS compared to placebo plus BSC (see Table 4 and Figure 2).

Table 4: Efficacy results from FRESCO and FRESCO-2 studies

	FRESCO		**FRESCO-2**	
Endpoint	**Fruquintinib N=278**	**Placebo N=138**	**Fruquintinib N=461**	**Placebo N=230**
OS				
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				
Median in months (95% CI)	3.7 (3.7, 4.6)	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 to 0.34)		0.32 (0.27 to 0.39)	
p-value[b]	< 0.001		< 0.001	
ORR				
Confirmed ORR (CR + PR) (%)	13 (4.7)	0	7 (1.5)	0
DCR				
DCR (CR + PR + SD), n (%)	173 (62.2)	17 (12.3)	256 (55.5)	37 (16.1)

Abbreviations: CI=confidence interval; HR=hazard ratio; N=number of patients; OS=overall survival; PFS=progression-free survival; ORR = objective response rate; DCR = disease control rate

The median OS and PFS were calculated using the Kaplan-Meier method.

[a]The HR and its 95% CI were estimated using stratified Cox's proportional hazards model (accounting for the stratification factors), in which the 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.

Figure 1: Kaplan-Meier curve for Overall Survival in FRESCO study

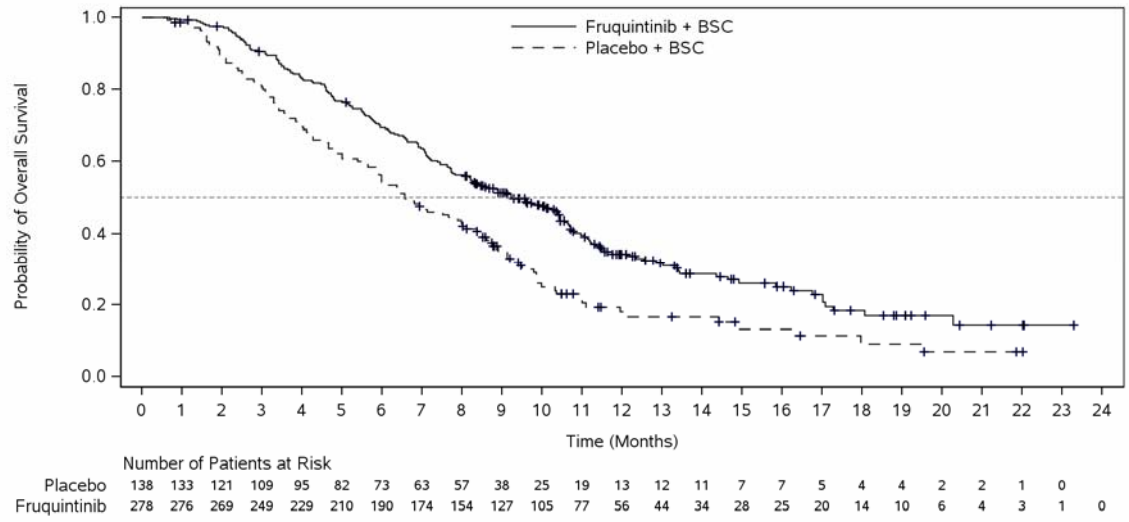
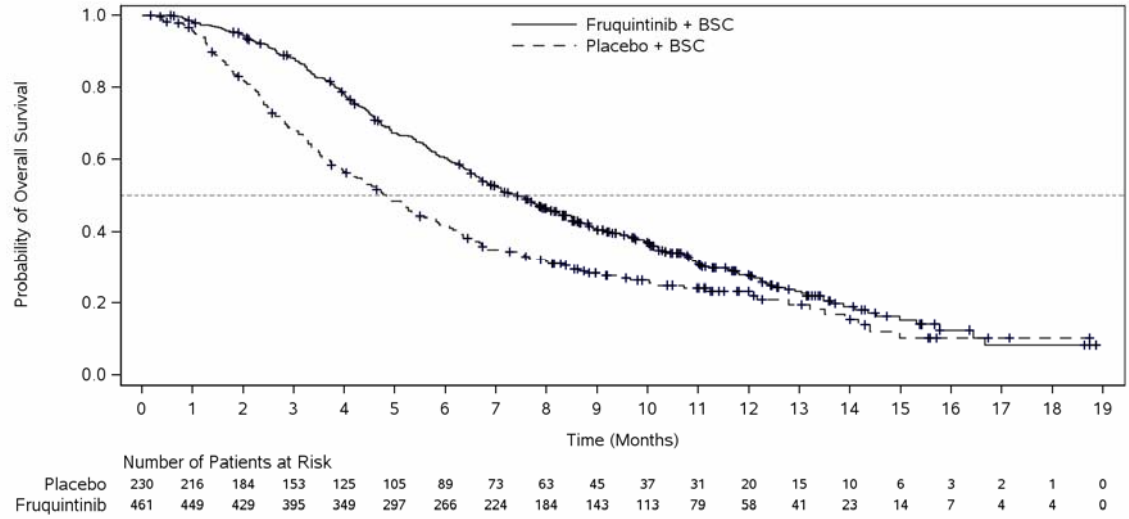


Figure 2: Kaplan-Meier curve for Overall Survival in FRESCO-2 study



Paediatric population

The Licencing Authority has waived the obligation to submit the results of studies with FRUZAQLA in all subsets of the paediatric population in metastatic colorectal cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

After oral administration of fruquintinib, the median time to achieve peak plasma fruquintinib concentration (T_{max}) was approximately 2 hours. Following repeat once-daily dosing, fruquintinib exposure (C_{max} and AUC_{0-24h}) increased in a dose-proportional manner across the dose range of 1 to 6 mg (0.2 to 1.2 times the recommended dosage). Following administration of fruquintinib 5 mg once daily for 21 days with 7 days off of each 28-day cycle in patients with advanced solid tumours,

steady state of fruquintinib was achieved after 14 days, and the mean accumulation based on AUC_{0-24h} was 4-fold relative to a single dose. At the recommended dose of 5 mg of FRUZAQLA, the geometric mean (%CV) C_{max} and AUC_{0-24h} for fruquintinib at steady-state were 300 ng/mL (28%) and 5880 ng*h/mL (29%), respectively.

Effect of food
Compared to the fasting state, a high-fat meal had no clinically meaningful effect on fruquintinib pharmacokinetics in healthy subjects. Fruquintinib can be administered with or without food.

Distribution
The apparent volume of distribution of fruquintinib is approximately 48.5 L. Plasma protein binding of fruquintinib is approximately 95% *in vitro*.

Biotransformation
Fruquintinib is metabolised by multiple enzymes, including CYP450 (CYP3A and CYP2C subfamilies) and non-CYP450 enzyme systems. The *in vivo* metabolism and mass balance study of [14C] labeled fruquintinib showed that fruquintinib mainly exists in human plasma in its unchanged form, accounting for approximately 72% of total exposure in the plasma, and the CYP3A4-mediated N-demethyl metabolite of fruquintinib account for approximately 17% of total exposure in plasma. Other metabolic pathways include multi-site mono-oxidation, O-demethylation, N-demethylation, O-dequinazoline ring, and amide hydrolysis. The phase II metabolites are mainly glucuronic acid and sulphuric acid conjugates of phase I products.

In vitro studies
Cytochrome P450 enzymes: Fruquintinib is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A, or an inducer of CYP1A2, CYP2B6, CYP3A at therapeutically relevant concentrations.

Transporter systems: Fruquintinib is not a substrate of P-glycoprotein (P-gp), organic anion transport protein (OATP)1B1, or OATP1B3. Fruquintinib is not an inhibitor of OATP1B1, OATP1B3, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, multidrug and toxin extrusion protein (MATE)1, or MATE2-K at therapeutically relevant concentrations.

Elimination
The apparent clearance (CL/F) of fruquintinib is 14.8 mL/min at steady-state after once daily dosing in patients with advanced solid tumours. The mean elimination half-life of fruquintinib is approximately 42 hours.

Following administration of a single 5 mg radiolabelled fruquintinib in healthy subjects, approximately 60% of the dose was recovered in urine (0.5% of the dose as unchanged fruquintinib), and 30% of the dose was recovered in faeces (5% of the dose as unchanged fruquintinib).

Special Populations

Renal impairment
No dose adjustment for fruquintinib is recommended for patients with mild to severe renal impairment (CrCL 15 to 89 mL/min) Based on the population pharmacokinetic analyses, mild to moderate renal impairment (CrCL 30 to 89 mL/min) had no clinically meaningful impact on fruquintinib pharmacokinetics. Based on a dedicated pharmacokinetic study, moderate (CrCL 30 to 59 mL/min, N=8) or severe renal

impairment (CrCL 15 to 29 mL/min, N=8) had no clinically meaningful impact on fruquintinib pharmacokinetics.

Hepatic impairment
No clinically meaningful differences in the pharmacokinetics of fruquintinib were observed between patients with normal hepatic function and patients with mild (total bilirubin ≤ ULN with AST greater than ULN or total bilirubin > 1 to 1.5 times ULN with any AST) hepatic impairment based on population pharmacokinetic analyses. Based on a dedicated hepatic impairment pharmacokinetic study, following administration of a single 2 mg oral dose of FRUZAQLA, no clinically meaningful differences in the dose-normalised AUC of fruquintinib were observed in subjects with moderate (Child Pugh B, N=8) hepatic impairment compared to subjects with normal hepatic function.

Age, body weight, gender or race
Population pharmacokinetic analyses showed that age (18 to 82 years), body weight (48 to 108 kg), gender or race had no clinically relevant impact on the pharmacokinetics of fruquintinib.

Paediatric population
No pharmacokinetic studies were performed with fruquintinib in patients under 18 years of age.

5.3 Preclinical safety data

In repeat-dose animal toxicity studies, the main target organ effects were identified in the gastrointestinal tract, hepatobiliary system, immune system, skeletal system (femur and teeth), kidneys, hematopoietic system, and adrenal gland and occurred at clinically relevant fruquintinib plasma exposure levels. All findings were reversible after 4 weeks without treatment, apart from the skeletal system (broken/lost teeth).

In a fertility and early embryonic development study in rats, male and female reproductive indices were decreased at exposures approximately 3.2 and 0.8-fold the human AUC, respectively. Dose-dependent increases in pre-implantation loss were observed in the same study.

In an embryo-foetal developmental study in rats at an exposure below the clinical exposure, embryotoxic and teratogenic effects were observed, consisting of foetal external, visceral, and skeletal malformations.

No evidence of genotoxicity was observed in *in vitro* and *in vivo* studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Maize starch

Cellulose, microcrystalline

Talc

Capsule shell

Gelatin

Titanium dioxide

Allura red AC (E129)

Brilliant blue FCF

Printing ink

Dewaxed shellac

Propylene glycol

Potassium hydroxide

Iron oxide black

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original container to protect from moisture. Keep the bottle tightly closed. Do not remove desiccant from the bottle.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottle (45 mL) with polypropylene (PP) child-resistant closure and a silica gel desiccant cartridge.

Each white bottle contains 21 hard capsules. Each bottle is packaged in a carton with an insert and sealed with tamper-evident seal.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Takeda UK Limited

1 Kingdom Street,

London,

W2 6BD,

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 16189/0147

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/09/2024

10 DATE OF REVISION OF THE TEXT

14/08/2025