I am pleased to announce that the US Food and Drug Administration has approved FRUZAQLA™ (fruquintinib), an oral therapy for adult patients with previously treated metastatic colorectal cancer (mCRC).[1,*]

*FRUZAQLA is a kinase inhibitor indicated for the treatment of adult patients with 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]

CRC is the 4th most common cancer in the US, and up to 50% of patients with CRC will progress to mCRC. The 5-year relative survival rate of mCRC is only ~15%.[2,3]

FRUZAQLA is now available in the following strengths and package sizes[1]:

Trade Name	Description	NDC	WAC[4]
FRUZAQLA (fruquintinib)	1 mg capsules (21 count)	63020-210-21	$6300
	5 mg capsules (21 count)	63020-225-21	$25,200

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).[1]

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.[1]

DISTRIBUTION

FRUZAQLA is available by prescription through Biologics and Onco360 Specialty Pharmacies. Practices may also arrange for in-office dispensing via ASD Healthcare, Cardinal Health Specialty Distribution, McKesson Plasma & Biologics, McKesson Specialty Care Distribution, and Oncology Supply.

Takeda Oncology Here2Assist®

Takeda Oncology Here2Assist is a comprehensive support program committed to helping your patients navigate coverage requirements, identify available financial assistance, and connect with helpful resources throughout their treatment.

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, 8AM–8PM ET, or visit us at www.Here2Assist.com/hcp to learn more.

Please share this exciting announcement about FRUZAQLA with your society members.
Please click here to review more information on FRUZAQLA.

I look forward to meeting with you soon to provide more information about FRUZAQLA and to answer any questions you may have.

Please see Important Safety Information below.

STUDY DESIGN[1]

- The efficacy and safety of FRUZAQLA were evaluated in 2 randomized, double-blind, placebo-controlled, multicenter studies
  - FRESCO-2 (NCT04322539) was an international study involving 691 patients with previously treated mCRC
  - FRESCO (NCT02314819) was conducted in China involving 416 patients with mCRC who had disease progression during or after prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy
- The primary endpoint was OS
- The key secondary endpoint was PFS according to RECIST v1.1

MECHANISM OF ACTION[1]

- Fruquintinib is a small molecule kinase inhibitor of VEGF receptor-1, -2, and -3

EFFICACY[1]

	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		-	

Unadjusted, indirect comparison for illustration only; clinical significance is not implied. Cross-trial comparisons are potentially confounded by differences in trial design and study population.

†The hazard ratio and its 95% CI were estimated using stratified Cox proportional hazards model.

‡*P*-value (2-sided) was calculated using the stratified log-rank test.

§*P*-value for the PFS analysis in FRESCO was not included due to lack of multiplicity adjustment for this analysis.

SAFETY[1]

	FRESCO-2 (N=456)	FRESCO (N=278)
Serious ARs (% of patients)	38	15
	Serious ARs in ≥2% of patients treated with FRUZAQLA included hemorrhage (2.2%) and gastrointestinal perforation (2.0%)	Serious ARs in ≥2% of patients treated with FRUZAQLA included intestinal obstruction (2.9%) and hemorrhage (2.2%)
Fatal ARs (% of patients)	3.1	2.5
	Fatal ARs occurring in ≥2 patients included pneumonia (n=3), sepsis/septic shock (n=2), and hepatic failure/ encephalopathy (n=2)	Fatal ARs included 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)
Treatment discontinuations due to an AR (% of patients)	20	15
	ARs leading to treatment discontinuations of FRUZAQLA in ≥1% of patients were asthenia and gastrointestinal perforation	ARs leading to treatment discontinuations of FRUZAQLA in ≥1% were intestinal obstruction, proteinuria, and hepatic function abnormalities
Dose interruptions due to ARs (% of patients)	47	35
	ARs leading to dose interruptions of FRUZAQLA in ≥2% of patients were PPE, proteinuria, asthenia, abdominal pain, hypertension, vomiting, and diarrhea	ARs leading to dose interruptions of FRUZAQLA in ≥2% of patients were PPE, proteinuria, platelet count decreased, ALT increased, hypertension, and diarrhea
Dose reductions due to ARs (% of patients)	24	24
	ARs leading to dose reductions of FRUZAQLA in ≥2% of patients were PPE, hypertension, and asthenia	ARs leading to dose reduction of FRUZAQLA in ≥2% of patients were PPE, proteinuria, and hypertension

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.
- **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.
- **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.**

Please see full **Prescribing Information**.

To learn more about FRUZAQLA, please visit fruzaqlahcp.com.

You may always reach me by phone or email at stephanie.rinks@takeda.com and 817-914-2929.

Best,

Stephanie Rinks
Director, Strategic Account Management

ALT, alanine transaminase; AR, adverse reaction; BSC, best supportive care; CI, confidence interval; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; FRESCO, Fruquintinib Efficacy and Safety in 3+ Line Colorectal Cancer Patients; NDC, National Drug Code; OS, overall survival; PFS, progression-free survival; PPE, palmar-plantar erythrodysesthesia; *RAS*, rat sarcoma virus; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; USP, United States Pharmacopeia; VEGF, vascular endothelial growth factor; WAC, wholesale acquisition cost.

References: 1. FRUZAQLA. Prescribing Information. Takeda Pharmaceuticals U.S.A., Inc.; November 2023. **2.** Surveillance, Epidemiology, and End Results (SEER) Program. Accessed August 7, 2023. https://seer.cancer.gov/statfacts/html/colorect.html **3.** Biller LH et al. *JAMA*. 2021;325(7):669-685. **4.** Data on File. Takeda Pharmaceuticals U.S.A., Inc.

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