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 1 mg hard capsules
FRUZAQLA 5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FRUZAQLA 1 mg hard capsules

Each hard capsule contains 1 mg fruquintinib.

Excipients with known effect

Each 1 mg hard capsule contains 0.0247 mg of tartrazine (E102) and 0.0004 mg of sunset yellow FCF (E110) colourants.

FRUZAQLA 5 mg hard capsules

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.

FRUZAQLA 1 mg hard capsules

Opaque hard gelatin capsule, size 3 (approximate length 16 mm), with a yellow cap and a white body imprinted with “HM013” over “1mg” in black ink.

FRUZAQLA 5 mg hard capsules

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 as monotherapy is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine-tipiracil or regorafenib.

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 prescribed 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 modification 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	Grade 2 or 3 liver function test abnormalities	• 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.
	Grade ≥ 2 elevation (> 3 x ULN) of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with concurrent total bilirubin elevation > 2 x ULN in the absence of cholestasis; Grade 4 liver function test abnormalities	Permanently discontinue.
Palmar-plantar erythrodysaesthesia 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

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

Paediatric population

There is no relevant use of FRUZAQLA in the paediatric population for the indication of metastatic colorectal cancer.

Method of administration

FRUZAQLA is for oral use.

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

The capsules should not be chewed, dissolved, or opened, as the potential effects of these alterations are unknown.

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 monitored and adequately controlled in accordance with standard medical practices 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.

Haematologic and coagulation profiles should be monitored in accordance with standard medical practices 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).

Gastrointestinal 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.

Proteinuria

Proteinuria events have occurred in patients treated with fruquintinib.

Proteinuria should be monitored before initiation and during treatment with fruquintinib in accordance with standard medical practices. 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 erythrodysaesthesia 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 in 1 patient (0.1%) treated with fruquintinib in clinical studies (see also 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

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

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 and venous 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.

Excipients

Fruquintinib 1 mg capsules contain tartrazine (E102) and sunset yellow FCF (E110), which may cause allergic reactions.

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

Effects of other medicinal products on the pharmacokinetics of fruquintinib

CYP3A inducers

Co-administration of fruquintinib with rifampicin (a strong CYP3A inducer) 600 mg once daily decreased fruquintinib AUC_{inf} by 65% and decreased C_{max} by 12%. The concomitant use of fruquintinib with strong and moderate CYP3A inducers should be avoided.

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. No dose adjustment of fruquintinib is needed during concomitant use with CYP3A inhibitors.

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. No dose adjustment of fruquintinib is needed during concomitant use with gastric acid lowering agents.

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%. No dose adjustment is recommended for P-gp substrates during concomitant use with fruquintinib.

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%. No dose adjustment is recommended for BCRP substrates during concomitant use with fruquintinib.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Women of childbearing potential should be advised to use highly effective contraception during treatment 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. Animal studies have shown reproductive toxicity, including foetal malformations (see section 5.3). FRUZAQLA should not be used during pregnancy unless the clinical condition of the woman requires treatment with fruquintinib.

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

The safe use of fruquintinib during breast-feeding has not been established. It is not known whether fruquintinib or its metabolites are excreted in human milk. There are no animal data on the excretion of fruquintinib in animal milk. A risk to the breast-feeding newborns/infants cannot be excluded.

Breast-feeding should be discontinued during treatment and for 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

Fruquintinib has 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 most common adverse reactions are 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 most common adverse reactions of Grade ≥ 3 are hypertension (19.1%) and PPES (8.3%).

The most common serious adverse reactions are gastrointestinal haemorrhage (1.5%), pneumonia (1.5%), hypertension (1.5%), and gastrointestinal perforation (1.3%).

The frequency of treatment discontinuation due to adverse reactions is 7.6%. The most common adverse reaction leading to treatment discontinuation is proteinuria (1.6%).

The frequency of dose reduction due to adverse reactions is 20.5%. The most common adverse reactions leading to dose reduction are PPES (6.4%), hypertension (3.7%), and proteinuria (3.4%).

Tabulated list of adverse reactions

The frequencies of adverse reactions are based on pooled data from clinical studies with 911 patients with previously treated mCRC. Patients were exposed to at least 1 dose (5 mg) of fruquintinib monotherapy (5 mg once daily 3 weeks on/1 week off) during a median of 3.68 months.

Adverse reactions reported in clinical studies or from post-marketing use of fruquintinib are listed in Table 3 by MedDRA 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 frequency not known (cannot be estimated from available post-marketing data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse reactions reported 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] Bacterial infections[2]
Blood and lymphatic system disorders	Very common	Thrombocytopaenia[3]
	Common	Leukopenia[4] Neutropenia[5]
Endocrine disorders	Very common	Hypothyroidism[6]
Metabolism and nutrition disorders	Very common	Anorexia[7]
	Common	Hypokalaemia
Nervous system disorders	Uncommon	Posterior reversible encephalopathy syndrome*****
Vascular disorders	Very common	Hypertension[8]
	Not known	Aortic dissection[†]
Respiratory, thoracic and mediastinal disorders	Very common	Dysphonia[9]
	Common	Epistaxis Throat pain[10]
Gastrointestinal disorders	Very common	Diarrhoea Stomatitis[11]
	Common	Gastrointestinal haemorrhage[12] Gastrointestinal perforation[13] Pancreatic enzymes increased[14] Oral pain[15]
	Uncommon	Pancreatitis[16]
Hepatobiliary disorders	Very common	Aspartate aminotransferase increased Total bilirubin increased[17] Alanine aminotransferase increased
	Uncommon	Cholecystitis[18]
	Very common	Palmar-plantar erythrodysaesthesia syndrome

Skin and subcutaneous tissue disorders	Common	Rash[19]
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal discomfort[20] Arthralgia
Renal and urinary disorders	Very common	Proteinuria[21]
General disorders and administrative site conditions	Very common	Asthenia Fatigue
	Common	Mucosal inflammation
	Uncommon	Impaired wound healing*, [22]

The safety data is based on all patients with mCRC who received at least 1 dose (5 mg) of fruquintinib monotherapy (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.

*Reported in clinical studies and in the post-marketing setting.

†Reported in the post-marketing setting.

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]Bacterial infections includes asymptomatic bacteriuria, bacterial infection, bacteriuria, cellulitis, clostridium difficile colitis, clostridium difficile infection, enterobacter sepsis, escherichia urinary tract infection, folliculitis, furuncle, paronychia, pharyngitis streptococcal, streptococcal bacteraemia, urinary tract infection bacterial, urinary tract infection staphylococcal

[3]Thrombocytopaenia includes platelet count decreased, thrombocytopaenia

[4]Leukopenia includes leukopenia, white blood cell count decreased

[5]Neutropenia includes neutropenia, neutrophil count decreased

[6]Hypothyroidism includes blood thyroid stimulating hormone increased, hypothyroidism

[7]Anorexia includes appetite decreased, weight loss

[8]Hypertension includes blood pressure diastolic increased, blood pressure increased, diastolic hypertension, hypertension, hypertensive crisis

[9]Dysphonia includes aphonia, dysphonia

[10]Throat pain includes laryngeal discomfort, laryngeal pain, oropharyngeal discomfort, oropharyngeal pain

[11]Stomatitis includes aphthous ulcer, gingival ulceration, mouth ulceration, stomatitis, tongue ulceration

[12]Gastrointestinal haemorrhage includes anal haemorrhage, anastomotic haemorrhage, gastric haemorrhage, gastrointestinal haemorrhage, haematochezia, haemorrhoidal haemorrhage, intestinal haemorrhage, lower gastrointestinal haemorrhage, rectal haemorrhage, upper gastrointestinal haemorrhage

[13]Gastrointestinal perforation includes gastric perforation, gastric ulcer perforation, gastrointestinal perforation, intestinal perforation, large intestine perforation, rectal perforation, small intestinal perforation

[14]Pancreatic enzymes increased includes amylase increased, hyperamylasaemia, hyperlipasaemia, lipase increased

[15]Oral pain includes gingival pain, oral pain, toothache

[16]Pancreatitis includes pancreatitis, pancreatitis acute

[17]Total bilirubin increased includes bilirubin conjugated increased, blood bilirubin increased, blood bilirubin unconjugated increased, hyperbilirubinaemia, jaundice, jaundice cholestatic

[18]Cholecystitis includes cholecystitis, cholecystitis acute, cholecystitis infective

[19]Rash includes rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic

[20]Musculoskeletal discomfort includes bone pain, muscle spasms, musculoskeletal chest pain, musculoskeletal pain, neck pain, pain in extremity

[21]Proteinuria includes albuminuria, protein urine present, proteinuria

[22]Impaired wound healing includes impaired healing, wound dehiscence

Description of selected adverse reactions

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. Approximately half of these events occurred during the first 2 weeks after initiating treatment with fruquintinib. Grade ≥ 3 hypertension events were reported in 18.4% of patients in the fruquintinib arm. Median time to onset in fruquintinib-treated patients was 15 days (range: 1 day to 7.6 months). Three patients (0.4%) treated

with fruquintinib experienced hypertensive crisis. 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, 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 (incidence of Grade ≥ 3 haemorrhagic events was 2.0% in the fruquintinib 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. The incidence of haemorrhagic events leading to dose discontinuation was 1.2%. 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

Events of gastrointestinal perforation were reported in 1.5% of patients in the fruquintinib 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%). The incidence of GI perforation events leading to dose discontinuation was 1.0%.

Proteinuria

Proteinuria was reported in 32.9% of the patients in the fruquintinib arm. Most proteinuria events in patients treated with fruquintinib were mild to moderate in severity (incidence of Grade ≥ 3 proteinuria events was 2.8% in the fruquintinib arm). Median time to onset in fruquintinib-treated patients was 28 days (range: 6 days to 1.3 years). Most 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 erythrodysaesthesia syndrome (PPES)

Palmar-plantar erythrodysaesthesia syndrome was reported in 32.7% of patients in the fruquintinib arm. The incidence of Grade ≥ 3 PPES in the fruquintinib arm was 8.5%. The 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 for PPES led to permanent treatment discontinuation.

Posterior reversible encephalopathy syndrome (PRES)

One case (0.1%) of PRES (Grade 4) was reported in patients who received fruquintinib monotherapy in clinical studies. PRES has also been reported in post-marketing experience. All the events of PRES resolved after treatment and dose discontinuation.

Hypothyroidism

Hypothyroidism was reported in 31.5% of the patients in the fruquintinib arm. The incidence of Grade ≥ 3 thyroid dysfunction 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.

Infections

Infections were reported in 23.4% of the patients in the fruquintinib arm and 13.3% in the placebo arm. Most infection events in patients treated with fruquintinib were mild to moderate in severity

(incidence of Grade ≥ 3 infections was 6% in the fruquintinib arm). Serious infections were reported in 4.1% of patients and fatal infection events were reported in 1.0% of patients in the fruquintinib arm. The incidence of infections leading to dose discontinuation was 0.9%. The most common infection reaction was upper respiratory tract infection (5.0%). The most frequently reported serious infection was pneumonia (1.4%).

Liver function test abnormalities

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 was 8.8% in the fruquintinib 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 and fatal liver function test abnormalities were reported in 0.3% of patients in the fruquintinib 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.

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 national reporting system:

Belgium
Federal Agency for Medicines and Health Products
www.fagg.be
Vigilance Division:
Website: www.eenbijwerkingmelden.be
e-mail: adr@fagg-afmps.be

Luxembourg
Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé
Site internet : www.guichet.lu/pharmacovigilance

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, vascular endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitors, ATC code: L01EK04

Mechanism of action and pharmacodynamic effects

Fruquintinib is a selective tyrosine kinase inhibitor of VEGFR-1, -2, and -3 with antitumor effects resulting from suppression of tumour angiogenesis.

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 and safety of fruquintinib plus best supportive care (BSC) was evaluated in a randomised, placebo-controlled, double-blind, phase III study (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-2 study is described below.

FRESCO-2 Study

The clinical efficacy and safety of fruquintinib were evaluated in a global, randomised, double-blind, placebo-controlled, multicentre, phase III study (FRESCO-2) in 691 patients with mCRC who had been previously treated with standard approved therapies including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF biological therapy; an anti-EGFR therapy if RAS wild-type, and have progressed on or had intolerance to trifluridine/tipiracil and/or regorafenib. Patients were considered intolerant to trifluridine/tipiracil or regorafenib if they received at least 1 dose of either agent and were discontinued from therapy for reasons other than progressive disease. Patients with MSI-H or dMMR tumours were previously treated with immune checkpoint inhibitors, and patients with BRAF V600E mutant tumours were previously treated with a BRAF inhibitor, if approved and available in the patients' respective country or region. Randomisation was stratified by prior therapy (trifluridine/tipiracil vs. regorafenib vs. both trifluridine/tipiracil and regorafenib), RAS status (wild-type vs. mutant), and duration of metastatic disease (≤ 18 months vs. > 18 months).

Patients with an Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2, left ventricular fraction ≤ 50%, systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg, urine protein ≥ 1 g/24h, or body weight < 40 kg were excluded. The primary efficacy endpoint was overall survival (OS). The key secondary efficacy endpoint was progression-free survival (PFS; as assessed by the investigator using Response Evaluation Criteria in Solid Tumours [RECIST], version 1.1) and other supportive secondary endpoints included disease control rate.

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) plus BSC (hereafter denoted as fruquintinib and placebo, respectively), 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 wild-type was reported in 36.9% of patients at study entry. The median duration of metastatic disease of 39 months (range: 6 months to 16.1 years). The median number of prior lines of therapy for metastatic disease was 4 (range: 2 to 16).
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, 4.6% received immunotherapy, and 2.3% received BRAF inhibitor.

In FRESCO-2, 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 1).

Table 4: Efficacy results from the FRESCO-2 study

Endpoint	**Fruquintinib (N=461)**	**Placebo (N=230)**

OS		
Median in months (95% CI)	7.4 (6.7, 8.2)	4.8 (4.0, 5.8)
Hazard Ratio[1] (95% CI)	0.66 (0.55, 0.80)	
p-value[2]	< 0.001	
PFS[3]		
Median in months (95% CI)	3.7 (3.5, 3.8)	1.8 (1.8, 1.9)
Hazard Ratio[1] (95% CI)	0.32 (0.27 to 0.39)	
p-value[2]	< 0.001	

Abbreviations: CI=confidence interval; HR=hazard ratio; N=number of patients; OS=overall survival; PFS=progression-free survival

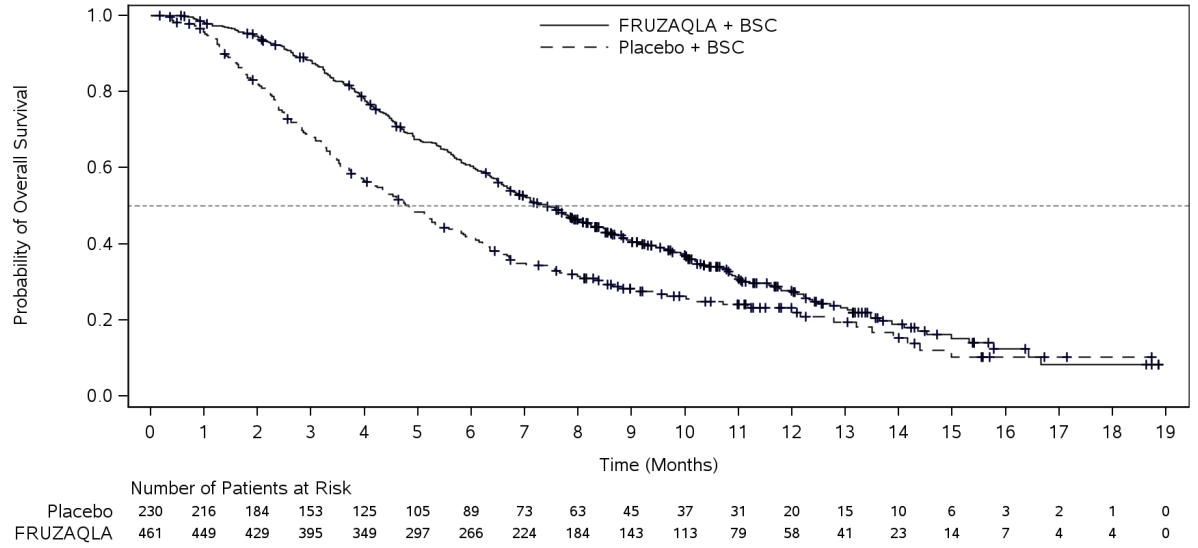
The median OS and PFS were calculated using the Kaplan-Meier method.

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

[2]p-value (2-sided) was calculated using the stratified log-rank test to account for the stratification factors.

[3]Assessed by the investigator using RECIST, version 1.1.

Figure 1: Kaplan-Meier curve for overall survival in FRESCO-2 study



Paediatric population

The European Medicines Agency 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. Fruquintinib showed a second absorption peak approximately 24 hours after drug administration. Following repeat once-daily dosing, fruquintinib exposure (C_{max} and $AUC_{0\text{-}24h}$) 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 $AUC_{0\text{-}24h}$ was 4-fold relative to a single dose. At the recommended dose of 5 mg of fruquintinib, 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* and mainly bound to human serum albumin.

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] labelled 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
CYP3A4 was the main enzyme among the CYP isoforms involved in the metabolism of fruquintinib, with minor contributions from CYP2C8, CYP2C9 and CYP2C19. 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 inhibited P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) in a dose-dependent manner *in vitro* and demonstrated pH-dependent aqueous solubility. 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

Based on the population pharmacokinetic analyses, mild to moderate renal impairment (creatinine clearance [CrCL] 30 to 89 mL/min) had no clinically meaningful impact on fruquintinib pharmacokinetics. In a pharmacokinetic study, unbound fruquintinib AUC_{0-inf} and C_{max} were similar in

subjects with moderate (CrCL 30 – 59 mL/min, N = 8) or severe (CrCL 15 – 29 mL/min, N = 8) renal impairment as compared to subjects with normal renal function (CrCL ≥ 90 mL/min, N = 8).

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 fruquintinib, no clinically meaningful differences in the dose-normalised AUC of fruquintinib were observed in subjects with moderate (Child Pugh B) 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 and reproductive toxicity studies, toxicity was observed at fruquintinib average plasma concentrations below the expected human therapeutic concentrations.

Repeat dose toxicity

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 appear related to the pharmacology of VEGFR inhibition and/or disruption of VEGF signalling pathway. All findings were reversible after 4 weeks without treatment, apart from the skeletal system (broken/lost teeth).

Impairment of fertility

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.

Reproductive toxicity

In an embryo-foetal developmental study in rats, embryotoxic and teratogenic effects were observed at subclinical exposure levels in the absence of excessive maternal toxicity, consisting of foetal external, visceral, and skeletal malformations. Malformations affected primarily the head, tail, tongue, blood vessels, heart, thymus, and developing skeleton (notably vertebrae).

Genotoxicity

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

Carcinogenesis

Carcinogenicity studies have not been performed with fruquintinib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Maize starch
Cellulose, microcrystalline (E460)
Talc (E553b)

Capsule shell (1 mg hard capsules only)

Gelatin
Titanium dioxide (E171)
Tartrazine (E102)
Sunset yellow FCF (E110)

Capsule shell (5 mg hard capsules only)

Gelatin
Titanium dioxide (E171)
Allura red AC (E129)
Brilliant blue FCF (E133)

Printing ink

Shellac (E904)
Propylene glycol (E1520)
Potassium hydroxide
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottle (45 mL) with polypropylene (PP) child-resistant closure and a HDPE desiccant cartridge containing silica gel. The desiccant must be kept inside the bottle.

Each bottle contains 21 hard capsules. Each bottle is packaged in a carton.

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

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50-58 Baggot Street Lower
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8. MARKETING AUTHORISATION NUMBERS

EU/1/24/1827/001
EU/1/24/1827/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 June 2024

10. DATE OF REVISION OF THE TEXT

06/2024

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.