PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrFRUZAQLA

Fruquintinib capsules

Capsules, 1 mg and 5 mg, Oral

Antineoplastic agent

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

FRUZAQLA (fruquintinib capsules) is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with or are not considered candidates for available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF agent, an anti-EGFR agent (if RAS wild-type), and either trifluridine-tipiracil or regorafenib.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): There were no observed overall differences in safety and effectiveness of FRUZAQLA in geriatric compared to younger patients.

2 CONTRAINDICATIONS

FRUZAQLA is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of FRUZAQLA is 5 mg (one 5 mg capsule) administered orally 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.

Treatment with FRUZAQLA should be continued until disease progression or unacceptable toxicity occurs.

Dose Adjustments for Adverse Reactions

FRUZAQLA 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 or baseline. • Resume at a reduced dose as per Table 1. • If the patient still experiences Grade 2 hemorrhagic 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) or bilirubin greater than 1.5 times ULN	• 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.
	ALT or AST greater than 3 times ULN with concurrent total bilirubin greater than 2 times ULN (in the	Permanently discontinue.

	absence of alternative etiologies)	
	AST or ALT greater than 20 times ULN or bilirubin greater than 10 times ULN	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.

ULN = upper limit of normal
[1]Graded per national cancer institute common terminology criteria for adverse events. Version 5.0 (NCI CTCAE v5).

Special Population

Pediatrics: Health Canada has not authorized an indication for pediatric use.

Geriatric: No dosage adjustment is required in patients 65 years or above.

Hepatic Impairment: No dosage adjustment is required for patients with mild hepatic impairment (total bilirubin less than or equal to the ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST*)* (see 10 CLINICAL PHARMACOLOGY).

Limited data are available for patients with moderate hepatic impairment (total bilirubin greater than 1.5 times and less than 3 times ULN and any AST) (see 10 CLINICAL PHARMACOLOGY).

FRUZAQLA is not recommended for use in patients with severe hepatic impairment (total bilirubin greater than 3 times ULN and any AST) as FRUZAQLA has not been studied in this population.

Renal Impairment: No dosage adjustment is required for patients with mild, moderate, or severe renal impairment (see 10 CLINICAL PHARMACOLOGY).

4.4 Administration

FRUZAQLA is for oral use. FRUZAQLA can be taken with or without food and should be swallowed whole.

4.5 Missed Dose

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.

5 OVERDOSAGE

The highest dose of FRUZAQLA studied in clinical studies was 6 mg per day. The most frequently observed adverse drug reactions at this dose were increased blood thyroid stimulating hormone, palmar-plantar erythrodysaesthesia syndrome, proteinuria, and arthralgia.

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsule / 1 mg, 5 mg / fruquintinib	Corn starch, FD&C Blue No. 1 (brilliant blue FCF) (5 mg), FD&C Red No. 40 (allura red AC) (5 mg), FD&C Yellow No. 5 (tartrazine) (1 mg), FD&C Yellow No. 6 (sunset yellow FCF) (1 mg), gelatin, microcrystalline cellulose, pharmaceutical grade printing ink, talc, titanium dioxide

FRUZAQLA is supplied as capsules as follows:

- 1 mg: Size 3 hard gelatin capsule with yellow opaque cap and white opaque body, imprinted with "HM013" over "1mg" on the body in black ink
- 5 mg: Size 1 hard gelatin capsule with red opaque cap and white opaque body, imprinted with "HM013" over "5mg" on the body in black ink

White high-density polyethylene (HDPE) bottle with child-resistant closure packaged in a carton. Each bottle contains 21 capsules and a desiccant cartridge to protect the capsules from moisture.

7 WARNINGS AND PRECAUTIONS

Cardiovascular

Hypertension

In 911 patients with mCRC treated with FRUZAQLA, hypertension, including hypertensive crisis (0.3%), has been reported in 49.4% of patients treated with FRUZAQLA. Approximately half of these events occurred during the first 2 weeks after initiating treatment with FRUZAQLA. The incidence of Grade ≥3 hypertension was 19.1%. Median time to onset in FRUZAQLA-treated patients was 14 days (range: 1 day to 7.6 months). Three patients (0.3%) treated with FRUZAQLA experienced life-threatening hypertension. The majority of the events resolved. Hypertension leading to dose interruption or reduction, was reported in 3.1% and 3.7% of patients, respectively. In 0.5% of patients treated with FRUZAQLA, hypertension led to permanent treatment discontinuation.

Preexisting hypertension should be adequately controlled before starting FRUZAQLA treatment.

Hypertension should be medically managed with antihypertensive medicinal products and adjustment of the FRUZAQLA dose, if necessary (see 4 DOSAGE AND ADMINISTRATION). FRUZAQLA should be permanently discontinued for hypertension that cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis.

Driving and Operating Machinery

Studies to evaluate the effects of FRUZAQLA on the ability to drive or operate machinery have not been conducted. FRUZAQLA may have a minor influence on the ability to drive and use machines. Fatigue may occur following administration of FRUZAQLA (see 8 ADVERSE REACTIONS).

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Gastrointestinal

Gastrointestinal (GI) perforation

In 911 patients with mCRC treated with FRUZAQLA, GI perforation events were reported in 2.5% of patients. Fatal GI perforation was reported in 0.1% of patients treated with FRUZAQLA. The most common GI perforation event was intestinal perforation (0.7%). In 1.2% of patients treated with FRUZAQLA, GI perforation events led to dose discontinuation.

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

FRUZAQLA should be permanently discontinued in patients developing GI perforation.

Hepatic

Liver function test abnormalities

FRUZAQLA can cause liver injury.

In 911 patients with mCRC treated with FRUZAQLA, liver function test abnormalities have been reported in 37.7% of patients treated with FRUZAQLA, including fatal events in clinical studies (see 8 ADVERSE REACTIONS).

Most hepatobiliary disorders in patients treated with FRUZAQLA were mild to moderate in severity. The incidence of Grade ≥3 liver function test abnormalities were 8.8%. The most common liver function test abnormality events were AST increase (18.9%), ALT increase (16.4%), and total bilirubin increase (14.5%). Median time to onset in FRUZAQLA treated patients was 27 days (range: 4 days to 12 months).

Serious liver function test abnormalities were reported in 2.4% of patients. Fatal liver function test abnormalities were reported in 0.2% of patients. Liver function test abnormalities led to dose interruption and reduction in 5.0% and 1.9% of patients, respectively, and to permanent discontinuation in 1.9% of patients.

Liver function test abnormalities should be monitored before initiation and throughout the treatment with FRUZAQLA. 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.

Infections

Infections, including fatalities, have been reported in patients treated with FRUZAQLA.

In 911 patients with mCRC treated with FRUZAQLA, infections were reported in 24.4% of the patients (see 8 ADVERSE REACTIONS). Most infection events in patients treated with FRUZAQLA were mild to moderate in severity. The incidence of Grade ≥3 infections was 6.9%. Serious infections were reported in 4.7% of patients. The incidence of infections leading to dose discontinuation was 0.8%. The most common infection were upper respiratory tract infection (3.2%) and pneumonia (2.5%). The most frequently reported serious and fatal infection was pneumonia (1.5% and 0.4% respectively).

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

Monitoring and Laboratory Tests

Hypertension should be monitored and managed using standard antihypertensive therapy during treatment with FRUZAQLA as clinically indicated.

The pregnancy status of females of reproductive potential should be verified prior to starting treatment with FRUZAQLA.

Urine protein should be monitored regularly.

Monitor hematologic and coagulation parameters in patients at risk of bleeding.

Monitor liver function before inititiation and periodically through out treatment.

Symptoms of GI perforation should be monitored periodically.

Neurologic

Posterior reversible encephalopathy syndrome (PRES)

In 911 patients with mCRC treated with FRUZAQLA, PRES has been reported with the use of FRUZAQLA (0.1%). 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).

FRUZAQLA should be permanently discontinued in patients developing PRES. Control of hypertension and supportive medical management of other symptoms are recommended.

Peri-Operative Considerations

Impaired wound healing

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

In 911 patients with mCRC treated with FRUZAQLA, impaired wound healing has been reported in 1 patient (0.1%) treated with FRUZAQLA.

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

Renal

Proteinuria has occurred in patients treated with FRUZAQLA. In 911 patients with mCRC treated with FRUZAQLA, proteinuria was reported in 35.8% of the patients. Most of the events in patients treated with FRUZAQLA were mild to moderate severity; the incidence of Grade ≥3 proteinuria events was 2.5%. Median time to onset in FRUZAQLA-treated patients was 22 days (range: 1 day to 1.3 years). The majority of the events recovered or resolved following dose interruption or reduction. In 1.6% of patients treated with FRUZAQLA, proteinuria led to permanent treatment discontinuation.

Urine protein should be monitored regularly. If urine dipstick proteinuria ≥2 g / 24 hours is detected, dose interruptions, adjustments, or discontinuation may be necessary. FRUZAQLA should be permanently discontinued in patients developing nephrotic syndrome (see 4 DOSAGE AND ADMINISTRATION).

Reproductive Health: Female and Male Potential

- **Fertility**

There are no data on the effects of FRUZAQLA on human fertility. Results from animal studies indicate that FRUZAQLA may impair male and female fertility (see 16 NON-CLINICAL TOXICOLOGY).

- **Teratogenic Risk**

FRUZAQLA may cause harm to the developing fetus and/or result in a loss of pregnancy. Advise women of the potential hazard to a fetus and to avoid becoming pregnant by using effective contraception during treatment and for at least 2 weeks after the last dose of FRUZAQLA.

Pregnancy testing is recommended for females of reproductive potential prior to initiating FRUZAQLA

Advise men to avoid fathering a child while receiving FRUZAQLA and for two weeks after the last dose of FRUZAQLA.

Skin

Palmar-plantar erythrodysaesthesia syndrome (PPES) is the most frequently reported dermatological adverse reaction. In 911 patients with mCRC treated with FRUZAQLA, PPES was reported in 34.6% of patients. The incidence of Grade ≥3 PPES events were 8.3%. Median time to onset in FRUZAQLA-treated patients was 19 days (range: 1 day to 8.0 months). The majority of the events recovered or resolved. PPES leading to dose interruption or reduction were reported in 6.5% and 6.4% of patients, respectively. In 0.5% of patients treated with FRUZAQLA, PPES led to permanent treatment discontinuation.

If Grade ≥2 skin reactions are detected, dose interruptions, adjustments, or discontinuation may be necessary (see 4 DOSAGE AND ADMINISTRATION).

Vascular

Arterial thromboembolic events

It is recommended to avoid starting treatment with FRUZAQLA 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, FRUZAQLA should be discontinued immediately.

Hemorrhage

In 911 patients with mCRC treated with FRUZAQLA, hemorrhagic events were reported in 27.3% of patients. Most haemorrhagic events in patients treated with FRUZAQLA were mild to moderate in severity; the incidence of Grade ≥3 hemorrhagic events were 2.3%. Median time to onset in FRUZAQLA-treated patients was 22 days (range: 1 day to 9.8 months). Fatal hemorrhagic events were reported in 0.5% of patients in the FRUZAQLA arm. In 1.3% of patients treated with FRUZAQLA, haemorrhagic events led to dose discontinuation. The most common haemorrhagic reactions were gastrointestinal haemorrhage (6.7%) and epistaxis (6.7%). The most frequently reported serious haemorrhagic event was gastrointestinal haemorrhage, which was reported in 1.5% of patients.

Monitor hematologic 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 4 DOSAGE AND ADMINISTRATION).

Aneurysm and Artery Dissection

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

7.1 Special Populations

7.1.1 Pregnant Women

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

Based on its mechanism of action, FRUZAQLA has the potential to cause fetal harm when administered to pregnant women. Studies in pregnant animals have shown fetal lethality and fetal malformations (see 16 NON-CLINICAL TOXICOLOGY). Therefore, FRUZAQLA should not be used during pregnancy.

Women of childbearing potential should be advised to use effective contraception during treatment and for at least 2 weeks following the last dose of FRUZAQLA.

If FRUZAQLA is used during pregnancy or if a patient becomes pregnant while on treatment or a female is impregnated by a male partner being treated with FRUZAQLA, the pregnant individual must be informed of the potential hazard to the fetus.

7.1.2 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.

7.1.3 Pediatrics

Pediatrics (<18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The overall safety profile of FRUZAQLA is based on pooled data from clinical studies with 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). Patients were exposed to at least one dose (5 mg) of FRUZAQLA (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%).

Serious adverse events occurred in 30.1% of patients. The most common serious adverse reactions (incidence ≥ 1%) were gastrointestinal haemorrhage (1.5%), pneumonia (1.5%), hypertension (1.5%), and gastrointestinal perforation (1.3%).

The frequency of dose interruptions due to adverse events was 42.4%. The most common adverse reactions leading to dose interruption were palmar-plantar erythrodysaesthesia (6.5%) and proteinuria (5.5%).

The frequency of dose reduction due to adverse events was 24.7%. The most common adverse reactions leading to dose reduction were PPES (6.4%), hypertension (3.7%), and proteinuria (3.4%).

The frequency of treatment discontinuation due to adverse events was 18.0%. The most common adverse reactions leading to treatment discontinuation were proteinuria (1.6%), and gastrointestinal perforation (1%).

Deaths due to adverse events were reported in 7.1% of patients. The most common adverse reactions leading to death were pneumonia (0.4%) and gastrointestinal haemorrhage (0.2%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

FRESCO-2 Study

The safety of FRUZAQLA was evaluated in FRESCO-2, a randomized, double-blind, placebo-controlled study (see 14 CLINICAL TRIALS). Patients received either FRUZAQLA 5 mg daily for the first 21 days of each 28-day cycle plus best supportive care (BSC) (n=456) or matching placebo plus BSC (n=230).

The median duration of therapy with FRUZAQLA was 3 months (range: 0.3 to 19.1 months).

Table 4 summarizes the adverse reactions in FRESCO-2.

Table 4 Adverse Reactions Occurring in ≥10% (All Grades) of Patients treated with FRUZAQLA versus placebo in FRESCO-2.

Adverse Reactions	FRUZAQLA + BSC N=456		Placebo + BSC N=230	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Blood and Lymphatic Disorders				
Thrombocytopenia[1]	12	0.2	2	0.4
Endocrine Disorders				
Hypothyroidism[2]	26	0.4	2	0
Gastrointestinal Disorders				
Diarrhea[3]	24	4	11	0
Stomatitis[4]	15	2	4	0.4
General Disorders				
Asthenia	34	8	23	4
Fatigue	20	4	16	0.9
Mucosal inflammation	14	0.4	3	0
Hepatobiliary Disorders				
Total Bilirubin Increase[5]	12	4	7	5
Aspartate aminotransferase increased	11	2	5	1
Alanine aminotransferase increased	10	3	4	0.4
Metabolism Disorders				
Anorexia[6]	33	3	24	2
Musculoskeletal Disorders				
Musculoskeletal Discomfort[7]	14	0.7	4	0
Arthralgia	11	0.9	4	0
Renal Disorders				
Proteinuria[8]	18	2	5	0.9

Respiratory Disorders				
Dysphonia[9]	18	0	5	0
Skin and Subcutaneous Disorders				
Palmar-plantar erythrodysaesthesia[10]	19	6	3	0
Vascular Disorders				
Hypertension[11]	39	14	9	0.9

The following terms represent a group of related events that describe a medical condition rather than a single event:
1 Thrombocytopenia includes Platelet count decreased, Thrombocytopenia
2 Hypothyroidism includes Blood thyroid stimulating hormone increased, Hypothyroidism
3 Diarrhea includes Diarrhoea
4 Stomatitis includes Aphthous ulcer, Gingival ulceration, Mouth ulceration, Stomatitis, Tongue ulceration
5 Total Bilirubin Increase includes Bilirubin conjugated increased, Blood bilirubin increased, Blood bilirubin unconjugated increased, Hyperbilirubinaemia, Jaundice, Jaundice cholestatic
6 Anorexia includes Decreased appetite, Weight decreased
7 Musculoskeletal Discomfort includes Bone pain, Muscle spasms, Musculoskeletal chest pain, Musculoskeletal pain, Neck pain, Pain in extremity
8 Proteinuria includes Albuminuria, Protein urine present, Proteinuria
9 Dysphonia includes Aphonia, Dysphonia
10 Palmar-plantar erythrodysaesthesia includes Palmar-plantar erythrodysaesthesia syndrome
11 Hypertension includes Blood pressure diastolic increased, Blood pressure increased, Diastolic hypertension, Hypertension, Hypertensive crisis

FRESCO Study

The safety of FRUZAQLA was evaluated in FRESCO, a randomized, double-blind, placebo-controlled study (see 14 CLINICAL TRIALS). Patients received either FRUZAQLA 5 mg daily for the first 21 days of each 28-day cycle plus BSC (n=278) or matching placebo plus BSC (n=137).

The median duration of therapy with FRUZAQLA was 3.68 months (range: 0.3 to 22.1 months).

Table 5 summarizes the adverse reactions in FRESCO.

Table 5 Adverse Reactions Occurring in ≥10% (All Grades) of Patients treated with FRUZAQLA versus placebo in FRESCO.

Adverse Reactions	FRUZAQLA + BSC N=278		Placebo + BSC N=137	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Blood and Lymphatic Disorders				
Thrombocytopenia[1]	21	4	3	0
Leukopenia[2]	16	0.4	4	0.7
Neutropenia[3]	10	0.4	3	0
Endocrine Disorders				
Hypothyroidism[4]	41	0	4	0

Gastrointestinal Disorders				
Diarrhea[5]	25	3	5	0
Stomatitis[6]	24	0.7	0.7	0
Gastrointestinal Haemorrhage[7]	13	1	5	0
General Disorders				
Fatigue	14	2	11	2
Asthenia	13	0.7	2	0
Hepatobiliary Disorders				
Total Bilirubin Increase[8]	28	4	16	7
Aspartate aminotransferase increased	28	1	18	2
Alanine aminotransferase increased	23	0.7	11	2
Metabolism Disorders				
Anorexia[9]	38	4	20	0.7
Musculoskeletal Disorders				
Arthralgia	13	0.4	2	0
Musculoskeletal Discomfort[10]	13	2	3	2
Renal Disorders				
Proteinuria[11]	55	5	30	0
Respiratory Disorders				
Dysphonia	38	0	2	0
Throat Pain[12]	10	0	2	0
Skin and Subcutaneous Disorders				
Palmar-plantar erythrodysaesthesia[13]	49	11	3	0
Vascular Disorders				
Hypertension[14]	61	23	17	2

The following terms represent a group of related events that describe a medical condition rather than a single event:
1 Thrombocytopenia includes Platelet count decreased, Thrombocytopenia
2 Leukopenia includes Leukopenia, White blood cell count decreased

3 Neutropenia includes Neutropenia, Neutrophil count decreased
4 Hypothyroidism includes Blood thyroid stimulating hormone increased, Hypothyroidism
5 Diarrhea includes Diarrhoea
6 Stomatitis includes Aphthous ulcer, Gingival ulceration, Mouth ulceration, Stomatitis, Tongue ulceration
7 Gastrointestinal Haemorrhage includes Anal haemorrhage, Anastomotic haemorrhage, Gastric haemorrhage, Gastrointestinal haemorrhage, Haematochezia, Haemorrhoidal haemorrhage, Intestinal haemorrhage, Lower gastrointestinal haemorrhage, Rectal haemorrhage, Upper gastrointestinal haemorrhage
8 Total Bilirubin Increase includes Bilirubin conjugated increased, Blood bilirubin increased, Blood bilirubin unconjugated increased, Hyperbilirubinaemia, Jaundice, Jaundice cholestatic
9 Anorexia includes Decreased appetite, Weight decreased
10 Musculoskeletal Discomfort includes Bone pain, Muscle spasms, Musculoskeletal chest pain, Musculoskeletal pain, Neck pain, Pain in extremity
11 Proteinuria includes Albuminuria, Protein urine present, Proteinuria
12 Throat Pain includes Laryngeal discomfort, Laryngeal pain, Oropharyngeal discomfort, Oropharyngeal pain
13 Palmar-plantar erythrodysaesthesia includes Palmar-plantar erythrodysaesthesia syndrome
14 Hypertension includes Blood pressure diastolic increased, Blood pressure increased, Diastolic hypertension, Hypertension, Hypertensive crisis

8.3 Less Common Clinical Trial Adverse Reactions

Other clinically important adverse reactions (all grades) that occurred in <10% of patients treated with FRUZAQLA included:

Gastrointestinal disorders: gastrointestinal perforation, oral pain, pancreatic enzymes increased, pancreatitis (includes pancreatitis, pancreatitis acute)
Infections and infestations: upper respiratory tract infection
Metabolism and Nutrition disorders: hypokalemia
Nervous system disorders: posterior reversible encephalopathy syndrome
Respiratory, thoracic and mediastinal disorders: epistaxis, pneumonia
Skin and subcutaneous tissue disorders: rash

8.4 Abnormal Laboratory Findings

Table 6 Select Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients in FRESCO-2

Laboratory Abnormality*	FRUZAQLA + BSC (N=456)†		Placebo + BSC (N=230)†	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Alanine Aminotransferase Increased	34	5	22	1
Albumin Decreased	35	2	32	1
Aspartate Aminotransferase Increased	36	4	24	2
Bilirubin Increased	30	7	21	8

Calcium Decreased	17	0.5	12	0
Calcium Increased	11	0.2	4	0
Cholesterol Increased	37	2	22	2
Creatinine Increased	17	0	13	0.9
Magnesium Decreased	20	0.5	10	0.5
Potassium Decreased	19	4	7	0.9
Sodium Decreased	35	1	27	0.9
Triglycerides Increased	53	3	22	1
Hematology				
Activated Partial Thromboplastin Time Increased	21	3	18	2
Leukocytes Decreased	13	0.5	3	0.5
Platelets Decreased	30	0.2	5	0

* Graded according to NCI CTCAE version 5.0.
† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available.

Table 7 Select Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients in FRESCO

Laboratory Abnormality*	FRUZAQLA + BSC (N=456)†		Placebo + BSC (N=230)†	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Alanine aminotransferase increased	32	2	17	2
Alkaline phosphatase increased	38	4	34	5
Aspartate aminotransferase increased	40	4	29	2

Blood bilirubin increased	38	5	33	6
Creatinine increased	87	0.4	75	2
Hypermagnesemia	15	4	6	2
Hyperglycemia	43	1	31	2
Hypernatremia	12	0	4	0
Hyperuricemia	26	26	20	20
Hypocalcemia	25	0.4	11	0
Hypokalemia	22	2	15	2
Hypomagnesemia	13	0	7	0
Hyponatremia	32	6	29	5
Serum amylase increased	13	3	4	0
Hematology				
Neutrophil count decreased	14	0.7	3	0
Platelet count decreased	29	4	6	0.7
White blood cell decreased	19	0.7	5	0

* Graded according to NCI CTCAE version 4.03.
† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available.

8.5 Post-Market Adverse Reactions

The following adverse drug reactions have been identified from the worldwide post-marketing experience with FRUZAQLA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Vascular disorders: Artery dissection and artery aneurysm (including rupture).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) *in vitro* and demonstrated pH-dependent aqueous solubility.

9.4 Drug-Drug Interactions

The drugs listed in this section are based on either drug interaction studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Effect of Other Drugs on Fruquintinib

Table 8 Established or Potential Drug-Drug Interactions for FRUZAQLA

Proper name	Source of Evidence	Effect	Clinical comment
Pharmacokinetic Interactions (Drugs that may affect the exposure to fruquintinib)			
Strong CYP3A Inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, St. John's Wort)	CT	Co-administration of fruquintinib with rifampin (a strong CYP3A inducer) 600 mg once daily decreased fruquintinib AUC by 65% and decreased C_{max} by 12%.	The concomitant use of FRUZAQLA with strong CYP3A inducers should be avoided.
Moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin)	T	Co-administration of fruquintinib with efavirenz (a moderate CYP3A inducer) 600 mg once daily is predicted to decrease fruquintinib AUC by 32% and decrease C_{max} by 4%.	If possible, avoid concomitant use of moderate CYP3A inducers with FRUZAQLA. If it is not possible to avoid concomitant use of a moderate CYP3A inducer and fruquintinib, continue to administer FRUZAQLA at the recommended dosage.
Weak CYP3A inducers	T	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.	No dose adjustment of FRUZAQLA is needed during concomitant use with weak CYP3A inducers.
CYP3A Inhibitors	CT	Co-administration of fruquintinib with itraconazole (a strong	No dose adjustment of FRUZAQLA is needed during concomitant

		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.	use with strong CYP3A inhibitors.
Gastric Acid Lowering Agents	CT	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 FRUZAQLA is needed during concomitant use with gastric acid lowering agents.
Pharmacokinetic Interactions (Fruquintinib may affect the exposure to other drugs)			
Substrate of P-gp	CT	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 FRUZAQLA.
Substrate of BCRP	CT	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 FRUZAQLA.

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.

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 MATE2K.

9.5 Drug-Food Interactions

FRUZAQLA can be administered with or without food (see 10 CLINICAL PHARMACOLOGY).

9.6 Drug-Herb Interactions

St. John's Wort (Hypericum perforatum) is a strong CYP3A inducer. Coadministration of St. John's Wort with FRUZAQLA should be avoided (see Table 8).

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Fruquintinib is a small molecule tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR) -1, -2, and -3 with half maximal inhibitory concentration (IC_{50}) values of 33, 35, and 0.5 nM, respectively. 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.

10.2 Pharmacodynamics

Cardiac Electrophysiology

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

10.3 Pharmacokinetics

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). Fruquintinib steady state was achieved after 14 days, and the mean accumulation based on $AUC_{0\text{-}24h}$ was 4-fold relative to a single dose.

Table 9 Summary of Fruquintinib Pharmacokinetic Parameters at Steady State in Adult Cancer Patients

	Cmax (ng/mL)[a]	Tmax (h)[b]	t½ (h)[c]	AUC0-24 (ng.h/mL)[a]	CL/F (mL/min)[a]	Vz/F (L)[d]
5 mg QD 3/1	300	2.00	42	5880	14.8	48.5
a: geometric mean; b: median; c: arithmetic mean; d: based on a population PK analysis; QD 3/1: once daily 3-week on/1-week off in a 28-day treatment cycle						

Absorption

After oral administration of fruquintinib capsules, the median time to achieve peak plasma fruquintinib concentration (T_{max}) was approximately 2 hours. At the recommended dose of 5 mg of fruquintinib capsules, the %coefficient of variation for fruquintinib C_{max} and $AUC_{0\text{-}24h}$ at steady-state were 28% and 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 capsules 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%.

Metabolism

Fruquintinib is primary metabolised by CYP450 (CYP3A and CYP2C subfamilies) and non-CYP450 enzyme systems (sulfation and glucuronidation). CYP3A and to a lesser extent CYP2C8, CYP2C9, and CYP2C19 are the CYP450 enzymes involved in fruquintinib metabolism.

Elimination

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

Special Populations and Conditions

Age, Body weight, Gender, Race

No clinically significant differences in the pharmacokinetics of fruquintinib were observed based on age (18 to 82 years), body weight (48 to 108 kg), gender or race.

Hepatic Insufficiency

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 a dedicated hepatic impairment pharmacokinetic study, following administration of a single 2 mg oral dose of fruquintinib, no clinically meaningful differences in the dose-normalized AUC of fruquintinib were observed in subjects with moderate (Child Pugh B) hepatic impairment compared to subjects with normal hepatic function.

FRUZAQLA is not recommended for use in patients with severe hepatic impairment (Child Pugh C or total bilirubin greater than 3 times ULN and any AST) as FRUZAQLA has not been studied in this population.

Renal Insufficiency

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.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C to 30°C). Store in the original container to protect from moisture. Keep the bottle tightly closed. Do not remove desiccant from the bottle.

12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

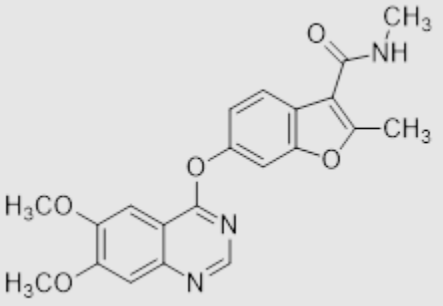
Drug Substance

Proper/Common name: fruquintinib

Chemical name: 6-[(6,7-dimethoxyquinazolin-4-yl)oxy]-*N*,2-dimethyl-1-benzofuran-3- carboxamide

Molecular formula and molecular mass: $C_{21}H_{19}N_3O_5$ 393.39 g/mol

Structural formula:



Physicochemical properties:

Fruquintinib is a white to off-white powder with a dissociation constant (pKa) of 2.78. The aqueous solubility of fruquintinib is pH dependent, with a solubility of 0.9 µg/mL at pH 6.8 that increases under acidic conditions to 129.9 µg/mL at pH 1, at 37 °C.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Table 10 Summary of patient demographics for clinical trials in adult patients with previously treated metastatic colorectal cancer

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
FRESCO-2	Randomized, double-blind, placebo-controlled, multicentre, phase III study	Fruquintinib: 5mg orally once daily plus BSC, for 21 days on therapy followed by 7 days off therapy in a 28-day treatment cycle Placebo: orally once daily plus BSC, for 21 days on therapy followed by 7 days off therapy in a 28-day treatment cycle	Total: N=691 Fruquintinib plus BSC: N=461 Placebo plus BSC: N=230	64 years (25-86)	Male and female

FRESCO	Randomized, double-blind, placebo-controlled, multicentre phase III study	Fruquintinib: 5mg orally once daily plus BSC, for 21 days on therapy followed by 7 days off therapy in a 28-day treatment cycle Placebo: orally once daily plus BSC, for 21 days on therapy followed by 7 days off therapy in a 28-day treatment cycle	Total: N=416 Fruquintinib plus BSC: N=278 Placebo plus BSC: N=138	56 years (23-75)	Male and female

Abbreviations: BSC=Best Supportive Care

The safety and efficacy of FRUZAQLA plus best supportive care (BSC) was evaluated in two randomized, placebo-controlled, double-blind, phase III studies (FRESCO-2 and FRESCO) in patients with metastatic colorectal cancer (mCRC) previously treated with but not limited to oxaliplatin- and irinotecan-based chemotherapies.

FRESCO-2 Study

The efficacy of FRUZAQLA was evaluated in a global, randomized, 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 tumors were previously treated with immune checkpoint inhibitors, and patients with BRAF V600E mutant tumors were previously treated with a BRAF inhibitor, if approved and available in the patients' respective country or region.

Randomization 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 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 body weight < 40 kg were excluded. The primary efficacy endpoint was overall survival (OS). The key secondary efficacy endpoint was PFS as assessed by the investigator using RECIST, version 1.1. Other supportive secondary endpoints included tumour objective response rate (ORR), disease control rate (DCR; including complete response, partial response, and stable disease), duration of response (DoR), and safety.

Among the 691 randomized 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, 8.8% Asian, 2.9% Black or African American, and had an ECOG PS of 0 (43.1%) or 1 (56.9%). Tumor RAS wild-type was reported in 36.9% of patients at study entry. The median duration of metastatic disease was 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, 8.4% received regorafenib, 39.4% received both trifluridine/tipiracil and

regorafenib, 4.6% received immunotherapy, and 2.3% received BRAF inhibitor. The addition of FRUZAQLA to BSC resulted in a statistically significant improvement in OS and PFS compared to placebo plus BSC (see Table 11 and Figure 1).

FRESCO Study

The efficacy of FRUZAQLA was evaluated in a randomized, double-blind, placebo-controlled, multicentre phase III study (FRESCO) conducted in China in 416 patients with previously treated mCRC. Randomisation was stratified by prior use of VEGF inhibitor (yes vs. no) and K RAS gene status (wild type vs. mutant).

Patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥ 2, left ventricular fraction ≤ 50%, systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg, urine protein ≥ 1 g/24h, and body weight < 40 kg were excluded. The primary efficacy endpoint was overall survival (OS). Secondary efficacy endpoints included progression-free survival (PFS) as assessed by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, tumour objective response rate (ORR), disease control rate (DCR; including complete response, partial response and stable disease), duration of response (DoR), and safety.

Among the 416 randomized 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 ECOG PS of 0 (27%) or 1 (73%). The median number of prior lines of therapy for metastatic disease was 2 (range: 2 to 3). Tumor K-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 FRUZAQLA to BSC resulted in a statistically significant improvement in OS and PFS compared to placebo plus BSC (see Table 11 and Figure 2).

Table 11 Efficacy Results from FRESCO-2 and FRESCO Studies

	FRESCO-2		**FRESCO**	
Endpoint	**FRUZAQLA + BSC N=461**	**Placebo + BSC N=230**	**FRUZAQLA + BSC N=278**	**Placebo + BSC N=138**
OS				
Median in months (95% CI)	7.4 (6.7, 8.2)	4.8 (4.0, 5.8)	9.3 (8.2, 10.5)	6.6 (5.9, 8.1)
Hazard ratio[1] (95% CI)	0.66 (0.55, 0.80)		0.65 (0.51, 0.83)	
p-value[2]	< 0.001		< 0.001	
PFS[3]				
Median in months (95% CI)	3.7 (3.5, 3.8)	1.8 (1.8, 1.9)	3.7 (3.7, 4.6)	1.8 (1.8, 1.8)
Hazard ratio[1] (95% CI)	0.32 (0.27 – 0.39)		0.26 (0.21 – 0.34)	

p-value[2]	< 0.001	< 0.001

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; CR=complete response; PR=partial response; SD=stable disease; BSC: Best Standard of Care.

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

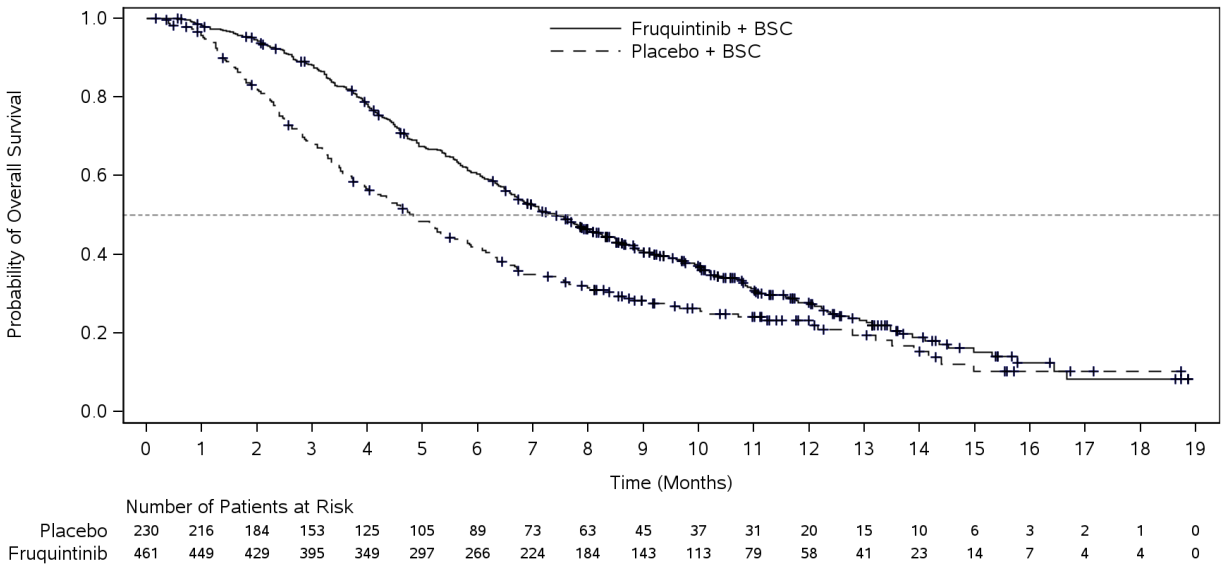
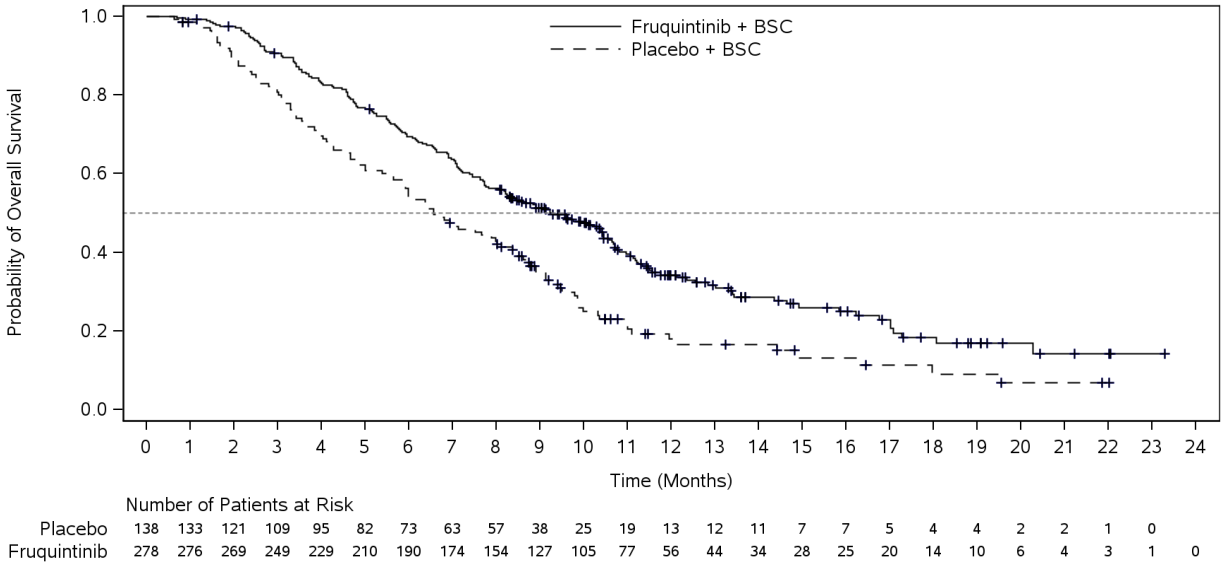


Figure 2. Kaplan-Meier curve for Overall Survival in FRESCO study



14.2 Comparative Bioavailability Studies

Not applicable.

14.3 Immunogenicity

Not applicable.

15 MICROBIOLOGY

Not Applicable.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

In repeat dose animal toxicity studies, the main target organ effects were identified in the gastrointestinal tract (diarrhea and gastrointestinal bleeding, degeneration, necrosis, and inflammation in the Brunner's gland), hepatobiliary system (elevated ALP, ALT, AST, CHOL, TBIL, and TG, along with hepatocyte necrosis/degeneration, hepatocyte swelling, vacuolation, granulomatous inflammation and bile duct hyperplasia), immune system (decreased lymphocytes and atrophy of thymus, atrophy of spleen, mast cell infiltration in the mesenteric lymph nodes), skeletal system (increased thickness of the physis in the femur, brown teeth, and broken/lost teeth), kidneys (elevated BUN, degeneration of renal glomerulus, and hyaline casts, vacuolation of tubular epithelial cells, urine protein), hematopoietic system (decreased hematopoietic cells in the bone marrow), pancreas (increased amylase and lipase) and adrenal gland (congestion, hemorrhage, and vacuolation). All findings were reversible or partially reversible after 4 weeks without treatment, apart from the skeletal system (brown teeth, broken/lost teeth) and adrenal gland vacuolation. These toxicities were observed at exposures that were below those achieved clinically at steady state.

Carcinogenicity:

Carcinogenicity studies have not been conducted with fruquintinib.

Genotoxicity:

Fruquintinib was considered negative for mutagenic or clastogenic potential in the in vitro bacterial reverse mutation (Ames) test or the in vitro Chinese hamster ovary chromosome aberration assay, respectively. Fruquintinib was also negative for clastogenic and aneugenic potential in the in vivo rat micronucleus test or alkaline comet assays.

Reproductive and Developmental Toxicology:

In a rat fertility and early embryonic development study with fruquintinib, male and female reproductive indices were decreased at exposures approximately 3.2 and 0.8 fold the human AUC respectively. However, females had increases in the number and percent of resorptions, post-implantation loss and a decrease in the number and percent of viable fetuses.

In an embryo-fetal developmental study in rats, embryo lethality and teratogenic effects consisting of external visceral and skeletal anomalies were observed. External anomalies included head and tail malformations and edema. Visceral evaluation showed an increase in malformations of malpositioned or absent blood vasculature. Skeletal evaluations showed increases in vertebral anomalies as well as increased incidences of variations, such as unossified forelimb metacarpals and/or phalanxes.

These findings occurred at exposures that were below those achieved clinically at steady state.

Special Toxicology

Fruquintinib was not considered to have phototoxic potential in the skin based on an in vivo phototoxicity study in guinea pigs. This finding occurred at exposures that were greater than those observed clinically at steady state.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]FRUZAQLA

Fruquintinib capsules

Read this carefully before you start taking **FRUZAQLA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **FRUZAQLA**.

What is FRUZAQLA used for?

FRUZAQLA is used to treat adult patients with colorectal cancer (CRC) that has spread to other parts of the body (metastatic). It is used when other treatments have not worked or when other treatments are not suitable for you.

How does FRUZAQLA work?

FRUZAQLA stops tumors from making new blood vessels and therefore slows down the growth of cancer. Blood vessels would usually provide the tumor with nutrients and oxygen.

If you have any questions about how this medicine works or why this medicine has been prescribed for you, please ask your healthcare professional.

What are the ingredients in FRUZAQLA?

Medicinal ingredients: fruquintinib

Non-medicinal ingredients: corn starch, FD&C Blue No. 1 (brilliant blue FCF) (5 mg), FD&C Red No. 40 (allura red AC) (5 mg), FD&C Yellow No. 5 (tartrazine) (1 mg), FD&C Yellow No. 6 (sunset yellow FCF) (1 mg), gelatin, microcrystalline cellulose, pharmaceutical grade printing ink, talc, titanium dioxide.

FRUZAQLA comes in the following dosage forms:

Capsule: 1 mg and 5 mg

Do not use FRUZAQLA if:

- You are allergic to fruquintinib, any of the other ingredients in this medicine or any parts of the container (see **What are the ingredients in FRUZAQLA?**).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take FRUZAQLA. Talk about any health conditions or problems you may have, including if you:

- have high blood pressure. Your healthcare professional should make sure that your blood pressure is under control before starting and while taking FRUZAQLA.
- have any bleeding problems. Tell your healthcare professional if you:

    - had or have bleeding problems
    - are taking medicines to thin the blood and prevent blood clots (like warfarin and acenocoumarol).
- have severe stomach and bowel problems. If you get severe stomach and bowel problems, talk to your healthcare professional immediately.
- have kidney problems.
- have any skin problems, which may include redness, pain, swelling, or blisters on the palms of your hands or soles of your feet.
- had severe and persistent headache, visual disturbances, seizures or altered mental status (such as confusion, memory loss or loss of orientation). If you notice any of these changes, talk to your healthcare professional immediately.
- had or are going to have surgery or have an unhealed wound. FRUZAQLA may affect the way your wounds heal.
- had problems with blood clots in your veins and arteries (types of blood vessels), including stroke, heart attack, embolism (blockage in your blood vessels), or thrombosis (blood clot forming in your blood vessels).
- have liver problems.
- have or have had infections.

Other warnings you should know about:

Pregnancy

FRUZAQLA has not been studied in pregnant women. FRUZAQLA should not be used during pregnancy. FRUZAQLA may harm your unborn child.

If you are pregnant, think you may be pregnant or are planning to become pregnant, talk to your healthcare professional for advice before taking this medicine. Your healthcare professional will discuss with you the potential risks of taking this medicine during pregnancy.

Breastfeeding

Tell your healthcare professional if you are breastfeeding or planning to breast-feed. It is unknown if FRUZAQLA passes into breast milk, and may harm the baby.

You should not breast-feed during treatment with this medicine and for at least 2 weeks following the last dose of FRUZAQLA. Talk to your healthcare professional about the best way to feed your baby during treatment with FRUZAQLA.

Fertility

The effects of FRUZAQLA on your ability to have children has not been studied.

Contraception – for men and women

Women who are able to become pregnant and male patients with female partners who are able to become pregnant should use highly effective birth control methods during treatment, and for at least 2 weeks following the last dose of FRUZAQLA.

Driving and Using Machines:

It is not known if FRUZAQLA changes your ability to drive or use machines. Do NOT drive or use any tools or machines if you experience tiredness, drowsiness, dizziness, lightheadedness, or any other symptoms that may affect your ability to concentrate and react.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with FRUZAQLA:

- Medicines used to treat seizures such as carbamazepine, phenobarbital, and phenytoin.
- Medicines used to treat tuberculosis such as rifampin.
- Medicines used to treat certain infections such as rifabutin.
- Herbs such as St. John's Wort.
- Medicines used to treat HIV-1 infection such as efavirenz and etravirine.
- Medicines used to treat high blood pressure such as bosentan.
- Medicines used to treat certain sleep disorders such as modafinil.
- Antibiotics used to treat bacterial infections such as nafcillin.

How to take FRUZAQLA:

- Take exactly as prescribed for you by your healthcare professional. Continue to take FRUZAQLA unless your healthcare professional tells you to stop.
- Take with or without food.
- Swallow whole. Do not open or dissolve the capsules.
- If you vomit after taking a dose, you should not take another dose on the same day. Take the dose as prescribed by your healthcare professional on the next day.

Usual dose:

The recommended dose is 5 mg once daily at around the same time each day for 21 days (3 weeks), followed by 7 days (1 week) of no treatment (rest period). This is 1 cycle of treatment.

Overdose:

If you think you, or a person you are caring for, have taken too much FRUZAQLA, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose and you are less than 12 hours late, take the missed dose as soon as you remember. Take the next dose at your regular time.

If you are more than 12 hours late, do NOT take the missed dose. Wait until the regular time for your next dose.

Do not take two doses to make up for a missed dose.

What are possible side effects from using FRUZAQLA?

These are not all the possible side effects you may have when taking FRUZAQLA. If you experience any side effects not listed here, tell your healthcare professional.

- reduced number of blood platelets (cells that help blood to clot) may show in your blood tests (thrombocytopenia) – can cause easy bruising or bleeding.
- reduced number of white blood cells may show in your blood tests (leukopenia).
- reduced number of neutrophils (type of white blood cell) may show in your blood tests (neutropenia).
- reduced activity of the thyroid gland (hypothyroidism).
- weight loss and loss of appetite (anorexia).
- voice changes or hoarseness (dysphonia).
- diarrhea.
- painful or dry mouth, mouth sores or ulcers (stomatitis).
- bone, muscle, chest, or neck pain.
- joint pain (arthralgia).
- weakness, lack of strength and energy, excessive tiredness and unusual sleepiness (asthenia/fatigue).
- low levels of potassium in blood (hypokalaemia).
- throat pain.
- increased pancreatic enzymes.
- toothache, gum, or lip pain (oral pain).
- rash.
- mouth sores (mucosal inflammation).
- inflammation of the pancreas (pancreatitis).

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
High blood pressure: very high blood pressure, severe headache, severe chest pain		✓	
Bleeding: blood in stools, black stools, blood in urine, stomach pain, coughing or vomiting up blood, nosebleed, bleeding in the digestive system such as stomach, rectum or intestine (gastrointestinal haemorrhage)			✓
Infections: fever, sever cough with or without an increase in mucus		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
production, severe sore throat, trouble breathing, burning or pain when you urinate, redness, swelling or pain in the body, infection of the lungs (pneumonia), nose and throat infection			
Liver problems: yellowing of your skin or the white parts of your eyes, dark coloured (tea coloured) urine, pain in your right upper stomach-area (abdomen), loss of appetite, nausea, vomiting, bleeding, bruising, increased levels of liver enzymes in blood tests, (including aspartate aminotransferase and alanine aminotransferase), abnormal liver function test (increased amounts of bilirubin in blood)		✓	
Palmar-plantar erythrodysaesthesia syndrome: redness, pain, blisters and swelling of the palms of the hands or soles of the feet (palmar-plantar erythrodysaesthesia syndrome)		✓	
Kidney problems: nausea, vomiting, fever, swelling of extremities, fatigue, thirst, dry skin, irritability, dark urine, increased or decreased urine output, blood in the urine, rash, weight gain (from retaining fluid), loss of appetite, abnormal blood test results, mental status changes (drowsiness, confusion, coma), protein in your urine		✓	
COMMON			
Severe stomach and bowel problems: coughing or vomiting up blood, severe stomach or abdominal pain that doesn't go away, vomiting blood, red or black stools			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON			
Reversible swelling of the brain (posterior reversible encephalopathy syndrome): headache, confusion, seizure (fits), changes in vision with or without high blood pressure			✓
Impaired wound healing: wounds heal slower		✓	
Arterial thromboembolic events: chest pain, shortness of breath, dizziness, face drooping on one side, weakness in one arm, slurred speech, limbs may become painful, skin on limb may be pale or blue in colour and cold			✓
UNKNOWN			
Arterial Dissection (tear along the inside of an artery): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at 15°C to 30°C. Store in the original container to protect from moisture. Keep the bottle tightly closed. Do not remove desiccant from the bottle**.**

Do not use this medicine after the expiry date (EXP) shown on the pack.

Keep out of reach and sight of children.

If you want more information about FRUZAQLA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website https://takeda.info/ca-medicines, or by calling 1-800-268-2772.

This leaflet was prepared by:

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