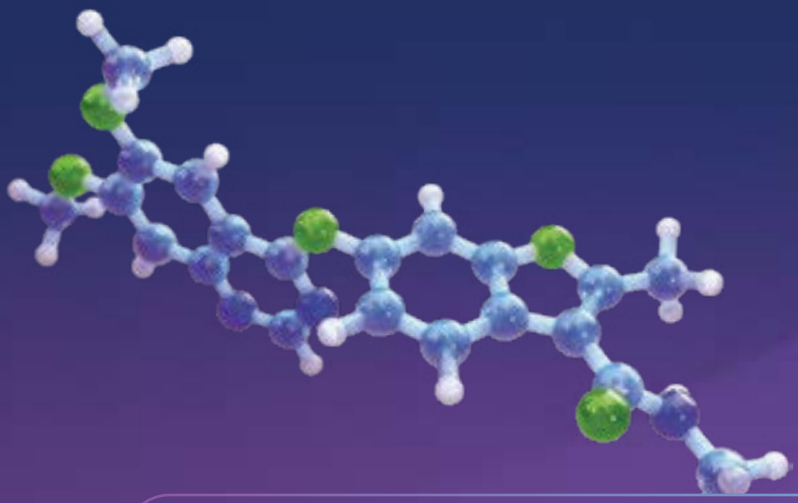
Fruzaqla®
(fruquintinib) capsules
5 mg • 1 mg



FRUZAQLA Mechanism of Action

FRUZAQLA® (fruquintinib) is a non-chemotherapy that selectively inhibits VEGF receptors to restrict tumor growth in mCRC[1-4]

VEGF=vascular endothelial growth factor.

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

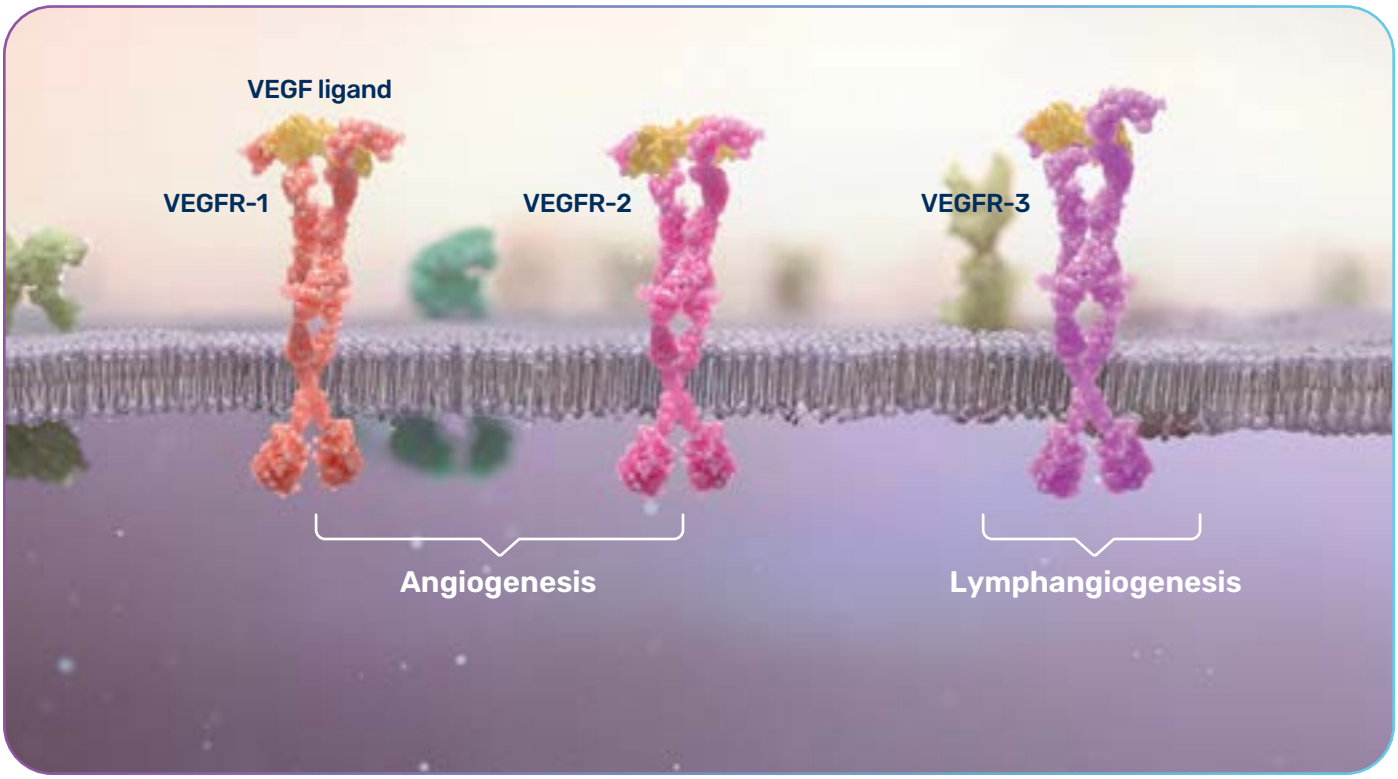
- **Hypertension** occurred in 49% of 911 patients with mCRC treated with FRUZAQLA, including Grade 3-4 events in 19%, and hypertensive crisis in three patients (0.3%). Do not initiate FRUZAQLA unless blood pressure is adequately controlled. Monitor blood pressure weekly for the first month and at least 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 on pages 4-5, and Patient Information in the Full Prescribing Information.

VEGFR-1, -2, and -3 induce the growth and progression of solid tumors[5]

The binding of VEGF to VEGFR-1, -2, and -3 activates the receptors and induces phosphorylation of the kinase domain, leading to[6,7]:

- Angiogenesis signaling by VEGFR-1 and -2, which aids in tumor development[8]
- Lymphangiogenesis signaling by VEGFR-3, which enables tumor metastasis[5,8]



Continued innovation in therapies targeting VEGF is vital for previously treated mCRC[9,10]

VEGFR=vascular endothelial growth factor receptor.

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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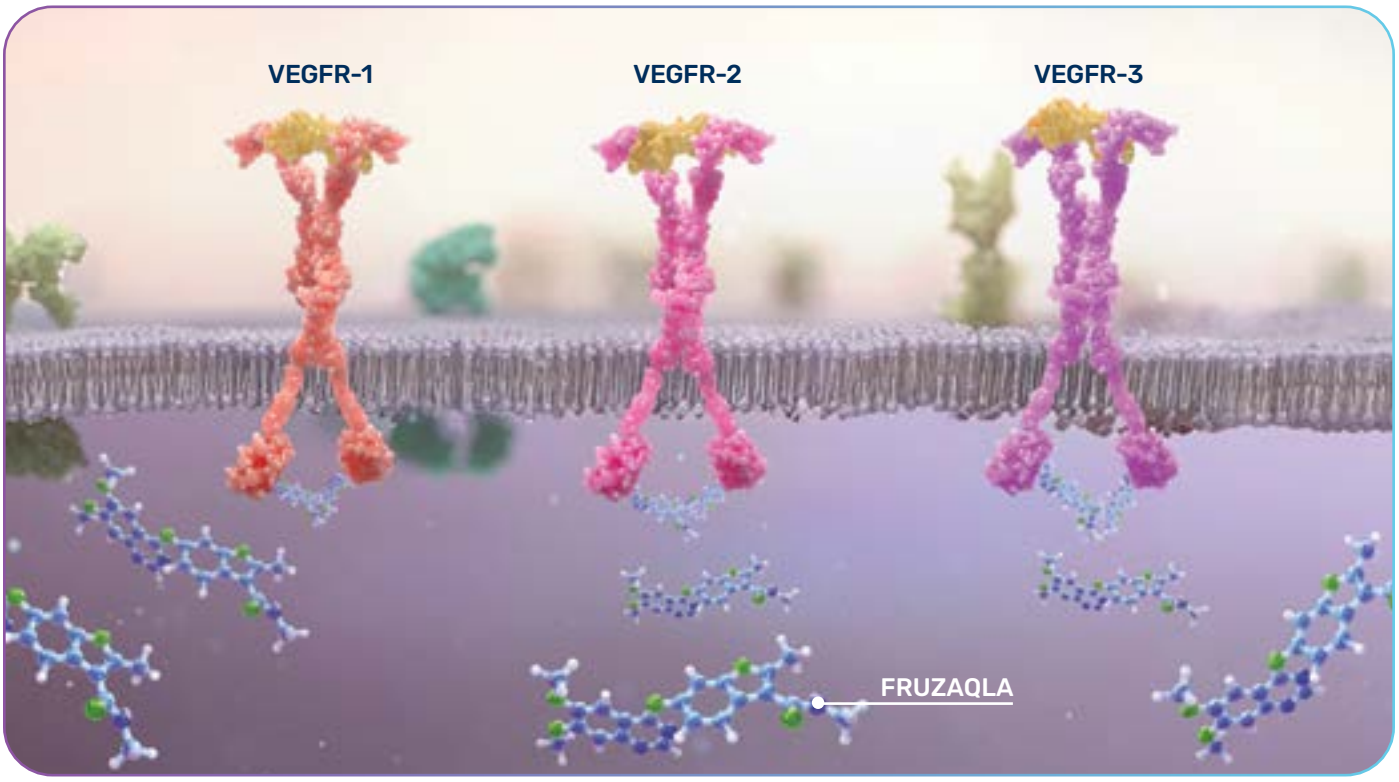
FRUZAQLA is a non-chemotherapy that restricts tumor growth by inhibiting all 3 VEGFRs[1-4]

Most first-generation treatments target the VEGF ligand outside the cell, while FRUZAQLA binds and inhibits VEGFRs intracellularly[2,11]

Phosphorylation of the kinase domain is prevented, blocking VEGFR signaling and leading to[2]:

- Restricted tumor growth and progression (VEGFR-1 and VEGFR-2)[2,3]
- Potential inhibition of lymphangiogenesis (VEGFR-3)[2,4]



Preclinical activity does not necessarily correlate with clinical outcomes.

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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Important Safety Information

IMPORTANT SAFETY INFORMATION

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- **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.

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IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **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.

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.
- **Females and Males of Reproductive Potential**
  - **Pregnancy Testing:** Verify pregnancy status of females of reproductive potential prior to initiating FRUZAQLA.
  - **Contraception:** 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.
  - **Infertility:** Advise females of reproductive potential that FRUZAQLA may cause post-implantation loss.

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 additional Important Safety Information throughout, and Patient Information in the Full Prescribing Information.

References: 1. FRUZAQLA. Prescribing Information. Takeda Pharmaceuticals America, Inc; 2025. **2.** Sun Q, Zhou J, Zhang Z, et al. Discovery of fruquintinib, a potent and highly selective small molecule inhibitor of VEGFR 1, 2, 3 tyrosine kinases for cancer therapy. *Cancer Biol Ther*. 2014;15(12):1635-1645. **3.** Xu WW, Li B, Lam AKY, et al. Targeting VEGFR1- and VEGFR2-expressing nontumor cells is essential for esophageal cancer therapy. *Oncotarget*. 2015;6(3):1790-1805. **4.** Mumprecht V, Detmar M. Lymphangiogenesis and cancer metastasis. *J Cell Mol Med*. 2009;13(8A):1405-1416. **5.** Liu Z-L, Chen H-H, Zheng L-L, Sun L-P, Shi L. Angiogenic signaling pathways and anti-angiogenic therapy for cancer. *Signal Transduct Target Ther*. 2023;8(1):198. **6.** Geindreau M, Ghiringhelli F, Bruchard M. Vascular endothelial growth factor, a key modulator of the anti-tumor immune response. *Int J Mol Sci*. 2021;22(9):4871. **7.** Koch S, Claesson-Welsh L. Signal transduction by vascular endothelial growth factor receptors. *Cold Spring Harb Perspect Med*. 2012;2(7):a006502. **8.** Lopez A, Harada K, Vasilakopoulou M, Shanbhag N, Ajani JA. Targeting angiogenesis in colorectal carcinoma. *Drugs*. 2019;79(1):63-74. **9.** Li J, Qin S, Xu R, et al. Effect of fruquintinib vs placebo on overall survival in patients with previously treated metastatic colorectal cancer: the FRESCO randomized clinical trial. *JAMA*. 2018;319(24):2486-2496. **10.** 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. **11.** Clarke JM, Hurwitz HI, Rangwala F. Understanding the mechanisms of action of antiangiogenic agents in metastatic colorectal cancer: a clinician's perspective. *Cancer Treat Rev*. 2014;40(9):1065-1072. **12.** Leighton JK. Stivarga Pharmacology/Toxicology New Drug Application Review and Evaluation, September 10, 2012. US Food and Drug Administration, Department of Health and Human Services. Accessed September 3, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203085Orig1s000PharmR.pdf **13.** Fox E, et al. Lenvima Pharmacology/Toxicology NDA Review and Evaluation, August 14, 2014. US Food and Drug Administration, Department of Health and Human Services. Accessed September 3, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206947Orig1s000PharmR.pdf

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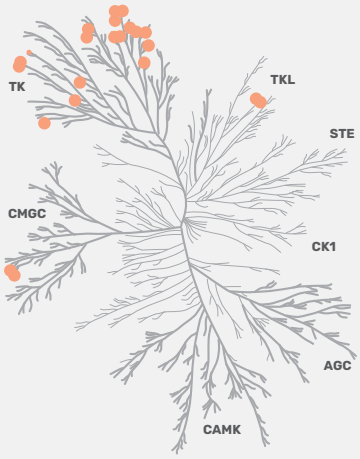
FRUZAQLA: a novel, selective inhibitor of all 3 VEGFRs[1,2,12,13]

Unlike earlier-generation VEGF inhibitors with activity at multiple off-target kinases, FRUZAQLA inhibits VEGFR-1, -2, and -3 with limited effects on other kinases[2,12,13]

First-generation VEGF inhibitor[12]

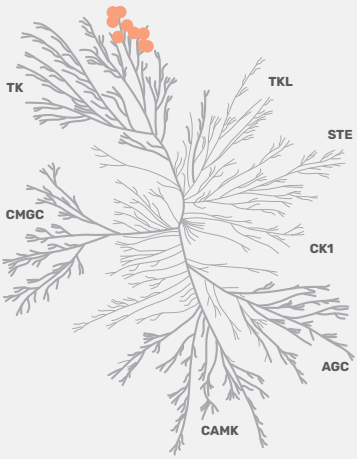
Limited selectivity



Kinome selectivity of regorafenib at 1 µM against a panel of 175 kinases

Second-generation VEGF inhibitor[13]

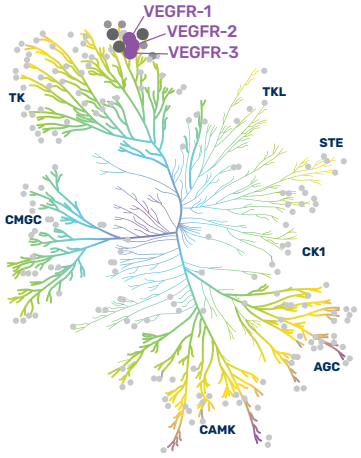
Moderate selectivity



Kinases with IC <100 nM in 66 selected kinases for lenvatinib

FRUZAQLA

Limits off-target kinase activity, allowing for drug exposure achieving sustained target inhibition[2]



Kinome selectivity of FRUZAQLA against a panel of 253 kinases

Inhibition at 1 µM

>90% 70-90% 40-70% <40%

Preclinical activity does not necessarily correlate with clinical outcomes.

AGC=protein kinase A, G, and C families; CAMK=calcium/calmodulin-dependent protein kinases; CK1=casein kinase 1; CMGC=cyclin-dependent kinase, mitogen-activated protein kinase, glycogen synthase kinase, and cyclin-dependent-like kinase; IC=inhibitory concentration; MOA=mechanism of action; STE=serine/threonine-specific protein kinase; TK=tyrosine kinase; TKL=tyrosine kinase-like kinase.

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.

To see more about the FRUZAQLA MOA, visit FRUZAQLAhcp.com

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