NAME OF THE MEDICINAL PRODUCT

FRUZAQLA 1 mg
FRUZAQLA 5 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION

FRUZAQLA 1 mg

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

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 9.

PHARMACEUTICAL FORM

Hard capsules - Please refer to section 3.

1. INDICATIONS AND USAGE

FRUZAQLA is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type and medically appropriate, an anti-EGFR therapy.

2. DOSAGE AND ADMINISTRATION

2.1. Recommended Dosage

The recommended dose of FRUZAQLA is 5 mg orally once daily for the first 21 days of each 28-day cycle until disease progression or unacceptable toxicity. Take FRUZAQLA with or without food *[see Clinical Pharmacology (10.3)]* at approximately the same time each day.

Swallow the FRUZAQLA capsule whole.

Take a missed dose if less than 12 hours have passed since the missed scheduled dose. Do not take two doses on the same day to make up for a missed dose.

Do not take an additional dose if vomiting occurs after taking FRUZAQLA but continue with the next scheduled dose.

2.2. Dosage Modifications for Adverse Reactions

The recommended dose reductions for adverse reactions are provided in Table 1.

Table 1: Recommended Dose Reductions for FRUZAQLA

Dose Level	FRUZAQLA Dosage
First dose reduction	4 mg orally once daily
Second dose reduction	3 mg orally once daily

Permanently discontinue FRUZAQLA in patients unable to tolerate 3 mg orally once daily.

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

Table 2: Recommended Dosage Modifications for FRUZAQLA

Adverse Reaction	Severity[1]	FRUZAQLA Dosage Modification
Hypertension *[see Warnings and Precautions (5.1)]*	Grade 3	• Withhold FRUZAQLA for Grade 3 hypertension that persists despite optimal anti-hypertensive therapy. • If hypertension fully resolves or recovers to Grade 1, resume at the next lower dose level.
	Grade 4	Permanently discontinue FRUZAQLA.
Hemorrhagic Events *[see Warnings and Precautions (5.2)]*	Grade 2	• Withhold FRUZAQLA until bleeding fully resolves or recovers to Grade 1. • Resume at the next lower dose level.
	Grade 3 or Grade 4	Permanently discontinue FRUZAQLA.

Adverse Reaction	Severity[1]	FRUZAQLA Dosage Modification
Hepatotoxicity *[see Warnings and Precautions (5.5)]*	Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 3 times upper limit of normal (ULN) with total bilirubin less than or equal to 2 times ULN	• Withhold FRUZAQLA and monitor AST/ALT and total bilirubin until resolution to Grade 1 or baseline. • Resume at the next lower dose level.
	ALT or AST greater than 3 times ULN with concurrent total bilirubin greater than 2 times ULN (in the absence of cholestasis or hemolysis)	Permanently discontinue FRUZAQLA.
	AST or ALT greater than 20 times ULN Or bilirubin greater than 10 times ULN	Permanently discontinue FRUZAQLA.
Proteinuria *[see Warnings and Precautions (5.6)]*	2 grams or greater proteinuria in 24 hours	• Withhold FRUZAQLA until proteinuria fully resolves or is <1 gram/24 hours. • Upon recovery, resume at the next lower dose level. Permanently discontinue FRUZAQLA for nephrotic syndrome or if proteinuria does not recover to <1 gram/24 hours.
Palmar-plantar erythrodysesthesia (PPE) *[see Warnings and Precautions (5.7)]*	Grade 2	• Withhold FRUZAQLA and initiate supportive treatment. • If toxicity fully resolves or recovers to Grade 1, resume at the same dose level.
	Grade 3	• Withhold FRUZAQLA and initiate supportive treatment. • If toxicity fully resolves or recovers to Grade 1, resume at the next lower dose level.
Other Adverse Reactions *[see Adverse Reactions (6.1)]*	Grade 3	• Withhold FRUZAQLA. • If toxicity fully resolves or recovers to Grade 1, resume at the next lower dose level.

Adverse Reaction	Severity[1]	FRUZAQLA Dosage Modification
	Grade 4	Discontinue FRUZAQLA. Consider resuming FRUZAQLA at the next lower dose level only if the toxicity is non-life threatening and fully resolves or recovers to Grade 1 and the potential benefit outweighs the risks.

[1] Severity as defined by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

3. DOSAGE FORMS AND STRENGTHS

Capsules:

- 1 mg: size 3 hard gelatin capsule with standard yellow opaque cap and white opaque body, imprinted with “HM013” over “1 mg” on the body in black ink.
- 5 mg: size 1 hard gelatin capsule with a red opaque cap and white opaque body, imprinted with “HM013” over “5 mg” on the body in black ink.

4. CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 9.

5. WARNINGS AND PRECAUTIONS

5.1. Hypertension

FRUZAQLA can cause hypertension. Hypertension occurred in 450 of 911 (49%) patients with mCRC treated with FRUZAQLA, including Grade 3-4 events in 19%, and hypertensive crisis in three patients (0.3%). The median time to first onset of hypertension was 14 days from first dose of FRUZAQLA.

Do not initiate FRUZAQLA unless blood pressure is adequately controlled. Monitor blood pressure weekly the first month, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue FRUZAQLA based on the severity of hypertension *[see Dosage and Administration (2.2)]*.

5.2. Hemorrhagic Events

FRUZAQLA can cause serious hemorrhagic events, which may be fatal. In 911 patients with mCRC treated with FRUZAQLA, 6% of patients experienced a gastrointestinal hemorrhage, including 13 patients (1%) with a Grade ≥3 event and 2 patients with fatal hemorrhages.

Permanently discontinue FRUZAQLA in patients with severe or life-threatening hemorrhage. Monitor the International Normalized Ratio (INR) levels in patients receiving anticoagulants *[see Dosage and Administration (2.2)]*.

5.3. Infections

FRUZAQLA can cause an increased risk of infections, including fatal infections. In 781 patients treated with FRUZAQLA across three randomized, placebo-controlled trials, the overall incidence of infections was higher (18% vs. 12%) including for fatal infections (1% vs. 0.3%) as compared to the placebo arms (n=391).

In 911 patients with mCRC treated with FRUZAQLA, the most common infections were urinary tract infections (6.8%), upper respiratory tract infections (3.2%) and pneumonia (2.5%); fatal infections included pneumonia (0.4%), sepsis (0.2%), bacterial infection (0.1%), lower respiratory tract infection (0.1%), and septic shock (0.1%).

Withhold FRUZAQLA for Grade 3 or 4 infections, or worsening infection of any grade. Resume FRUZAQLA at the same dose when the infection has resolved.

5.4. Gastrointestinal Perforation

FRUZAQLA can cause gastrointestinal perforation. In 911 patients with mCRC treated with FRUZAQLA, 12 patients (1.3%) experienced a Grade ≥3 gastrointestinal perforation, including one fatal event.

Permanently discontinue FRUZAQLA in patients who develop gastrointestinal perforation or fistula.

5.5. Hepatotoxicity

FRUZAQLA can cause liver injury. In 911 patients with mCRC treated with FRUZAQLA, 48% experienced increased ALT or AST, including Grade ≥3 events in 5%, and fatal events in 0.2%. Median time to first onset of elevated liver enzymes was 29 days from first dose of FRUZAQLA.

Monitor liver function tests (ALT, AST, and bilirubin) before initiation and periodically throughout treatment with FRUZAQLA. Temporarily hold and then reduce or permanently discontinue FRUZAQLA depending on the severity and persistence of hepatotoxicity as manifested by elevated liver function tests *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*.

5.6. Proteinuria

FRUZAQLA can cause proteinuria. In 911 patients with mCRC treated with FRUZAQLA, 36% experienced proteinuria and 2.5% of patients experienced Grade ≥3 events. Median time to first onset of proteinuria was 22 days from first dose of FRUZAQLA.

Monitor for proteinuria before initiation and periodically throughout treatment with FRUZAQLA. For proteinuria ≥2 g/24 hours, withhold FRUZAQLA until improvement to ≤Grade 1 proteinuria, resume FRUZAQLA at a reduced dose. Discontinue FRUZAQLA in patients who develop nephrotic syndrome *[see Dosage and Administration (2.2)].*

5.7. Palmar-Plantar Erythrodysesthesia (PPE)

FRUZAQLA can cause PPE. In 911 patients with mCRC treated with FRUZAQLA, PPE occurred in 35%, including 8% with Grade 3 events. Median time to first onset of PPE was 19 days from first dose of FRUZAQLA.

Based on severity, withhold FRUZAQLA and then resume at the same or reduced dose *[see Dosage and Administration (2.2)].*

5.8. Posterior Reversible Encephalopathy Syndrome (PRES)

FRUZAQLA can cause PRES, a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI. PRES occurred in one of 911 patients with mCRC treated with FRUZAQLA.

Perform an evaluation for PRES in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinue FRUZAQLA in patients who develop PRES.

5.9. Impaired Wound Healing

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. In 911 patients with mCRC treated with FRUZAQLA, 1 patient experienced a Grade 2 event of wound dehiscence.

Do not administer FRUZAQLA for at least 2 weeks prior to major surgery.

Do not administer FRUZAQLA for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of FRUZAQLA after resolution of wound healing complications has not been established.

5.10. Arterial Thromboembolic Events

FRUZAQLA may increase the risk of arterial thromboembolic events. In 911 patients with mCRC treated with FRUZAQLA, 7 patients (0.8%) experienced an arterial thromboembolic event; additionally, FRUZAQLA studies excluded patients with clinically significant cardiovascular disease, uncontrolled hypertension, or with thromboembolic events within the prior 6 months. Initiation of FRUZAQLA in patients with a recent history of thromboembolic events should be carefully considered. In patients who develop arterial thromboembolism discontinue FRUZAQLA.

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

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

FRUZAQLA 1 mg contains FD&C Yellow No. 6 (sunset yellow FCF), which may cause allergic reactions.
FRUZAQLA 5 mg contain Allura red AC (E129), which may cause allergic reactions.

5.12. Embryo-Fetal Toxicity

Based on findings in animal studies and its mechanism of action, FRUZAQLA can cause fetal harm when administered to pregnant women. In an embryo-fetal developmental study in rats, embryotoxic and teratogenic effects were observed at exposures below the clinical exposure *[see Use in Specific Populations (8.1)]*.
Advise pregnant women of the potential risk to a fetus. Advise females of childbearing potential and males with female partners of childbearing potential to use effective contraception during treatment with FRUZAQLA and for 2 weeks after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.13 Effects on ability to drive and use machines

FRUZAQLA has minor influence on the ability to drive and use machines. Fatigue may occur following administration of FRUZAQLA.

6. ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypertension *[see Warnings and Precautions (5.1)]*.
- Hemorrhagic Events *[see Warnings and Precautions (5.2)]*.
- Infections *[see Warnings and Precautions (5.3)]*.
- Gastrointestinal Perforation *[see Warnings and Precautions (5.4)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.5)].*
- Proteinuria *[see Warnings and Precautions (5.6)]*.
- Palmar-Plantar Erythrodysesthesia (PPE) *[see Warnings and Precautions (5.7)]*.
- Posterior Reversible Encephalopathy Syndrome (PRES) *[see Warnings and Precautions (5.8)]*.

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il.

6.1. Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in the WARNINGS AND PRECAUTIONS and below reflects exposure to FRUZAQLA as a single agent in 911 patients with mCRC who were enrolled in three randomized, placebo-controlled studies (FRESCO-2, FRESCO and 2012-013-00CH1) (N=781); three open-label studies (2009-013-00CH1, 2012-013-00CH3 and 2015-013-00US1) (N=124); and an open-label lead-in cohort of FRESCO-2 (N=6). Among the 911 patients who received FRUZAQLA, 23% were exposed for 6 months or longer and 3.5% were exposed for greater than one year. These patients received at least one dose of FRUZAQLA at the recommended dosage of 5 mg daily for the first 21 days of each 28-day cycle. The median age was 60 years (range: 23 to 82) and 34% were 65 years of age or older. The most common adverse reactions (incidence ≥20%) that occurred in pooled monotherapy studies were hypertension, PPE, proteinuria, dysphonia, abdominal pain, diarrhea, and asthenia.

Metastatic Colorectal Cancer

FRESCO-2 Study

The safety of FRUZAQLA was evaluated in FRESCO-2, a randomized, double-blind, placebo-controlled study *[see Clinical Studies (12.1)]*. 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).

Serious adverse reactions occurred in 38% of patients treated with FRUZAQLA. Serious adverse reactions in ≥2% of patients treated with FRUZAQLA included hemorrhage (2.2%) and gastrointestinal perforation (2.0%). Fatal adverse reaction(s) occurred in 14 (3.1%) patients who received FRUZAQLA. Fatal adverse reactions occurring in ≥2 patients include pneumonia (n=3), sepsis/septic shock (n=2), and hepatic failure/encephalopathy (n=2).

Adverse reactions leading to treatment discontinuation occurred in 20% of patients treated with FRUZAQLA. Adverse reactions leading to treatment discontinuations of FRUZAQLA in ≥1% of patients were asthenia and gastrointestinal perforation.

Dose interruptions of FRUZAQLA due to an adverse reaction occurred in 47% of patients. Adverse reactions leading to dose interruptions of FRUZAQLA in ≥2% of patients were PPE, proteinuria, asthenia, abdominal pain, hypertension, vomiting, and diarrhea.

Dose reductions of FRUZAQLA due to an adverse reaction occurred in 24% of patients. Adverse reactions leading to dose reductions of FRUZAQLA in ≥2% of patients were PPE, hypertension and asthenia.

Table 3 summarizes the adverse reactions in FRESCO-2.

Table 3: Adverse Reactions (≥10%) in Patients who Received FRUZAQLA and with a Difference Between Arms of ≥5% Compared to Placebo in FRESCO-2 (All Grades)

Adverse Reaction	FRUZAQLA (N=456)		Placebo (N=230)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
General				
Fatigue[1]	53	12	39	4.8
Vascular				
Hypertension[1]	38	14	9	0.9
Gastrointestinal				
Stomatitis[1]	31	2.2	7.8	0.4
Abdominal Pain[1]	25	3.5	20	3
Diarrhea[1]	24	3.7	11	0
Endocrine Disorders				
Hypothyroidism	21	0.4	0.4	0
Skin and Subcutaneous				
Palmar-plantar erythrodysesthesia (hand-foot skin reactions)	19	6	2.6	0
Renal				
Proteinuria[1]	18	1.8	5	0.9
Respiratory				
Dysphonia[1]	18	0	5	0
Musculoskeletal				
Musculoskeletal Pain[1]	16	1.1	7	0
Arthralgia	11	0.9	4.3	0

[1] Represents a composite of multiple related terms.

Other important adverse reactions (all grades) that occurred in <10% of patients treated with FRUZAQLA included urinary tract infection (4.6%), epistaxis (3.9%), proctalgia (3.5%), pneumonia (2.4%), gastrointestinal hemorrhage (1.5%), gastrointestinal perforation (1.3%), pancreatitis (0.7%), thrombotic microangiopathy (0.2%), and posterior reversible encephalopathy syndrome (0.2%).

Table 4 provides laboratory abnormalities observed in FRESCO-2.

Table 4: Select Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients in FRESCO-2

Laboratory[1] Abnormality	FRUZAQLA (N=456)[2]		Placebo (N=230)[2]	
	All Grade (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
Triglycerides Increased	53	2.8	22	1.0
Cholesterol Increased	37	1.9	22	1.9
Aspartate Aminotransferase Increased	36	4.3	24	1.9
Albumin Decreased	35	1.6	32	1.4
Sodium Decreased	35	1.1	27	0.9
Alanine Aminotransferase Increased	34	5	22	1.4
Bilirubin Increased	30	7	21	8
Alkaline Phosphatase Increased	20	1.6	27	0.5
Magnesium Decreased	20	0.5	10	0.5
Hematology				
Lymphocytes Decreased	30	6	32	4.7
Platelets Decreased	30	0.2	4.7	0
Activated Partial Thromboplastin Time Increased	21	2.7	18	1.5

[1] Graded according to NCI CTCAE version 5.0.
[2] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: FRUZAQLA (range: 409-444) and placebo (range: 195-216).

Other clinically relevant laboratory abnormalities (all grades) that occurred in <20% of patients treated with FRUZAQLA included pancreatic enzymes increased (3.9%).

FRESCO Study
The safety of FRUZAQLA was evaluated in FRESCO, a randomized, double-blind, placebo-controlled study *[see Clinical Studies (12.1)]*. 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).

Serious adverse reactions occurred in 15% of patients treated with FRUZAQLA. Serious adverse reactions in ≥2% of patients included intestinal obstruction (2.9%) and hemorrhage (2.2%). Fatal adverse reaction(s) occurred in 7 (2.5%) patients who received FRUZAQLA including cerebral infarction (n=1), gastrointestinal hemorrhage (n=1), hemoptysis (n=1), bacterial infection (n=1), lung/lower respiratory infection (n=2), and multiple organ dysfunction (n=1).

Adverse reactions leading to treatment discontinuation occurred in 15% of patients who received FRUZAQLA. Adverse reactions leading to treatment discontinuations of FRUZAQLA in ≥1% were intestinal obstruction, proteinuria and hepatic function abnormalities.

Dose interruptions of FRUZAQLA due to an adverse reaction occurred in 35% of patients. Adverse reactions leading to dose interruptions of FRUZAQLA in ≥2% of patients were PPE, proteinuria, platelet count decreased, ALT increased, hypertension, and diarrhea.

Dose reductions of FRUZAQLA due to an adverse reaction occurred in 24% of patients. Adverse reactions leading to dose reduction of FRUZAQLA in ≥2% of patients were PPE, proteinuria, and hypertension.

Table 5 summarizes the adverse reactions in FRESCO.

Table 5: Adverse Reactions (≥10%) in Patients who Received FRUZAQLA and with a Difference Between Arms of ≥5% Compared to Placebo in FRESCO (All Grades)

Adverse Reaction	Fruquintinib (N=278)		Placebo (N=137)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Vascular				
Hypertension[1]	61	23	17	2.2
Hemorrhage[1]	28	1.1	14	0
Renal				
Proteinuria[1]	55	4.7	30	0
Skin and Subcutaneous				
Palmar-plantar erythrodysesthesia (hand-foot skin reactions)	49	11	2.9	0
Respiratory				
Dysphonia[1]	38	0	1.5	0
Throat Pain	10	0	1.5	0
Gastrointestinal				
Stomatitis[1]	33	0.7	2.9	0
Abdominal Pain[1]	29	4	17	1.5
Diarrhea[1]	25	3.6	5	0
General				
Fatigue[1]	25	2.5	13	1.5
Metabolism				
Anorexia[1]	21	1.4	9	0
Musculoskeletal				
Musculoskeletal Pain[1]	22	2.2	6	1.5
Back Pain	15	1.8	7	0
Arthralgia	13	0.4	2.2	0

Endocrine Disorders				
Hypothyroidism	17	0	2.2	0

[1] Represents a composite of multiple related terms.

Other clinically important adverse reactions (all grades) that occurred in <10% of patients treated with FRUZAQLA included urinary tract infection (9%), rash (9%), upper respiratory tract infection (4.7%), proctalgia (3.6%), pneumonia (2.9%), and gastrointestinal perforation or fistula (2.2%).

Table 6 provides laboratory abnormalities observed in FRESCO.

Table 6: Select Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients in FRESCO

Laboratory[1] Abnormality	FRUZAQLA (N=278)[2]		Placebo (N=137)[2]	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
Creatinine Increased	87	0.7	75	1.5
Glucose Increased	43	1.1	31	3.0
Aspartate Aminotransferase Increased	42	3.6	31	1.5
Alkaline Phosphatase Increased	40	4.3	34	6
Bilirubin Increased	39	4.7	34	8
Alanine Aminotransferase Increased	33	2.2	18	1.5
Sodium Decreased	33	6	31	5
Urate Increased	26	26	22	22
Calcium Decreased	25	0.4	13	0
Potassium Decreased	22	1.8	15	2.3
Hematology				
Platelets Decreased	29	3.6	6	0.7
Hemoglobin Decreased	23	0.7	33	4.5

[1] Graded according to NCI CTCAE version 4.03.
[2] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: FRUZAQLA (range: 257-277) and placebo (range: 126-134).

Other clinically relevant laboratory abnormalities (all grades) that occurred in <20% of patients treated with FRUZAQLA included pancreatic enzymes increased (4.3%).

7. DRUG INTERACTIONS

7.1. Effects of Other Drugs on FRUZAQLA

Strong CYP3A Inducers

Avoid concomitant use of drugs that are strong CYP3A inducers with FRUZAQLA.

Concomitant use with a strong CYP3A inducer may decrease fruquintinib C_{max} and AUC *[see Clinical Pharmacology (10.3)]*, which may reduce the efficacy of FRUZAQLA.

Moderate CYP3A Inducers

If possible, avoid concomitant use of drugs that are 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.

Concomitant use with a moderate CYP3A inducer may decrease fruquintinib C_{max} and AUC *[see Clinical Pharmacology (10.3)]*, which may reduce the efficacy of FRUZAQLA.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

Based on findings in animal studies and its mechanism of action, FRUZAQLA can cause fetal harm when administered to a pregnant woman. In an embryo-fetal developmental study in pregnant rats, oral administration of fruquintinib during the period of organogenesis resulted in teratogenicity and embryo lethality at exposures below the clinical exposure *(see Data)*. There are no data on the use of FRUZAQLA in pregnant women. Advise pregnant women of the potential risk to a fetus.

Data

Animal Data

In an embryo-fetal developmental study in pregnant rats, daily oral administration of fruquintinib at doses ≥0.1 mg/kg [approximately 0.2 times the recommended clinical dose of 5 mg based on body surface area (BSA)] during the period of organogenesis resulted in fetal external (edema and head and tail abnormalities), visceral, and skeletal malformations. At doses of 0.25 mg/kg (approximately 0.5 times the recommended clinical dose of 5 mg based on BSA), an increase in post-implantation loss and reduction in live fetuses was observed.

8.2. Lactation

Risk Summary

There are no data regarding the presence of fruquintinib or its metabolites in human milk or its effects on a breastfed child or on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with FRUZAQLA and for 2 weeks after the last dose.

8.3. Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiating FRUZAQLA.

Contraception

Females and Males

Females of childbearing potential and males with female partners of childbearing potential should use effective contraception during treatment and for 2 weeks after the last dose of FRUZAQLA *[see Warnings and Precautions (5.11) and Nonclinical Toxicology (11.1)]*.

Infertility

Females and Males

There are no data on the effects of fruquintinib on human fertility. Based on findings in animal studies, FRUZAQLA may impair female fertility *[see Nonclinical Toxicology (11.1)]*.

8.4. Pediatric Use
The safety and efficacy of FRUZAQLA in patients younger than 18 years of age have not been established.

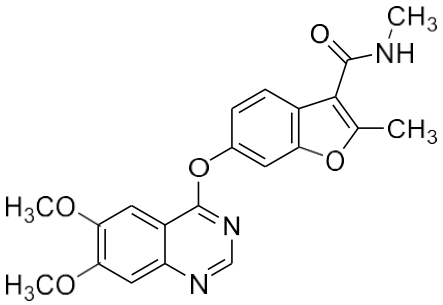
8.5. Geriatric Use
In FRESCO-2, 212 (46%) patients who received FRUZAQLA were ≥65 years of age and older, of whom 43 (20%) of patients were ≥75 years. There were no observed overall differences in safety and effectiveness of FRUZAQLA in geriatric compared to younger patients.

Of the total number of FRUZAQLA-treated patients in the FRESCO study, 50 (18%) were 65 years of age and older, and one patient was ≥75 years. There were no observed overall differences in safety and effectiveness of FRUZAQLA in geriatric compared to younger patients.

8.6. Hepatic Impairment
No dosage adjustment is recommended 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 Clinical Pharmacology (10.3)]*.

FRUZAQLA has not been sufficiently studied in patients with moderate hepatic impairment (total bilirubin greater than 1.5 times and less than 3 times ULN and any AST). FRUZAQLA is not recommended for use in patients with severe hepatic impairment (total bilirubin greater than 3 times ULN and any AST).

9. DESCRIPTION
Fruquintinib is a kinase inhibitor with the chemical name 6-[(6,7-dimethoxyquinazolin-4-yl)oxy]-*N*,2-dimethyl-1-benzofuran-3-carboxamide. Its molecular formula is $C_{21}H_{19}N_3O_5$, which corresponds to a molecular weight of 393.39 g/mol. Fruquintinib has the following chemical structure:



Fruquintinib is a white to off-white powder with a dissociation constant (pK_a) 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.
FRUZAQLA 1 mg and FRUZAQLA 5 mg (fruquintinib) capsules for oral administration contain 1 mg or 5 mg of fruquintinib. The inactive ingredients are microcrystalline cellulose or cellulose, microcrystalline (PH-101); corn starch or maize starch, and talc. The 1 mg capsule shell contains Gelatin; Titanium dioxide/E171; Tartrazine - FD&C Yellow 5/E102; Sunset yellow FCF - FD&C Yellow 6/E110. The 5 mg capsule shell contains Gelatin; Titanium dioxide/E171; Brilliant blue FCF-FD&C Blue 1/E133; Allura red AC-FD&C Red 40/E129. The printing ink for 1 mg and 5 mg capsules contains Shellac/Dewaxed shellac/E904; Dehydrated alcohol/Ethanol anhydrous; Isopropyl alcohol; Butyl alcohol/Butanol; Propylene glycol/E1520; Purified water; Strong ammonia solution /Ammonia solution, concentrated; Potassium hydroxide; Ferrosoferric oxide/Iron oxide black/E172.

10. CLINICAL PHARMACOLOGY

10.1. Mechanism of Action

Fruquintinib is a small molecule kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3 with 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

Fruquintinib exposure-response relationships and the time course of pharmacodynamic response are unknown.

Cardiac Electrophysiology

A mean increase in QTc interval >20 milliseconds (ms) was not observed at the approved recommended dosage.

10.3. Pharmacokinetics

The fruquintinib steady-state geometric mean (% coefficient of variation [CV]) maximum concentration (C_{max}) is 300 ng/mL (28%) and area under the concentration-time curve for the dosing interval (AUC_{0-24h}) is 5880 ng·h/mL (29%) at the recommended dosage. The fruquintinib C_{max} and AUC_{0-24h} are dose-proportional across the dosage range of 1 to 6 mg (0.2 to 1.2 times the recommended dosage). Fruquintinib steady state is achieved after 14 days with a mean AUC_{0-24h} accumulation of 4-fold.

Absorption

The fruquintinib median (min, max) time to C_{max} is approximately 2 hours (0, 26 hours).

Effect of Food

No clinically significant differences in fruquintinib pharmacokinetics were observed following administration of a high-fat meal (800 to 1000 calories, 50% fat).

Distribution

The mean (SD) apparent volume of distribution of fruquintinib is approximately 46 (13) L. Plasma protein binding of fruquintinib is approximately 95%.

Elimination

The fruquintinib mean (SD) elimination half-life is approximately 42 (11) hours and the apparent clearance is 14.8 (4.4) mL/min.

Metabolism

Fruquintinib is primarily eliminated by CYP450 and non-CYP450 (i.e., sulfation and glucuronidation) metabolism. CYP3A and to a lesser extent CYP2C8, CYP2C9, and CYP2C19 are the CYP450 enzymes involved in fruquintinib metabolism.

Excretion

Following oral administration of a 5 mg radiolabeled fruquintinib dose, approximately 60% of the dose was recovered in urine (0.5% unchanged) and 30% of the dose was recovered in feces (5% unchanged).

Specific Populations

No clinically significant differences in the pharmacokinetics of fruquintinib were observed based on age (18 to 82 years), sex, race (Asian, Black, and White), ethnicity (Hispanic/Latino vs. non-Hispanic/Latino), body weight (48 to 108 kg), mild to severe renal impairment (CLcr 15 to

89 mL/min estimated by the Cockcroft-Gault equation), mild hepatic impairment (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST).

The effect of moderate to severe hepatic impairment (total bilirubin greater than 1.5 times ULN and any AST) on fruquintinib pharmacokinetics is unknown.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Strong CYP3A inducers: Fruquintinib C_{max} decreased by 12% and AUC_{inf} by 65% following concomitant use with rifampin (strong CYP3A inducer).

Moderate CYP3A inducers: Fruquintinib C_{max} is predicted to decrease by 4% and AUC_{inf} by 32% following concomitant use with efavirenz (moderate CYP3A inducer).

Other Drugs: No clinically significant differences in fruquintinib pharmacokinetics were observed when used concomitantly with itraconazole (strong CYP3A inhibitor) or rabeprazole (proton pump inhibitor; gastric acid reducing agent).

No clinically significant differences in the pharmacokinetics of the following drugs were observed when used concomitantly with fruquintinib: dabigatran etexilate (P-gp substrate), or rosuvastatin (BCRP substrate).

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 transporting polypeptide (OATP)1B1 or OATP1B3. Fruquintinib is not an inhibitor of OATP1B1, OATP1B3, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, multidrug and toxin extrusion protein (MATE)1, or MATE2-K.

11. NONCLINICAL TOXICOLOGY

11.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with fruquintinib.

Fruquintinib was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay or clastogenic in the in vitro Chinese hamster ovary chromosome aberration assay. Fruquintinib was not genotoxic in the in vivo rat micronucleus or alkaline comet assays.

In a fertility and early embryonic development study in rats, post-implantation loss was observed at doses approximately equal to the recommended clinical dose of 5 mg based on BSA.

11.2. Animal Toxicology and/or Pharmacology

In repeat dose toxicity studies in rats, daily oral administration of fruquintinib at doses ≥0.6 mg/kg (approximately 1.2 times the recommended clinical dose of 5 mg based on BSA) resulted in broken or lost teeth.

12. CLINICAL STUDIES

12.1. Metastatic Colorectal Cancer

FRESCO-2 Study

The efficacy of FRUZAQLA was evaluated in FRESCO-2 (NCT04322539), an international, multicenter, randomized, double-blind, placebo-controlled study that enrolled 691 patients with metastatic colorectal cancer who had disease progression during or after prior treatment with fluoropyrimidine-, oxaliplatin-, irinotecan-based chemotherapy, an anti-VEGF biological therapy, if RAS wild type, an anti-EGFR biological therapy, and trifluridine/tipiracil, regorafenib, or both. Patients with an ECOG PS ≥2, left ventricular fraction ≤50%, systolic blood pressure >140 mm Hg or diastolic

blood pressure >90 mm Hg, urine protein ≥1 g/24h, or untreated brain metastases were ineligible. Randomization was stratified by prior use of trifluridine/tipiracil or regorafenib (trifluridine/tipiracil vs. regorafenib vs. trifluridine/tipiracil and regorafenib), RAS status (wild type vs. mutant), and duration of metastatic disease (≤18 months vs. >18 months).

Patients were randomized (2:1) to receive FRUZAQLA 5 mg orally once daily (N=461) for the first 21 days of each 28-day cycle plus BSC or placebo (N=230) plus BSC. Patients received either FRUZAQLA or placebo until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall survival (OS) and an additional efficacy outcome measure was progression-free survival (PFS) as determined by investigators according to RECIST v1.1.

The study population characteristics were median age of 64 years (range: 25 to 86), with 47% ≥65 years of age; 56% male; 81% White, 9% Asian, 2.9% Black or African American, and 0.7% Native Hawaiian/Pacific Islander; 43% had an ECOG PS of 0 and 57% had an ECOG PS of 1, and 63% had *RAS*-mutant tumors. Eighteen percent of the patients were enrolled in North America, 72% in Europe, and 10% in Asia Pacific (Japan and Australia) region.

All patients received prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy; 96% received prior anti-VEGF therapy, 39% received prior anti-EGFR therapy, 91% received trifluridine/tipiracil, 48% received regorafenib, and 39% received both trifluridine/tipiracil and regorafenib.

The addition of FRUZAQLA to BSC resulted in a statistically significant improvement in OS and PFS compared to placebo plus BSC (see Table 7, Figure 1).

FRESCO Study

The efficacy of FRUZAQLA was evaluated in FRESCO (NCT02314819), a multicenter, randomized, double-blind, placebo-controlled study conducted in China that enrolled 416 patients with metastatic colorectal cancer who had disease progression during or after prior treatment with fluoropyrimidine-, oxaliplatin, or irinotecan-based chemotherapy. Patients older than 75 years of age, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥2, left ventricular ejection fraction ≤50%, systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, urine protein ≥1 g/24h, or brain metastases were ineligible. Randomization was stratified by prior use of VEGF inhibitors (yes vs. no) and *K-RAS* status (wild type vs. mutant).

Patients were randomized (2:1) to receive FRUZAQLA 5 mg orally once daily (N=278) for the first 21 days of each 28-day cycle plus BSC or placebo (N=138) plus BSC. Patients received either FRUZAQLA or placebo until disease progression or unacceptable toxicity. The major efficacy outcome measure was OS and an additional efficacy outcome measure was PFS as determined by investigators according to RECIST v1.1.

The study population characteristics were median age of 56 years (range: 23 to 75), with 19% ≥65 years of age; 61% male; 100% Asian; 27% had an ECOG PS of 0 and 73% had an ECOG PS of 1 (73%), and 44% had *K-RAS* mutant tumors.

All patients received prior 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 compared to placebo plus BSC (see Table 7, Figure 2).

Table 7: 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				
Number of patients with event (%)	317 (69%)	173 (75%)	188 (68%)	109 (79%)
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[a] (95% CI)	0.66 (0.55, 0.80)		0.65 (0.51, 0.83)	
P-Value[b]	<0.001		<0.001	
PFS				
Number of patients with event (%)	392 (85%)	213 (93%)	235 (85%)	125 (91%)
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[a] (95% CI)	0.32 (0.27, 0.39)		0.26 (0.21, 0.34)	
P-Value[bc]	<0.001		-	

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

[a] The Hazard Ratio and its 95% CI were estimated using a stratified Cox proportional hazards model.

[b] *P*-Value (2-sided) was calculated using a stratified log-rank test.

[c] *P*-Value for the PFS analysis in FRESCO was not included due to lack of multiplicity adjustment for this analysis.

Figure 1: Kaplan-Meier Curve for Overall Survival in FRESCO-2

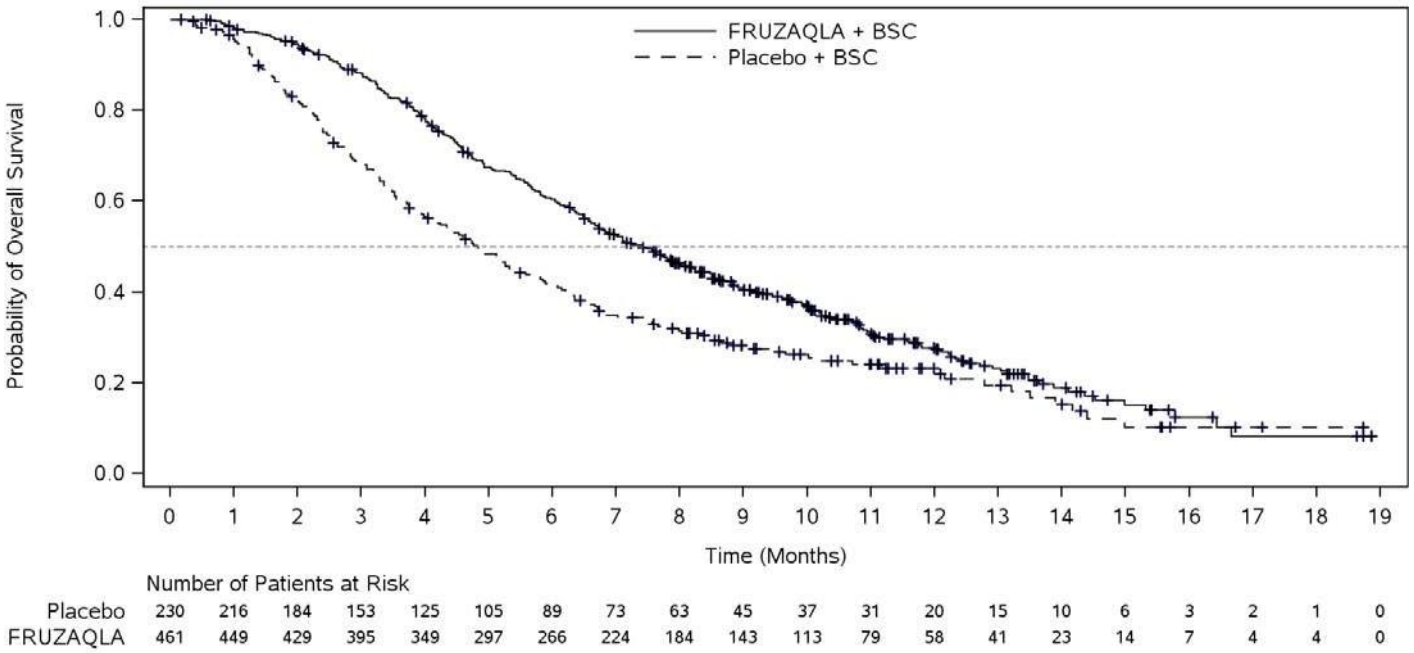
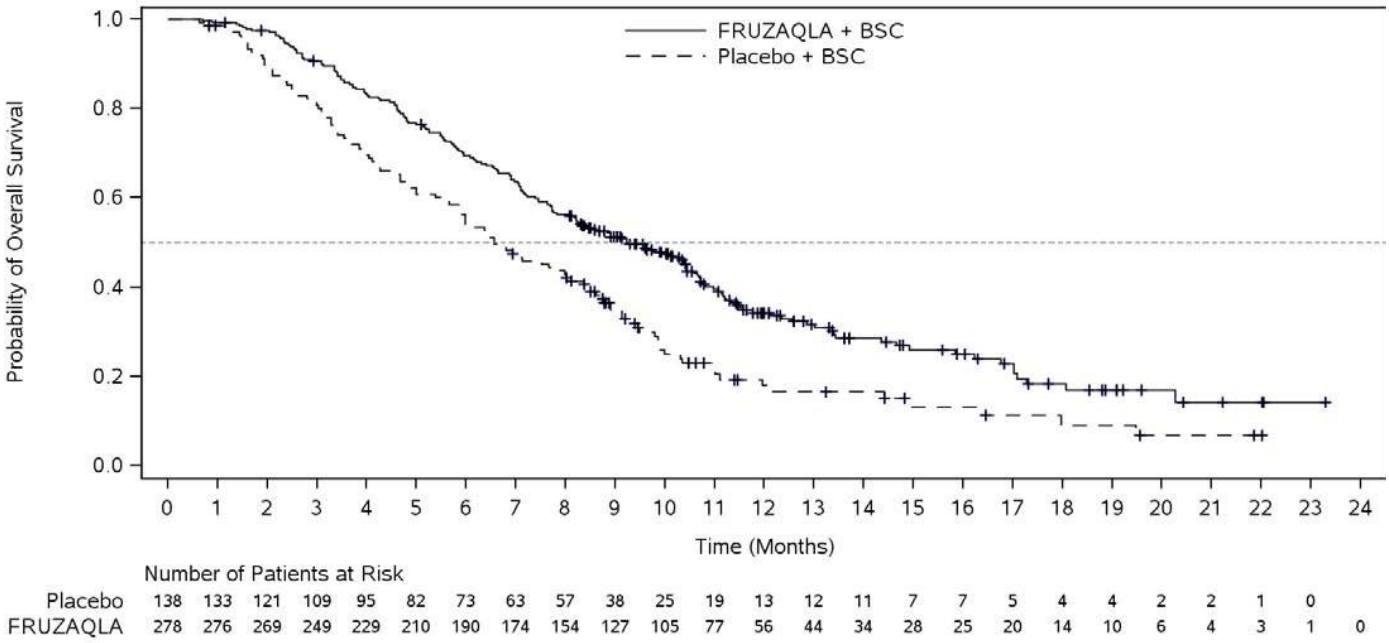


Figure 2: Kaplan-Meier Curve for Overall Survival in FRESCO



13. HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Capsule Strength	Description	Package Configuration	
1 mg	Size 3 hard gelatin capsule with standard yellow opaque cap and white opaque body, imprinted with “HM013” over “1 mg” 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.	
5 mg	Size 1 hard gelatin capsule with a red opaque cap and white opaque body, imprinted with “HM013” over “5 mg” on the body in black ink		

Storage and handling
Store below 30°C.
Store in the original container in order to protect from moisture.
Keep the bottle tightly closed.
Do not remove desiccant from the bottle.

The expiry date of the product is indicated on the packaging materials.

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

14. REGISTRATION HOLDER AND IMPORTER

Takeda Israel Ltd.,25 Efal st., POB 4140, Petach Tikva 4951125

15. REGISTRATION NUMBER(S)

178-42-37922-99
178-41-37923-99

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