Iowa Medicaid
IOWA HHS

PDL DRUG REVIEW

Proprietary Name: Fruzaqla®
Common Name: fruquintinib
PDL Category: Antineoplastics

Comparable Products	Preferred Drug List Status
Stivarga	Non-Recommended with Conditions

Pharmacology/Usage: Fruquintinib, the active ingredient of Fruzaqla®, is a small molecule kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3. In vitro studies demonstrated fruquintinib inhibited VEGF-mediated endothelial cell proliferation and tubular formation. In vivo studies demonstrated fruquintinib inhibited tumor growth in a tumor xenograft mouse model of colon cancer.

Indication: 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.

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings in animal studies and its mechanism of action, Fruzaqla® can cause fetal harm when administered to a pregnant woman. There are no data on the use in pregnant women. Advise pregnant women of the potential risk to a fetus. Verify pregnancy status of females of reproductive potential prior to using Fruzaqla®. 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®. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Capsules: 1mg, 5mg. Swallow capsules whole.

Recommended Dosage: Take 5mg PO QD for the first 21 days of each 28-day cycle until disease progression or unacceptable toxicity. Take with or without food at about the same time each day. 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.

Dose modifications may be required for adverse reactions, such as hypertension, hemorrhagic events, hepatotoxicity, proteinuria, palmar-plantar erythrodysesthesia (PPE), or other adverse reactions. The first dose reduction is 4mg QD, while the second dose reduction is 3mg QD. Permanently discontinue Fruzaqla® in patients unable to tolerate 3mg PO QD.

Dosage adjustments are not recommended for patients with mild hepatic impairment. Fruzaqla® has not been sufficiently studied in patients with moderate hepatic impairment, and Fruzaqla® is not recommended for use in patients with severe hepatic impairment.

Drug Interactions: Avoid concomitant use of drugs that are strong CYP3A inducers with Fruzaqla®.

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.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Fruzaqla®) minus reported % incidence for placebo for all grades in FRESCO-2. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included fatigue (14%), hypertension (29%), stomatitis (23.2%), abdominal pain (5%), diarrhea (13%), hypothyroidism (20.6%), palmar-plantar erythrodysesthesia (hand-foot skin reactions; 16.4%), proteinuria (13%), dysphonia (13%), musculoskeletal pain (9%), and arthralgia (6.7%). Select laboratory abnormalities included triglycerides increased (31%), cholesterol increased (15%), aspartate aminotransferase increased (12%), albumin decreased (3%), sodium decreased (8%), alanine aminotransferase increased (12%), bilirubin increased (9%), alkaline phosphatase increased (0%), magnesium decreased (10%), lymphocytes decreased (0%), platelets decreased (25.3%), and activated partial thromboplastin time increased (3%).

Fruzaqla® can cause hypertension. The median time to first onset of hypertension was 14 days from first dose of Fruzaqla®. Do not start 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 antihypertensive therapy as appropriate.

Fruzaqla® can cause serious hemorrhagic events, which may be fatal. Permanently discontinue Fruzaqla® in patients with severe or life-threatening hemorrhage. Monitor the INR levels in patients receiving anticoagulants.

Fruzaqla® can cause an increased risk of infections, including fatal infections. In patients with mCRC treated with Fruzaqla® (N=911), the most frequent 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.

Fruzaqla® can cause gastrointestinal perforation. Permanently discontinue Fruzaqla® in patients who develop gastrointestinal perforation or fistula.

Fruzaqla® can cause liver injury. 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.

Fruzaqla® can cause proteinuria. 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®. Discontinue Fruzaqla® in patients who develop nephrotic syndrome.

Fruzaqla® can cause palmar-plantar erythrodysesthesia (PPE), and the 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.

Fruzaqla® can cause Posterior Reversible Encephalopathy Syndrome (PRES), which 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.

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. 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.

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. In addition, 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®.

Fruzaqla® 1mg capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. While 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® 1mg contains FD&C Yellow No. 6 (sunset yellow FCF), which may cause allergic reactions.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Takeda Pharmaceuticals America, Inc.

Analysis: The efficacy of Fruzaqla® was assessed in *FRESCO-2*, an international, multicenter, randomized, double-blind, placebo-controlled study that included patients (N=691) 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. Note that patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥2, left ventricular fraction ≤50%, systolic blood pressure >140mmHg or diastolic blood pressure >90mmHg, urine protein ≥1g/24h, or untreated brain metastases were ineligible.

The study population included adults with a median age of 64 years (range 25 to 86), with 47% of them ≥65 years of age. In addition, 56% were male, 81% were white, 43% had an ECOG PS of 0, 57% had an ECOG PS of 1, and 63% had *RAS*-mutant tumors. All 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.

Patients were randomized to receive Fruzaqla® 5mg PO QD (N=461) for the first 21 days of each 28-day cycle plus best supportive care (BSC) or placebo (N=230) plus BSC until disease progression or unacceptable toxicity. The major efficacy outcome was overall survival (OS), while an additional efficacy outcome measure was progression-free survival (PFS) as determined by investigators per RECIST v1.1. Results suggested that the addition of Fruzaqla® to BSC resulted in a statistically significant improvement in OS and PFS as compared to placebo plus BSC.

The efficacy of Fruzaqla® was also assessed in *FRESCO*, a multicenter, randomized, double-blind, placebo-controlled study conducted in China that included adults (N=416) with metastatic colorectal cancer who had disease progression during or after prior treatment with fluoropyrimidine-, oxaliplatin, or irinotecan-based chemotherapy. Patients were randomized to receive Fruzaqla® 5mg PO QD (N=278) for the first 21 days of each 28-day cycle plus BSC or placebo (N=138) plus BSC, and received treatment until disease progression or unacceptable toxicity. The study population had a median age of 56 years (range 23 to 75), while 61% were male, 100% were Asian, 27% had an ECOG performance status of 0, 73% had an ECOG performance status of 1, and 44% had *K-RAS* mutant tumors. All received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; 30% received prior anti-VEGF therapy, and 14% received prior anti-EGFR therapy.

The major efficacy outcome measure was OS, and an additional efficacy outcome measure was PFS as determined by investigators per RECIST v1.1. The addition of Fruzaqla® to BSC resulted in a statistically significant improvement in OS compared to placebo plus BSC.

Efficacy results for both studies are presented in the table below, which was adapted from the prescribing information.

Endpoint	FRESCO-2		FRESCO	
	Fruzaqla® + BSC (N=461)	Placebo + BSC (N=230)	Fruzaqla® + BSC (N=278)	Placebo + BSC (N=138)
Overall Survival (OS)				
Number of patients with event (%)	317 (69%)	173 (75%)	188 (68%)	109 (79%)
Median in months	7.4	4.8	9.3	6.6
HR; p-value	0.66; p<0.001		0.65; p<0.001	
Progression Free Survival (PFS)				
Number of patients with event (%)	392 (85%)	213 (93%)	235 (85%)	125 (91%)
Median in months	3.7	1.8	3.7	1.8
HR; p-value	0.32; p<0.001		0.26[1]	

[1] The p-value for the PFS analysis in FRESCO was not included due to lack of multiplicity adjustment for this analysis.

Place in Therapy: Fruzaqla®, a kinase inhibitor, 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. Do not start treatment unless blood pressure is adequately controlled, and monitor blood pressure during treatment. Monitor liver function tests and proteinuria before the start of treatment and periodically during treatment. In addition, do not administer Fruzaqla® for at least 2 weeks prior to major surgery.

The efficacy of Fruzaqla® was assessed in FRESCO-2, a multicenter, randomized, double-blind, placebo-controlled study where patients with mCRC were randomized to receive Fruzaqla® 5mg daily for the first 21 days of each 28-day cycle plus best supportive care (BSC) or placebo plus BSC. The addition of Fruzaqla® to BSC resulted in a statistically significant improvement in overall survival and progression free survival compared to placebo plus BSC. In the FRESCO study, a multicenter, randomized, double-blind study conducted in China, patients were randomized to receive Fruzaqla® 5mg daily for the first 21 days of each 28 cycle plus BSC or placebo plus BSC. The addition of Fruzaqla® to BSC resulted in a statistically significant improvement in overall survival compared to placebo plus BSC.

It is recommended that Fruzaqla® should be non-recommended in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Fruzaqla® [package insert]. Lexington, MA: Takeda Pharmaceuticals America Inc; 2023.