Fruzaqla™

(fruquintinib) capsules

5 mg • 1 mg

Dosing guide

mCRC=metastatic colorectal cancer.

INDICATION

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.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Hypertension** occurred in 49% of 911 patients with mCRC treated with FRUZAQLA, including Grade 3-4 events in 19%, and hypertensive crisis in three patients (0.3%). Do not initiate FRUZAQLA unless blood pressure is adequately controlled. Monitor blood pressure weekly for the first month and at least monthly thereafter as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue FRUZAQLA based on severity of hypertension.

Please see Important Safety Information throughout and Full Prescribing Information.

Convenient, once-daily oral dosing with FRUZAQLA™ (fruquintinib)[1]

Recommended dose of FRUZAQLA

5 mg (one capsule) taken orally once daily for the first 21 days followed by 7 days off treatment for each 28-day cycle.

Days 1-21	Days 22-28
FRUZAQLA 5 mg	**Treatment break**

- After Day 28, a new treatment cycle begins with the same schedule
- Continue treatment until disease progression or unacceptable toxicity occurs

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Hemorrhagic Events** including serious, fatal events can occur with FRUZAQLA. In 911 patients with mCRC treated with FRUZAQLA, 6% of patients experienced gastrointestinal hemorrhage, including 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.

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Directions for taking FRUZAQLA[1]

With or without food

Capsules (5 mg or 1 mg) should be swallowed whole.

About the same time each day

Patients should take a missed dose if <12 hours have passed since the missed scheduled dose. Do not take 2 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

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Infections.** FRUZAQLA can increase the risk of infections, including fatal infections. 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.

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Recommended dose reductions[1]

Dose level	FRUZAQLA dose
Recommended dose	5 mg orally once daily
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 daily	

- FRUZAQLA can be taken in either 1 mg or 5 mg capsules. Talk to your patients about which capsule is right for them based on the dosage administered

Clear dose reductions and interruptions can help manage adverse reactions

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Gastrointestinal Perforation** occurred in patients treated with FRUZAQLA. In 911 patients with mCRC treated with FRUZAQLA, 1.3% experienced a Grade ≥3 gastrointestinal perforation, including one fatal event. Permanently discontinue FRUZAQLA in patients who develop gastrointestinal perforation or fistula.

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Recommended dosage modifications[1]

Adverse reaction	Severity[a]	FRUZAQLA dosage modification
Hypertension	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	Grade 2	• Withhold FRUZAQLA until bleeding fully resolves or recovers to Grade 1 • Resume at the next lower dose level
	Grade 3 or 4	Permanently discontinue FRUZAQLA.

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

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **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% of patients. 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.

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Recommended dosage modifications (continued)[1]

Adverse reaction	Severity[a]	FRUZAQLA dosage modification
Hepatotoxicity	ALT or AST >3 times upper limit of normal (ULN) with TB ≤2 times ULN	• Withhold FRUZAQLA and monitor AST/ALT and TB until resolution to Grade 1 or baseline • Resume at the next lower dose level
	ALT or AST >3 times ULN with concurrent total bilirubin >2 times ULN (in the absence of cholestasis or hemolysis)	Permanently discontinue FRUZAQLA.
	AST or ALT >20 times ULN or bilirubin >10 times ULN	Permanently discontinue FRUZAQLA.
Proteinuria	2 grams or greater proteinuria in 24 hours	• Withhold FRUZAQLA until proteinuria fully resolves or <1 gram proteinuria/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.

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

ALT=alanine aminotransferase; AST=aspartate aminotransferase; TB=total bilirubin.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

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

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Recommended dosage modifications (continued)[1]

Adverse reaction	Severity[a]	FRUZAQLA dosage modification
Palmar-plantar erythrodysesthesia	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

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

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Palmar-Plantar Erythrodysesthesia (PPE)** occurred in 35% of 911 patients treated with FRUZAQLA, including 8% with Grade 3 events. Based on severity of PPE, withhold FRUZAQLA and then resume at the same or reduced dose.

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Recommended dosage modifications (continued)[1]

Adverse reaction	Severity[a]	FRUZAQLA dosage modification
Other adverse reactions	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.

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

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Posterior Reversible Encephalopathy Syndrome (PRES),** a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in one of 911 patients 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.

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Drug interactions[1]

Strong CYP3A inducers

- Avoid concomitant use of drugs that are strong CYP3A inducers with FRUZAQLA
- Concomitant use with a strong CYP3A inducer may decrease FRUZAQLA C_{max} and AUC, 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, which may reduce the efficacy of FRUZAQLA

Hepatic impairment

- No dosage adjustment is recommended for patients with mild hepatic impairment (TB ≤ ULN with AST > ULN or TB >1 to 1.5 times ULN with any AST)
- FRUZAQLA has not been sufficiently studied in patients with moderate hepatic impairment (TB >1.5 times and <3 times ULN and any AST or ALT). FRUZAQLA is not recommended for use in patients with severe hepatic impairment (TB >3 times ULN and any AST or ALT)

AUC=area under the curve; C_{max}=maximum concentration; CYP3A=cytochrome P450, family 3, subfamily A.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Impaired Wound Healing.** 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.

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In FRESCO-2, the majority of ARs were manageable and predictable[1-3]

ARs occurring in ≥10% of patients

	FRUZAQLA + BSC (n=456)		Placebo + BSC (n=230)	
AR	**All grades (%)**	**Grades 3/4 (%)**	**All grades (%)**	**Grades 3/4 (%)**
Fatigue[a]	**53**	**12**	39	4.8
Hypertension[a]	**38**	**14**	9	0.9
Stomatitis[a]	**31**	**2.2**	7.8	0.4
Abdominal pain[a]	**25**	**3.5**	20	3
Diarrhea[a]	**24**	**3.7**	11	0
Hypothyroidism	**21**	**0.4**	0.4	0
Palmar-plantar erythrodysesthesia	**19**	**6**	2.6	0
Proteinuria[a]	**18**	**1.8**	5	0.9
Dysphonia[a]	**18**	**0**	5	0
Musculoskeletal pain[a]	**16**	**1.1**	7	0
Arthralgia	**11**	**0.9**	4.3	0

[a]Represents a composite of multiple related terms.

- Predictable refers to ARs consistent with inhibition of VEGF and VEGFR*
- Serious ARs occurred in 38% of patients treated with FRUZAQLA + BSC. Serious ARs in ≥2% of patients treated with FRUZAQLA + BSC included hemorrhage (2.2%) and gastrointestinal perforation (2.0%)
- Fatal ARs occurred in 14 (3.1%) patients treated with FRUZAQLA + BSC. Fatal ARs occurring in ≥2 patients treated with FRUZAQLA + BSC include pneumonia (n=3), sepsis/septic shock (n=2), and hepatic failure/encephalopathy (n=2)

AR=adverse reaction; BSC=best supportive care; VEGF=vascular endothelial growth factor; VEGFR=vascular endothelial growth factor receptor.

*Despite predictability, individual patient experiences may vary.

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FRUZAQLA had low Grade 3/4 laboratory abnormalities[1]

Select laboratory abnormalities worsening from baseline and occurring in ≥20% of patients in FRESCO-2 [a,b]

	FRUZAQLA + BSC (n=456)		Placebo + BSC (n=230)	
Laboratory abnormality	All grades (%)	Grades 3/4 (%)	All grades (%)	Grades 3/4 (%)
Triglycerides increased	**53**	**2.8**	22	1.0
Cholesterol increased	**37**	**1.9**	22	1.9
AST increased	**36**	**4.3**	24	1.9
Albumin decreased	**35**	**1.6**	32	1.4
Sodium decreased	**35**	**1.1**	27	0.9
ALT increased	**34**	**5**	22	1.4
Bilirubin increased	**30**	**7**	21	8
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
Alkaline phosphatase increased	**20**	**1.6**	27	0.5
Magnesium decreased	**20**	**0.5**	10	0.5

[a]Graded according to NCI CTCAE version 5.0.
[b]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).

Low rate of myelosuppression[1]

- Hematological abnormalities of any grade occurring in ≥20% of patients with either FRUZAQLA + BSC or placebo + BSC were decreased lymphocyte count (30% vs 32%), decreased platelet count (30% vs 4.7%), and increased activated partial thromboplastin time (21% vs 18%)

Dose interruptions or reductions due to ARs[3]

- Dose interruptions: 47% with FRUZAQLA + BSC vs 27% with placebo + BSC
- Dose reductions: 24% with FRUZAQLA + BSC vs 4% with placebo + BSC

Low rate of discontinuations due to ARs[3]

- 20% with FRUZAQLA + BSC vs 21% for placebo + BSC

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We're here to help patients with their coverage, financial, and educational resource needs

As our programs continuously evolve to adapt to your patients' needs, Takeda Oncology Here2Assist:

- Works with your patients' insurance company to help get your patient started on their medication
- Identifies available financial assistance that may be right for your patients
- May help eligible patients get started on treatment in the event of an insurance delay
- Identifies specific pharmacies to help fill and ship your patients' prescriptions appropriately
- Conducts regular follow-up calls to patients
- Sends text message status updates and reminders to patients*
- Connects your patients with nurse navigators to support their product education journey

Access support

Our case managers can work with your patients' insurance companies to conduct benefits verifications and create a summary of coverage options for each enrolled patient.

Financial assistance

Takeda Oncology Here2Assist can help identify financial assistance programs that may be able to help your patients with the cost of their Takeda Oncology treatment.

Helpful resources

Takeda Oncology Here2Assist case managers can provide your patients with information about additional resources that may assist with the day-to-day support they need.

Takeda Oncology Here2Assist®

For more information about patient access support and financial assistance that your patients may qualify for, call us at 1-844-817-6468, Option 2.
Let's Talk. We're available Monday-Friday, 8 AM-8 PM ET, or visit us at www.Here2Assist.com/hcp to learn more.

*Patients will need to enroll in the texting program to receive text messages.

Important Safety Information

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Arterial Thromboembolic Events.** In 911 patients with mCRC treated with FRUZAQLA, 0.8% of patients experienced an arterial thromboembolic event. Initiation of FRUZAQLA in patients with a recent history of thromboembolic events should be carefully considered. In patients who develop arterial thromboembolism, discontinue FRUZAQLA.
- **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. FRUZAQLA 1 mg contains FD&C Yellow No. 6 (sunset yellow FCF), which may cause allergic reactions.
- **Embryo-Fetal Toxicity.** Based on findings in animal studies and its mechanism of action, FRUZAQLA can cause fetal harm when administered to pregnant women. 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.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥20%) following treatment with FRUZAQLA included hypertension, palmar-plantar erythrodysesthesia (hand-foot skin reactions), proteinuria, dysphonia, abdominal pain, diarrhea, and asthenia.

DRUG INTERACTIONS: Avoid concomitant administration of FRUZAQLA with strong or moderate CYP3A inducers.

USE IN SPECIFIC POPULATIONS

- **Lactation:** Advise women not to breastfeed during treatment with FRUZAQLA and for 2 weeks after the last dose.

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

Please see FRUZAQLA (fruquintinib) Full Prescribing Information.

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Convenient, once-daily oral FRUZAQLA[1]

Convenient once-daily dosing

Available in 1-mg or 5-mg capsule

Clear dose modifications to help manage adverse reactions

References: 1. FRUZAQLA. Prescribing information. Takeda Pharmaceuticals America, Inc; 2023. **2.** National Cancer Institute, National Institutes of Health. Angiogenesis inhibitors. Updated April 2, 2018. Accessed October 6, 2023. https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/angiogenesis-inhibitors-fact-sheet#why-is-angiogenesis-important-in-cancer **3.** Dasari A, Lonardi S, Garcia-Carbonero R, et al; FRESCO-2 Study Investigators. Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): An international, multicentre, randomised, double-blind, phase 3 study. *Lancet*. 2023;402(10395):41-53.

IMPORTANT SAFETY INFORMATION

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