Potential patients for FRUZAQLA® (fruquintinib)

Example patient type: Presenting with liver metastasis*

*FRUZAQLA should not be used in patients with severe hepatic impairment (total bilirubin >3 times ULN and any AST).
Please see full Prescribing Information for more information.[1]

NCCN CATEGORY 2A† | **National Comprehensive Cancer Network® (NCCN®) recommends fruquintinib (FRUZAQLA®) as a potential treatment option for patients with previously treated mCRC, regardless of mutation status*[2,3]**

*For disease that has progressed through all available regimens.
AST=aspartate aminotransferase; ULN=upper limit of normal.
†Category 2A is based upon lower-level evidence; there is uniform NCCN consensus that the intervention is appropriate.

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 additional Important Safety Information throughout, full Important Safety Information, and full Prescribing Information for FRUZAQLA.

Fruzaqla®
(fruquintinib) capsules
5 mg • 1 mg

Barbara*
58-year-old patient with mCRC and liver metastasis

Diagnosis

- Diagnosed with unresectable left-sided mCRC 23 months ago
- Presented with metastasis in multiple sites, including liver
- Molecular profiling of primary tumor:
  - Microsatellite stable; MMR proficient with no actionable mutation

Treatment history

- Initiated treatment with FOLFOX + bevacizumab
- CT scans at 2 months and 4 months showed decreased size of liver lesions
- CT scan at 14 months revealed disease progression
  - Greater degree of metastasis, with an increase in liver lesion size
  - Progressive disease in the lymph nodes
- Subsequent treatment with FOLFIRI
- Disease progression after 6 months on treatment, with evidence of new lesions and pulmonary metastasis

CT=computed tomography; FOLFIRI=leucovorin calcium (folinic acid), fluorouracil, and irinotecan; FOLFOX=leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin; MMR=mismatch repair.

*Hypothetical patient. Individual patient results may vary.

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.

Please see additional Important Safety Information throughout, full Important Safety Information, and full Prescribing Information for FRUZAQLA.

Next steps

Considerations

- ECOG PS 1
- ALT: 22 IU/L; AST: 25 IU/L (normal levels)
- Would like to pursue more treatment

Barbara needs a treatment that

- Extends survival while delaying or maintaining time to deterioration of symptoms
- Has demonstrated prolongation of survival in patients with liver metastasis after 2 types of chemotherapy + bevacizumab
- Satisfies her desire to make fewer visits to the hospital for treatment administration
- Minimizes the impact of her treatment on her activities of daily life

Treatment decision:
Begin therapy with FRUZAQLA

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group performance status.

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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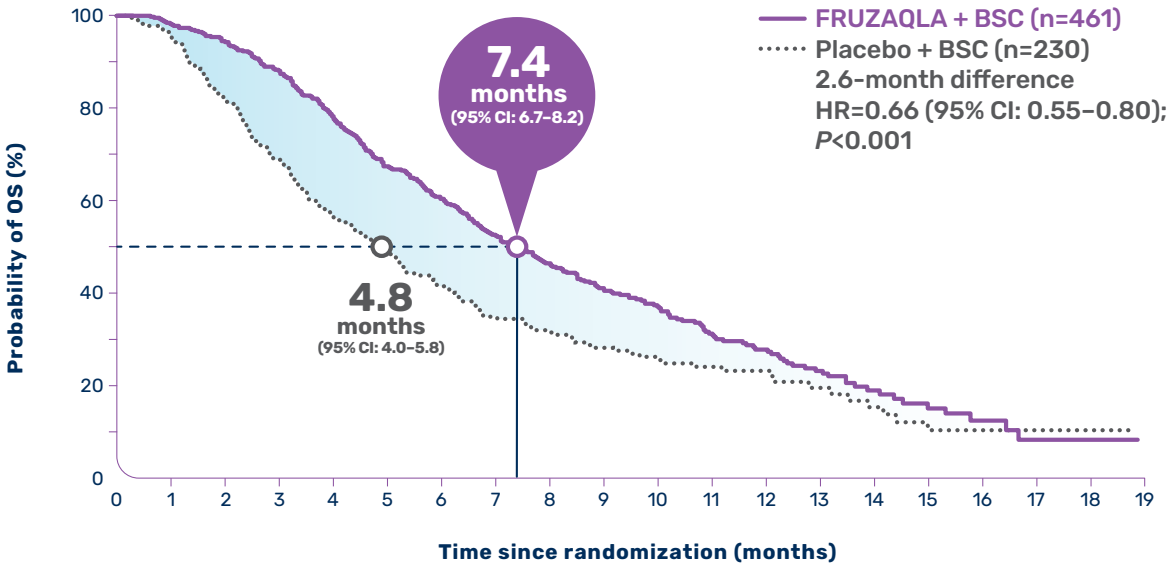
In a study of FRUZAQLA + BSC vs placebo + BSC in patients with previously treated mCRC

FRUZAQLA demonstrated significant overall survival benefit[1]

Median OS in patients with previously treated mCRC



Patients at risk

FRUZAQLA + BSC	461	449	429	395	349	297	266	224	184	143	113	79	58	41	23	14	7	4	4	0
Placebo + BSC	230	216	184	153	125	105	89	73	63	45	37	31	20	15	10	6	3	2	1	0

- **FRUZAQLA more than doubled median progression-free survival[1,4]**
  - 3.7 months mPFS with FRUZAQLA + BSC (95% CI: 3.5–3.8) vs 1.8 months with placebo + BSC (95% CI: 1.8–1.9), a 1.9-month difference; HR=0.32 (95% CI: 0.27–0.39); *P*<0.001

Study design: FRESCO-2 was a global, multicenter, randomized, double-blind, placebo-controlled study that enrolled 691 patients with mCRC who had disease progression during or after prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy, an anti-VEGF biological therapy, if *RAS* wild type, an anti-EGFR biological therapy, and trifluridine-tipiracil, regorafenib, or both.* Patients were randomized 2:1 to receive either FRUZAQLA 5 mg orally once daily + BSC† (3 weeks on, 1 week off) (n=461) or placebo + BSC (3 weeks on, 1 week off) (n=230). Treatment continued until progression, death, or unacceptable toxicity. Primary efficacy outcome measure was overall survival. Secondary efficacy outcome measures were progression-free survival, objective response rate, disease control rate,‡ duration of response, safety, and quality of life.[1,4]

BSC=best supportive care; CI=confidence interval; EGFR=epidermal growth factor receptor; HR=hazard ratio; mOS=median overall survival; mPFS=median progression-free survival; OS=overall survival; PFS=progression-free survival; VEGF=vascular endothelial growth factor.

*To prevent unintentional enrichment, the number of patients treated with previous regorafenib was limited to 50% of the total randomly assigned patients.[4]
†Best supportive care was determined by local clinical practice.[4]

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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In a study of FRUZAQLA + BSC vs placebo + BSC in patients with previously treated mCRC

FRUZAQLA extended survival in a subgroup analysis of patients with liver metastasis[4]

~3 MOS
IMPROVED SURVIVAL

Improved mOS results in patients with liver metastasis

6.4 months mOS with FRUZAQLA + BSC vs **3.7 months** with placebo + BSC, a 2.7-month difference; **HR=0.58** (95% CI: 0.47-0.71)

2x
PROGRESSION-FREE SURVIVAL

mPFS doubled in patients with liver metastasis

3.6 months mPFS with FRUZAQLA + BSC vs **1.8 months** with placebo + BSC, a 1.8–month difference; **HR=0.29** (95% CI: 0.23–0.36)

This study was not powered to show significance in OS or PFS in this specified subgroup.

Disease control rate was stable for more than half of patients treated with FRUZAQLA + BSC (FRESCO-2 ITT analysis)[1,4‡]

This study was not powered to show significance in disease control rate.

ITT=intention to treat.

‡Disease control was defined as the proportion of patients with a best overall response of confirmed complete response, partial response, or stable disease for ≥7 weeks.[4]

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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In FRESCO-2, the majority of ARs were predictable and manageable[1,4,5]

ARs occurring in ≥10% of patients[1]

	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[5]*
- 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%)[1]
- Fatal ARs occurred in 14 (3.1%) patients treated with FRUZAQLA + BSC. Fatal ARs occurring in ≥2% of patients treated with FRUZAQLA + BSC include pneumonia (n=3), sepsis/septic shock (n=2), and hepatic failure/encephalopathy (n=2)[1]

AR=adverse reaction; 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[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
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
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).

Manageable safety profile with FRUZAQLA[1,4]

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[1,4]

- 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[1,4]

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

NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

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Patients reported preserved QoL* across certain measures vs placebo[6†]

Patients treated with FRUZAQLA experienced delayed or maintained time to deterioration vs placebo in FRESCO-2

*Quality of life (QoL) refers to TTD.

Based on predefined MIDs for QLQ-C30 global health status, QLQ-C30 subscales, and EQ-5D-5L, the median TTD and the corresponding HR for all scales and subscales showed a trend favoring FRUZAQLA. Select QoL outcomes shown below measured TTD and were analyzed using Kaplan-Meier method, stratified log-rank test, and stratified Cox PH model

Delayed TTD subscales vs placebo

Emotional functioning
4.1 months vs 2.8 months
HR=0.8 (95% CI: 0.7–1.0)

Social functioning
3.2 months vs 2.3 months
HR=0.9 (95% CI: 0.8–1.1)

GHS QLQ-C30
2.1 months vs 1.8 months
HR=0.9 (95% CI: 0.7–1.0)

Fatigue
1.9 months vs 1.8 months
HR=0.8 (95% CI: 0.7–1.0)

Nausea/vomiting
4.5 months vs 3.1 months
HR=0.8 (95% CI: 0.7–1.0)

Insomnia
3.9 months vs 2.2 months
HR=0.8 (95% CI: 0.7–0.9)

Maintained TTD subscales vs placebo

Physical functioning
2.8 months vs 2.1 months
HR=1.0 (95% CI: 0.8–1.2)

Cognitive functioning
3.0 months vs 2.6 months
HR=1.0 (95% CI: 0.8–1.2)

Pain
2.2 months vs 2.0 months
HR=1.0 (95% CI: 0.8–1.2)

This study was not powered to show significance in QoL.

GHS=global health status; MID=minimally important difference; PH=proportional hazard; QLQ=quality of life questionnaire; TTD=time to deterioration.

†The data above show certain TTD subscales that were delayed or maintained. Other TTD subscales that were evaluated were EQ-5D-5L VAS, EQ-5D-5L index scores, role functioning, dyspnea, appetite loss, constipation, diarrhea, and financial difficulty.

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.

Please see additional Important Safety Information throughout, full Important Safety Information, and full Prescribing Information for FRUZAQLA.

Convenient, once-daily oral dosing with FRUZAQLA[1]

Simple once-daily treatment

The recommended dose of FRUZAQLA is 5 mg taken orally once daily for the first 21 days followed by 7 days off treatment for each 28-day cycle.

With or without food

Capsules (5 mg and 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. Patients should not take 2 doses on the same day to make up for a missed dose.

Clear dose reductions can help manage ARs

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	

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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Important Safety Information

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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- **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.
- **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.
- **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.
- **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.
- **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.
- **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.
- **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.

Please see additional Important Safety Information throughout, full Important Safety Information, and full Prescribing Information for FRUZAQLA.

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.
- **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**.

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Consider FRUZAQLA the next time you see a patient with previously treated mCRC...

- ☑ Who has liver metastasis*
- ☑ With ECOG PS 0–1
- ☑ Who prefers the convenience of an oral treatment that has the potential to delay or maintain time to deterioration of symptoms

Visit FRUZAQLAhcp.com to explore more efficacy and safety data

*FRUZAQLA should not be used in patients with severe hepatic impairment (total bilirubin >3 times ULN and any AST). FRUZAQLA has not been sufficiently studied in patients with moderate hepatic impairment (total bilirubin >1.5 times and <3 times ULN and any AST). Please see full Prescribing Information for more information.[1]

References: 1. FRUZAQLA. Prescribing Information. Takeda Pharmaceuticals America, Inc; 2023. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer V.5.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed August 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Rectal Cancer V.4.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed August 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. **4.** 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. **5.** National Cancer Institute, National Institutes of Health. Angiogenesis inhibitors. Updated April 2, 2018. Accessed March 26, 2024. https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/angiogenesis-inhibitors-fact-sheet#why-is-angiogenesis-important-in-cancer **6.** Data on file. Takeda Pharmaceuticals U.S.A., Inc.

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 (continued)

ADVERSE REACTIONS

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