FRUZAQLA- fruquintinib capsule
Takeda Pharmaceuticals America, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FRUZAQLA safely and effectively. See full prescribing information for FRUZAQLA.

FRUZAQLA® (fruquintinib) capsules, for oral use
Initial U.S. Approval: 2023

RECENT MAJOR CHANGES

Dosage and Administration (2.2)	2/2025

INDICATIONS AND USAGE

FRUZAQLA is a kinase inhibitor 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. (1)

DOSAGE AND ADMINISTRATION

The recommended dose of FRUZAQLA is 5 mg orally once daily, with or without food for the first 21 days of each 28-day cycle. (2.1)

DOSAGE FORMS AND STRENGTHS

Capsules: 1 mg and 5 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Hypertension: Control blood pressure prior to treatment and monitor during treatment. Manage with anti-hypertensive medications and adjustment of the dose of FRUZAQLA, if necessary. Withhold, dose reduce, or permanently discontinue based on severity of hypertension. (2.2, 5.1)
- Hemorrhagic Events: Closely monitor patients who are at risk for bleeding. Withhold, reduce dose, or permanently discontinue FRUZAQLA based on severity and persistence of hemorrhage. (2.2, 5.2)
- Infections: Monitor for infection during treatment and withhold FRUZAQLA during active infections. Do not start FRUZAQLA in patients with active infections. (5.3)
- Gastrointestinal (GI) Perforation: Periodically monitor for GI perforation. Permanently discontinue FRUZAQLA in patients who develop GI perforation or fistula. (5.4)
- Hepatotoxicity: Monitor liver laboratory tests prior to the start of FRUZAQLA and periodically during treatment. Withhold, reduce the dose, or permanently discontinue based on severity. (2.2, 5.5)
- Proteinuria: Monitor urine protein. Discontinue FRUZAQLA for nephrotic syndrome (2.2, 5.6)
- Palmar-Plantar Erythrodysesthesia: Withhold FRUZAQLA based on severity. (2.2, 5.7)
- Posterior Reversible Encephalopathy Syndrome (PRES): Immediately discontinue FRUZAQLA if PRES is suspected and confirmed via Magnetic Resonance Imaging (MRI). (5.8)
- Impaired Wound Healing: Withhold FRUZAQLA for 2 weeks before major surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of FRUZAQLA after resolution of wound healing complications has not been established. (5.9)
- Arterial Thromboembolic Events: Initiation of FRUZAQLA in patients with a recent history of thromboembolic events should be carefully considered. Discontinue FRUZAQLA in patients who develop arterial thromboembolism. (5.10)
- Allergic Reactions to FD&C Yellow No. 5 (Tartrazine) and No. 6 (Sunset Yellow FCF): Contains FD&C Yellow No. 5 (tartrazine) and No. 6 (sunset yellow FCF) as color additives, which may cause allergic reactions (including bronchial asthma) in certain susceptible patients. (5.11)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of reproductive potential of the potential risk to the fetus and to use effective contraception. (5.12, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥20%) are hypertension, palmar-plantar erythrodysesthesia, proteinuria, dysphonia, abdominal pain, diarrhea, and asthenia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals America, Inc. at 1-844-662-8532 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Strong or Moderate CYP3A Inducers: Avoid concomitant use. (7.1)

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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 (12.3)]* 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***	**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.
	Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 3 times upper limit of normal (ULN), or greater than 3 times baseline if baseline was abnormal; or bilirubin greater than 1.5 times ULN, or greater than 1.5 times baseline if baseline was abnormal	• Withhold FRUZAQLA and monitor AST, ALT and total bilirubin until resolution to Grade 1 or baseline. • Resume at the next lower dose level.

Hepatotoxicity *[see Warnings and Precautions (5.5)]*	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 if baseline was normal, or greater than 20 times baseline if baseline was abnormal; or bilirubin greater than 10 times ULN if baseline was normal, or greater than 10 times baseline if baseline was abnormal	Permanently discontinue 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.
		• Withhold FRUZAQLA and initiate supportive

	Grade 3	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.
	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.

* 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

None.

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.

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)]*.

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)]*.

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 (14.1)]*. 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*	53	12	39	4.8
Vascular				
Hypertension*	38	14	9	0.9
Gastrointestinal				
Stomatitis*	31	2.2	7.8	0.4
Abdominal Pain*	25	3.5	20	3
Diarrhea*	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*	18	1.8	5	0.9
Respiratory				
Dysphonia*	18	0	5	0
Musculoskeletal				
Musculoskeletal Pain*	16	1.1	7	0
Arthralgia	11	0.9	4.3	0

* 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* Abnormality	**FRUZAQLA (N=456)†**		**Placebo (N=230)†**	
	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

* 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: 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 (14.1)]*. 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*	61	23	17	2.2
Hemorrhage*	28	1.1	14	0
Renal				
Proteinuria*	55	4.7	30	0
Skin and Subcutaneous				
Palmar-plantar erythrodysesthesia (hand-foot skin reactions)	49	11	2.9	0
Respiratory				
Dysphonia*	38	0	1.5	0
Throat Pain	10	0	1.5	0
Gastrointestinal				
Stomatitis*	33	0.7	2.9	0
Abdominal Pain*	29	4	17	1.5
Diarrhea*	25	3.6	5	0
General				
Fatigue*	25	2.5	13	1.5
Metabolism				
Anorexia*	21	1.4	9	0
Musculoskeletal				
Musculoskeletal Pain*	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

* 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* Abnormality	**FRUZAQLA (N=278)†**		**Placebo (N=137)†**	
	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

* 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: 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 (12.3)]*, 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 (12.3)]*, 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.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

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 (13.1)]*.

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 (13.1)]*.

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.

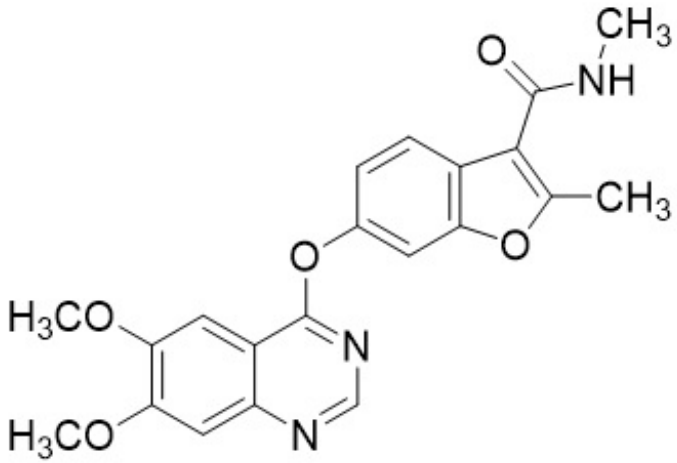
8.6. Hepatic Impairment

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 (12.3)]*.

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).

11. 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 (fruquintinib) capsules for oral administration contain 1 mg or 5 mg of fruquintinib. The inactive ingredients are corn starch, microcrystalline cellulose, and talc. The 1 mg capsule shell contains FD&C Yellow No. 5 (tartrazine), FD&C Yellow No. 6 (sunset yellow FCF), gelatin, and titanium dioxide. The 5 mg capsule shell contains FD&C Blue No. 1 (brilliant blue FCF), FD&C Red No. 40 (allura red AC), gelatin, and titanium dioxide. The printing ink for 1 mg and 5 mg capsules contains butanol, dehydrated alcohol, ferrosoferric oxide, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac and strong ammonia solution.

12. CLINICAL PHARMACOLOGY

12.1. 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.

12.2. 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.

12.3. 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.

13. NONCLINICAL TOXICOLOGY

13.1. 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.

13.2. 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.

14. CLINICAL STUDIES

14.1. 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* (95% CI)	0.66 (0.55, 0.80)		0.65 (0.51, 0.83)	
P-Value†	<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* (95% CI)	0.32 (0.27, 0.39)		0.26 (0.21, 0.34)	
P-Value†‡	<0.001		-	

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

* The Hazard Ratio and its 95% CI were estimated using a stratified Cox proportional hazards model.
† *P*-Value (2-sided) was calculated using a stratified log-rank test.
‡ *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

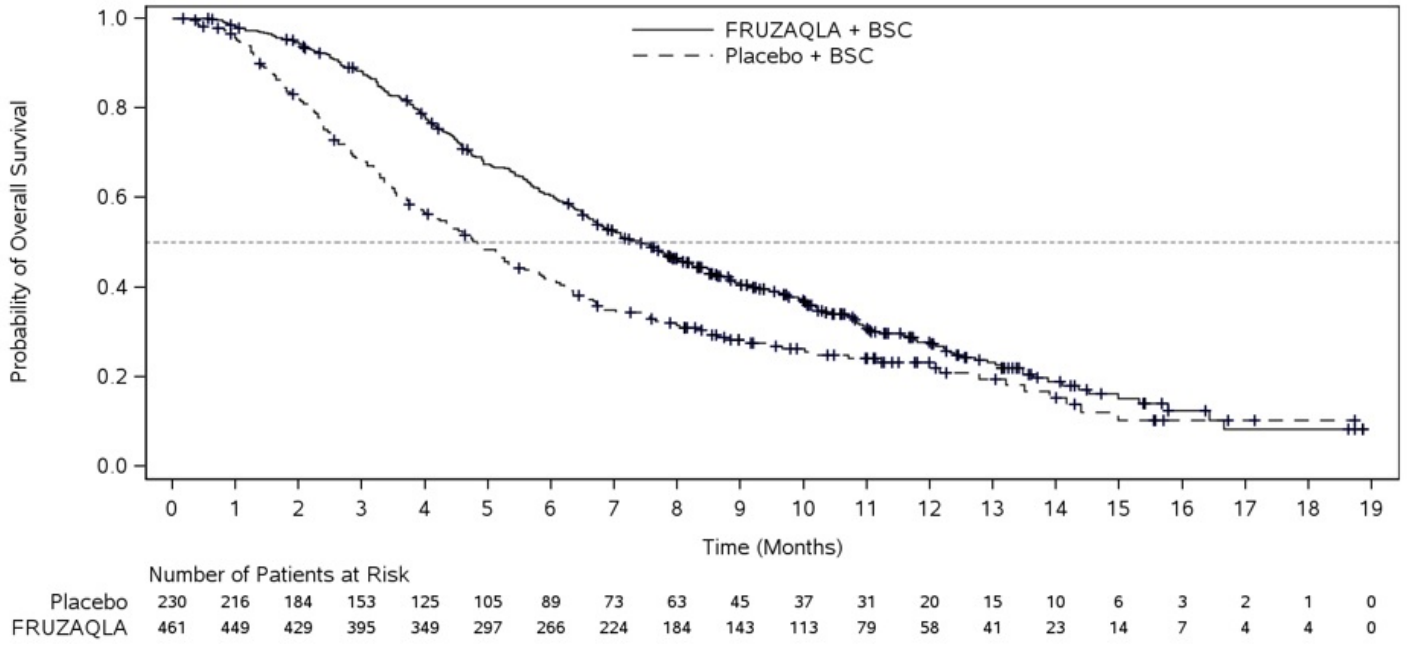
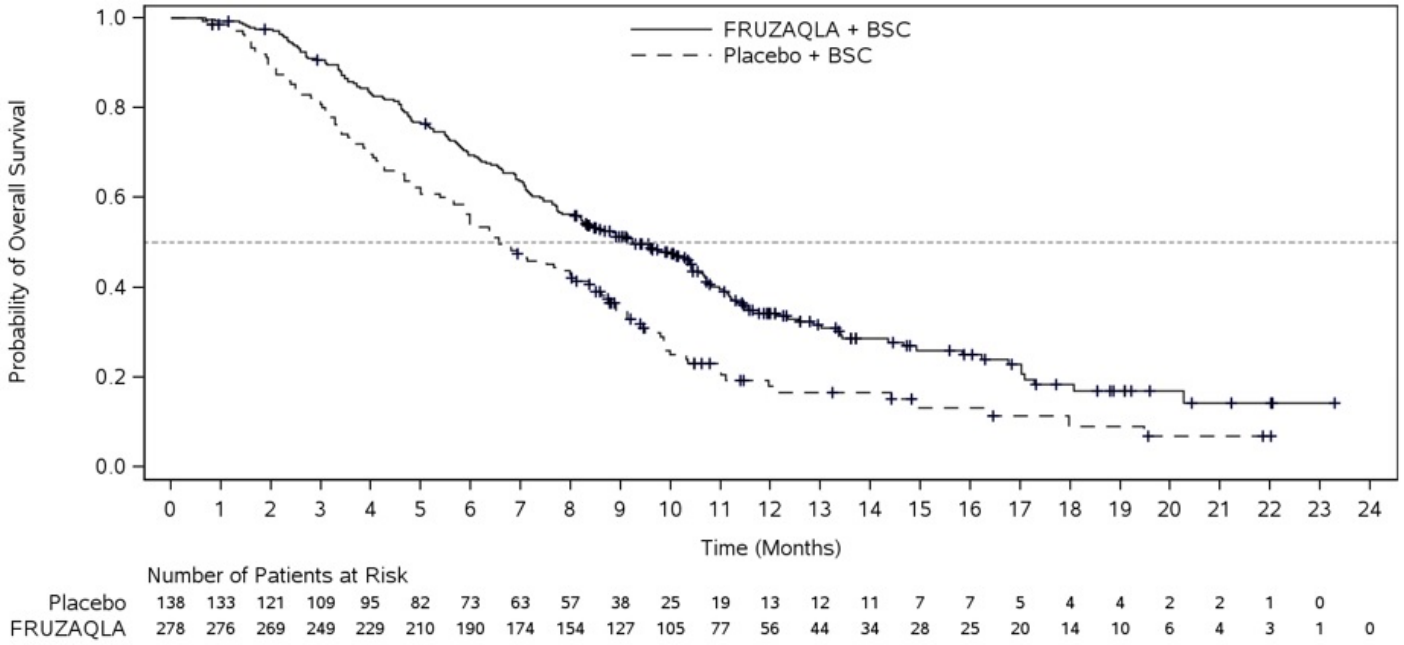


Figure 2: Kaplan-Meier Curve for Overall Survival in FRESCO



16. HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Capsule Strength	Description	Package Configuration	NDC Number
1 mg	Size 3 hard gelatin capsule with 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.	63020-210-21
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		63020-225-21

Storage and handling

Store at 20°C to 25°C (68°F to 77°F). Brief exposure to 15°C and 30°C (59°F to 86°F) permitted (see USP Controlled Room Temperature).

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

17. PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypertension

Advise patients to undergo regular blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if symptoms from hypertension occur including severe headache, lightheadedness, or new neurologic symptoms *[see Warnings and Precautions (5.1)]*.

Hemorrhages

Advise patients that FRUZAQLA may increase the risk of bleeding and to contact their healthcare provider for unusual, severe, or persistent bleeding, bruising, or symptoms of bleeding, such as lightheadedness *[see Warnings and Precautions (5.2)]*.

Infections

Advise patients to contact their healthcare provider if they experience signs and symptoms of infection *[see Warnings and Precautions (5.3)]*.

Gastrointestinal Perforation

Advise patients to contact a healthcare provider immediately if they experience severe abdominal pains, or other symptoms of gastrointestinal perforation or fistula *[see Warnings and Precautions (5.4)]*.

Hepatotoxicity

Advise patients that they will need to undergo laboratory tests to monitor liver function and to report any new symptoms indicating hepatic toxicity or failure *[see Warnings and Precautions (5.5)]*.

Proteinuria

Advise patients that they will need to undergo laboratory tests to monitor for proteinuria and to contact their healthcare provider for signs or symptoms of proteinuria *[see Warnings and Precautions (5.6)]*.

Palmar-plantar erythrodysesthesia (PPE)

Advise patients to contact their healthcare provider for progressive or intolerable rash *[see Warnings and Precautions (5.7)]*.

Posterior Reversible Encephalopathy Syndrome (PRES)

Advise patients to immediately contact their healthcare provider for new onset or worsening neurological function *[see Warnings and Precautions (5.8)]*.

Impaired Wound Healing

Advise patients that FRUZAQLA may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure *[see Warnings and Precautions (5.9)]*.

Arterial Thrombosis

Advise patients to seek immediate medical attention for new onset chest pain or acute neurologic symptoms consistent with myocardial infarction or stroke *[see Warnings and*

Precautions (5.10)].

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

Advise patients that FRUZAQLA 1 mg contains FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons or in patients who also have aspirin hypersensitivity *[see Warnings and Precautions (5.11)]*.

Advise patients FRUZAQLA 1 mg contains FD&C Yellow No. 6 (sunset yellow FCF) which may cause allergic-type reactions *[see Warnings and Precautions (5.11)]*.

Embryo-Fetal Toxicity

Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform females of the risk to a fetus and potential loss of pregnancy *[see Warnings and Precautions (5.12) and Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during treatment and for 2 weeks after the last dose of FRUZAQLA *[see Warnings and Precautions (5.12) and Use in Specific Populations (8.3)]*.

Advise males with female partners of reproductive potential to use effective contraception during treatment and for 2 weeks following the last dose of FRUZAQLA *[see Warnings and Precautions (5.11) and Use in Specific Populations (8.3)]*.

Lactation

Advise patients not to breastfeed during treatment with FRUZAQLA and for 2 weeks after the last dose of FRUZAQLA *[see Use in Specific Populations (8.2)]*.

Infertility

Advise females of reproductive potential that FRUZAQLA may cause post-implantation loss *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.

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Cambridge, MA 02142

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FRU380 R2

PATIENT INFORMATION
FRUZAQLA® (fru-zahk-la)
(fruquintinib)
capsules

What is FRUZAQLA?
FRUZAQLA is a prescription medicine used to treat adults with colon or rectal cancer

that has spread to other parts of the body (metastatic colorectal cancer [mCRC]) and who have received previous treatment with certain anti-cancer medicines.
It is not known if FRUZAQLA is safe and effective in children.

Before taking FRUZAQLA, tell your healthcare provider about all of your medical conditions, including if you:

- have high blood pressure.
- have bleeding problems.
- have an infection.
- have liver or kidney problems.
- plan to have surgery or have had recent surgery. You should stop taking FRUZAQLA at least 2 weeks before your planned surgery. Your healthcare provider will tell you when you can start FRUZAQLA again after your surgery. See **"What are the possible side effects of FRUZAQLA?"**
- have recently had a blood clot, stroke, or heart attack.
- are allergic to FD&C Yellow No. 5 (tartrazine) or FD&C Yellow No. 6 (sunset yellow FCF). See **"What are the possible side effects of FRUZAQLA?"**
- are pregnant or plan to become pregnant. FRUZAQLA can harm your unborn baby. You should not become pregnant during treatment with FRUZAQLA.
  Females who can become pregnant:
  - Your healthcare provider will do a pregnancy test before you start treatment with FRUZAQLA.
  - Use effective birth control (contraception) during treatment and for 2 weeks after your last dose of FRUZAQLA.
  - Tell your healthcare provider right away if you become pregnant during treatment with FRUZAQLA.

  Males with female partners who can become pregnant:
  - Use effective birth control during treatment and for 2 weeks after your last dose of FRUZAQLA.
  - Tell your healthcare provider right away if your partner becomes pregnant during your treatment with FRUZAQLA.
- are breastfeeding or plan to breastfeed. It is not known if FRUZAQLA passes into your breast milk. Do not breastfeed during treatment and for 2 weeks after your last dose of FRUZAQLA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. FRUZAQLA may affect the way other medicines work, and other medicines may affect how FRUZAQLA works. Especially tell your healthcare provider if you take blood thinners (anticoagulants).
Know the medicines you take. Keep a list of your medicines to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take FRUZAQLA?

- Take FRUZAQLA exactly as your healthcare provider tells you.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with FRUZAQLA if you have certain side effects. **Do not** change your dose or stop taking FRUZAQLA unless your healthcare provider tells you.
- You will usually take FRUZAQLA 1 time a day for 21 days (3 weeks) and then stop for 7 days (1 week). This is 1 cycle of treatment. Repeat this cycle for as long as your healthcare provider tells you.
- Take FRUZAQLA about the same time each day with or without food and swallow the

capsule whole.
- If you miss a dose of FRUZAQLA, you can take the missed dose within 12 hours on the same day. If more than 12 hours have passed, take your regularly scheduled dose the next day at the usual time. **Do not** take 2 doses at the same time to make up for the missed dose.
- **Do not** take another dose if you vomit after taking FRUZAQLA. Take your regularly scheduled dose the next day at the usual time.
- If you take too much FRUZAQLA, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of FRUZAQLA?
FRUZAQLA may cause serious side effects, including:

- **High blood pressure (hypertension).** High blood pressure is common with FRUZAQLA and can also be severe. Your healthcare provider will check your blood pressure before starting treatment with FRUZAQLA, 1 time every week for the first month of treatment, and then at least 1 time a month or more often if needed during treatment. Your healthcare provider may prescribe medicine to treat your high blood pressure if needed. Tell your healthcare provider if you get any of the following symptoms of hypertension during treatment:

  - severe headache
  - lightheadedness or dizziness
  - confusion
  - changes in vision
  - chest pain
  - trouble breathing
  - nosebleeds
  - vomiting

- **Severe bleeding (hemorrhage).** FRUZAQLA can cause bleeding that can be serious and may lead to death. Tell your healthcare provider if you get any of the following symptoms of bleeding during treatment:

  - unusual, severe, or bleeding that will not stop
  - bruising
  - lightheadedness
  - vomiting blood or your vomit looks like coffee grinds
  - blood in the stool or black stool that looks like tar
  - blood in the urine or urine that looks red, pink or brown
  - coughing up blood or blood clots
  - menstrual bleeding that is heavier than normal
  - unusual vaginal bleeding
  - nose bleeds that happen often

- **Infections.** FRUZAQLA can increase the risk of infections, including serious infections that can lead to death. The most common infections with FRUZAQLA happened in the urinary tract, nose or throat, and lungs. Tell your healthcare provider if you get any of the following symptoms of infection during treatment:

  - fever
  - severe cough with or without an increase in mucus (sputum) production
  - severe sore throat
  - trouble breathing
  - burning or pain when you urinate
  - redness, swelling or pain in any part of the body

- **A tear in your stomach or intestinal wall (gastrointestinal perforation).** FRUZAQLA can cause gastrointestinal perforation that can be serious and may lead to death. Tell your healthcare provider right away, if you get any of the following symptoms of gastrointestinal perforation during treatment:
  - severe stomach (abdominal) pain or stomach pain that does not go away
  - vomiting or vomiting blood
  - blood in the stool or black stool that looks like tar
  - fever or chills
  - nausea
- **Liver problems**. Increased liver enzymes in your blood are common with FRUZAQLA and can also be severe and may lead to death. Your healthcare provider will do blood tests before and during treatment with FRUZAQLA to check for liver problems. Tell your healthcare provider if you get any of the following symptoms of liver problems during treatment:
  - yellowing of your skin or the white part of your eyes
  - dark colored (tea colored) urine
  - pain in your right upper stomach-area (abdomen)
  - loss of appetite
  - nausea or vomiting
  - bleeding or bruising
- **Protein in your urine (proteinuria)**. Protein in your urine is common with FRUZAQLA and can also be severe. Your healthcare provider will check your urine for protein before starting and during treatment with FRUZAQLA. Tell your healthcare provider if you have to urinate more than usual, or if you get swelling of your face, hands, arms, legs, or feet during treatment.
- **Hand-foot skin reactions (Palmar-Plantar Erythrodysesthesia [PPE])**. Hand-foot skin reactions are common with FRUZAQLA and can also be severe. Tell your healthcare provider if you get a severe rash or redness, pain, blisters, bleeding, or swelling on the palms of your hands or soles of your feet during treatment.
- **Posterior Reversible Encephalopathy Syndrome (PRES).** PRES is a serious condition that can happen in your brain during treatment with FRUZAQLA. Tell your healthcare provider right away if you get any of the following symptoms during treatment:
  - headache
  - seizures
  - confusion
  - changes in vision
  - problems thinking
- **Wound healing problems.** Wounds may not heal properly during treatment with FRUZAQLA. Tell your healthcare provider if you plan to have any surgery before starting FRUZAQLA or during treatment.
  - You should stop taking FRUZAQLA at least 2 weeks before planned surgery.
  - Your healthcare provider will tell you when you may start taking FRUZAQLA again after surgery.

- **Blood clots in your blood vessels (arteries).** FRUZAQLA can cause blood clots or blockage in your blood vessels that may lead to heart attack, stroke, or death. Get medical help right away if you get any of the following symptoms during treatment:
    - severe chest pain or pressure
    - pain in your arms, legs, back, neck or jaw
    - shortness of breath
    - numbness or weakness of your face, arm, or leg, especially on one side of your body
    - feeling lightheaded or faint
    - sweating more than usual
    - sudden confusion, trouble talking, or understanding things
    - trouble walking
    - sudden severe headache
    - sudden vision changes in one or both eyes
    - dizziness, or loss of balance or coordination

- **Allergic reactions to FD&C Yellow No. 5 and FD&C Yellow No. 6**. FRUZAQLA 1 mg capsules contain the inactive ingredients FD&C Yellow No. 5 (tartrazine) and FD&C Yellow No. 6 (sunset yellow FCF). FD&C Yellow No. 5 (tartrazine) can cause allergic-type reactions (including bronchial asthma) in certain people, especially people who also have an allergy to aspirin. FD&C Yellow No. 6 (sunset yellow FCF) can also cause allergic reactions. Tell your healthcare provider if you get hives, rash, or trouble breathing during treatment with FRUZAQLA.

The most common side effects of FRUZAQLA include:

- voice changes or hoarseness
- stomach-area (abdominal) pain
- diarrhea
- weakness, lack of strength and energy, and feeling very tired or sleepy (asthenia)

FRUZAQLA may cause fertility problems in females, which may affect your ability to have children. Talk to your healthcare provider if you have concerns about fertility.

These are not all of the possible side effects of FRUZAQLA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store FRUZAQLA?

- Store FRUZAQLA at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep FRUZAQLA dry and away from moisture.
- The FRUZAQLA bottle comes with a child resistant closure.
- Safely throw away (discard of) any unused FRUZAQLA.

Keep FRUZAQLA and all medicines out of the reach of children.

General information about the safe and effective use of FRUZAQLA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use FRUZAQLA for a condition for which it was not prescribed. Do not give FRUZAQLA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about FRUZAQLA that is written for health professionals.

What are the ingredients in FRUZAQLA?

Active ingredient: fruquintinib

Inactive ingredients: corn starch, microcrystalline cellulose, talc

Capsule shell:

- 1 mg capsule: FD&C Yellow No. 5 (tartrazine), FD&C Yellow No. 6 (sunset yellow FCF), gelatin, and titanium dioxide
- 5 mg capsule: FD&C Blue No. 1 (brilliant blue FCF), FD&C Red No. 40 (allura red AC), gelatin, and titanium dioxide

Printing ink: butanol, dehydrated alcohol, ferrosoferric oxide, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, and strong ammonia solution.

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Takeda Pharmaceuticals America, Inc.
Cambridge, MA 02142

For more information, go to www.fruzaqla.com or call 1-844-217-6468.
FRU380 R2

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: 2/2025

PRINCIPAL DISPLAY PANEL - 1 mg Capsules

NDC 63020-210-21

Rx Only

Fruzaqla™
(fruquintinib) capsules

1 mg

Contains FD&C Yellow No. 5 (tartrazine) and No. 6 (sunset yellow FCF) as color additives.

21 capsules

Takeda

PRINCIPAL DISPLAY PANEL - 1 mg Capsules Label

NDC 63020-210-21

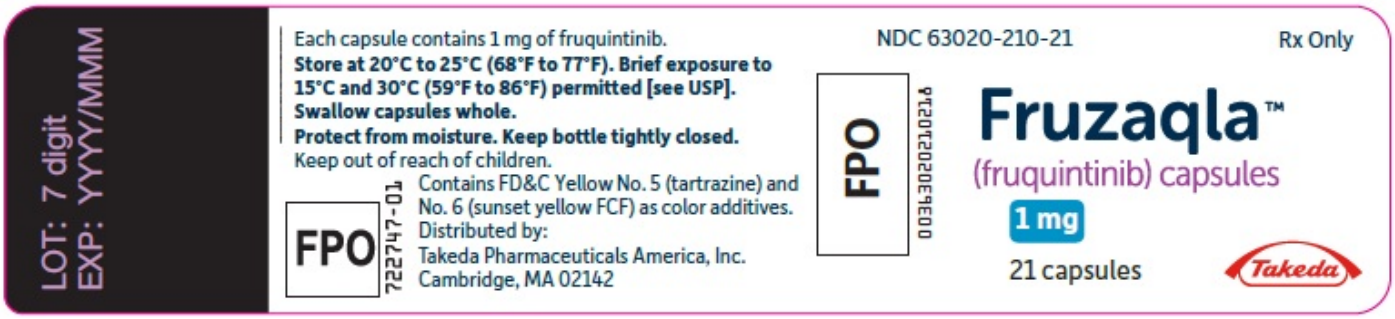
Rx Only

Fruzaqla™
(fruquintinib) capsules

1 mg

21 capsules

Takeda



PRINCIPAL DISPLAY PANEL - 5 mg Capsules

NDC 63020-225-21

Rx Only

Fruzaqla™
(fruquintinib) capsules

5 mg

21 capsules

Takeda

PRINCIPAL DISPLAY PANEL - 5 mg Capsules Label

NDC 63020-225-21

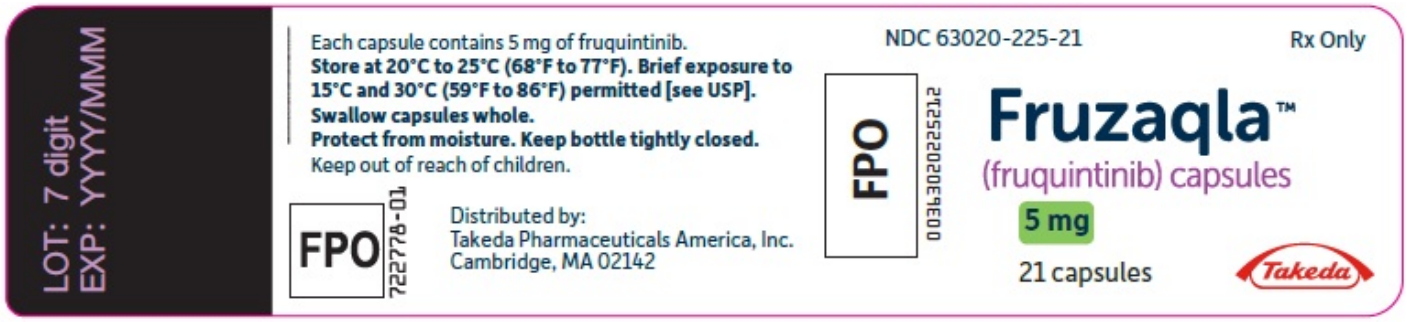
Rx Only

Fruzaqla™
(fruquintinib) capsules

5 mg

21 capsules

Takeda



FRUZAQLA

fruquintinib capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63020-210
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
FRUQUINTINIB (UNII: 49DXG3M5ZW) (FRUQUINTINIB - UNII:49DXG3M5ZW)	FRUQUINTINIB	1 mg

Inactive Ingredients	
Ingredient Name	**Strength**
TALC (UNII: 7SEV7J4R1U)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
STARCH, CORN (UNII: O8232NY3SJ)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C YELLOW NO. 5 (UNII: I753WB2F1M)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	

Product Characteristics			
Color	YELLOW (yellow opaque cap and white opaque body)	**Score**	no score
Shape	CAPSULE	**Size**	16mm
Flavor		**Imprint Code**	HM013;1mg
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:63020-210-21	1 in 1 CARTON	11/08/2023	
1		21 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA217564	11/08/2023	

FRUZAQLA

fruquintinib capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63020-225
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
FRUQUINTINIB (UNII: 49DXG3M5ZW) (FRUQUINTINIB - UNII:49DXG3M5ZW)	FRUQUINTINIB	5 mg

Inactive Ingredients

Ingredient Name	Strength
TALC (UNII: 7SEV7J4R1U)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
STARCH, CORN (UNII: O8232NY3SJ)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	

Product Characteristics

Color	RED (red opaque cap and white opaque body)	**Score**	no score
Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	HM013;5mg
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63020-225-21	1 in 1 CARTON	11/08/2023	
1		21 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA217564	11/08/2023	

Labeler - Takeda Pharmaceuticals America, Inc. (039997266)

Revised: 2/2026 Takeda Pharmaceuticals America, Inc.