fruquintinib (Fruzaqla™)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO290

Description

Fruquintinib (Fruzaqla) is a selective vascular endothelial growth factor (VEGF) receptor kinase inhibitor.

Length of Authorization

- Initial: six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
fruquintinib (Fruzaqla)	Metastatic colorectal cancer (mCRC)	1 mg cap	84 caps/28 days
		5 mg cap	21 caps/28 days

Initial Evaluation

I. **Fruquintinib (Fruzaqla)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. Medication is not used in combination with any other oncology therapy; **AND**
   D. A diagnosis of **metastatic colorectal cancer (mCRC)**; **AND**
      1. The member has been previously treated with a fluoropyrimidine (e.g., fluorouracil, capecitabine, etc.), oxaliplatin, and irinotecan-based chemotherapy; **AND**
      2. The member has been previously treated with an anti-VEGF therapy (e.g. bevacizumab, Zaltrap, Cyramza, etc.); **AND**
      3. Treatment with trifluridine-tipiracil (Lonsurf) has been ineffective, contraindicated, or not tolerated; **AND**
      4. The tumor has been tested and is documented to be RAS mutant-type; **OR**
         i. The tumor has been tested and is documented to be RAS wild-type; **AND**
            a. The tumor is a right-sided tumor; **OR**
            b. The tumor is a left-sided tumor; **AND**
               i. The member has been previously treated with an anti-EGFR therapy (e.g., cetuximab, panitumumab)

II. **Fruquintinib (Fruzaqla)** is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:

A. Fruquintinib (Fruzaqla) used in combination with another oncology therapy
B. Gastroesophageal junction adenocarcinoma
C. Breast cancer
D. Non-small cell lung cancer (NSCLC)
E. Soft tissue sarcoma
F. Advanced pancreatic cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Clinical documentation of response to treatment (e.g., stabilization of disease, decrease in tumor size or tumor spread, lack of disease progression); **AND**
IV. Medication is not used in combination with any other oncology therapy

Supporting Evidence

I. Colorectal cancer (CRC) is the third most prevalent cancer worldwide and the second most common cause of cancer death in the United States. Initial clinical presentation as mCRC occurs in approximately 20% of patients and nearly 70% of patients with localized disease eventually develop metastases. In 2023, approximately 150,000 individuals will be diagnosed with CRC and over 50,000 individuals will die from the disease. Given the complexity of management of mCRC, the treatment of mCRC must be initiated by, in or consultation with, an oncologist.
II. CRC originates from the epithelial tissue of the colon, and it may develop either on the right side or left side of the colon. Therapeutic responses, disease progression, and overall survival vary depending on the position of the tumor. The difference between left and right tumors can be attributed to anatomical and developmental origin, or distinct carcinogenic factors (such as difference in bacterial population) or a combination of both. Multiple retrospective analyses (CRYSTAL, FIRE-3, and Canadian NCIC CO.17 trial) found that left-sided CRC has a better prognosis and responds better to anti-EGFR therapy compared to right-sided CRC. Studies have demonstrated that anti-EGFR therapies improved the overall survival in patients with left-sided KRAS wild type tumors, but not in patients with right-sided wild type tumors.
    - Right-sided tumors occur in the ascending colon, and proximal two thirds of the transverse colon and mutations in the DNA mismatch repair pathway are commonly observed. These tumors generally have a flat histology and are harder to diagnose, which may result in more advanced and larger tumors at diagnosis. Right-sided CRC patients do not respond well to anti-EGFR therapy. Microsatellite DNA mismatch repair pathway (MSI or dMMR) may be an important prognostic factor to consider

when deciding whether to use adjuvant chemotherapy in patients with stage II disease.

- Left-sided tumors occur in the descending and sigmoid colon, and distal one third of the transverse colon and chromosomal instability pathway-related mutations, such as KRAS, APC, PIK3CA, p53 mutations, are more commonly observed. These tumors generally have polypoid-like morphology, which makes them easier to diagnose in early stages of carcinogenesis. Up to 85% of CRC are left-sided tumors. Left-sided CRC patients benefit more from targeted therapies such as anti- epidermal growth factor receptor (EGFR) therapy, due to the pathway-related mutation.

III. Fruquintinib (Fruzaqla) is the fifth FDA-approved anti-VEGF agent indicated for treatment of mCRC. Fruquintinib (Fruzaqla) is the first and only selective inhibitor of all three VEGF receptor kinases for previously treated mCRC regardless of biomarker status. It is FDA-approved for the treatment of metastatic colorectal cancer (mCRC) previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, anti-VEGF therapy, and, if RAS wild-type, an anti-EGFR therapy. Fruquintinib (Fruzaqla) is an oral capsule given once daily for 21 days out of a 28-day cycle.

IV. The National Comprehensive Cancer Network (NCCN) guidelines recommend fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy with or without bevacizumab as first and second line therapy, with immune checkpoint inhibitors, anti-epidermal growth factor receptor (EGFR) agents if RAS wildtype, and anti-VEGF therapy. NCCN guidelines recommend fruquintinib (Fruzaqla) as a third line treatment (category 2A) for mCRC, joining trifluridine-tipiracil (Lonsurf) ± bevacizumab and regorafenib (Stivagra) as category 2A recommended agents. NCCN guidelines recommend anti-EGFR therapy prior to fruquintinib (Fruzaqla) in mCRC, RAS wild type, left-sided tumors.

- NCCN guidelines remain silent on the best sequence of therapy in the third- and fourth-line setting. The FRESCO-2 trial permitted previous treatment with trifluridine-tipiracil (Lonsurf) prior to randomization, and 91% of participants received prior trifluridine-tipiracil (Lonsurf) therapy. As the majority of participants had prior trifluridine-tipiracil (Lonsurf) therapy, requiring step through trifluridine-tipiracil (Lonsurf) is both clinically appropriate and cost-effective.

V. Fruquintinib (Fruzaqla) was studied in a Phase 3, international, multicenter, randomized (2:1), double-blinded, placebo-controlled study (FRESCO-2) in 691 patients with mCRC who had received all current standard approved cytotoxic and targeted therapies [fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy, anti-VEGF therapy, and anti- EGFR therapy (if RAS wild type)] and progressed on, or were intolerant to, trifluridine-tipiracil and/or regorafenib. Participants were randomized to receive fruquintinib (Fruzaqla) 5mg daily in addition to best supportive care (BSC) or placebo with BSC. Baseline characteristics were similar between both groups: median age 64 years, 63% of patients had RAS mutation, median number of previous therapies was four (96% of patients received previous anti-VEGF therapy and all participants received trifluridine-tipiracil (Lonsurf) and/or regorafenib (Stivara). The median OS was 7.4 months for the fruquintinib-treated group compared to 4.8 months for the placebo group, HR 0.66 (95% CI 0·55–0·80; p<0·0001).

VI. Fruquintinib (Fruzaqla) was also studied in a randomized, double-blinded, placebo-controlled, multicenter, Phase 3 clinical trial completed in China (FRESCO). A total of 416 participants aged 18-75 years with mCRC that progressed after 2 lines of chemotherapy were randomized in a 2:1 ratio to receive either fruquintinib (Fruzaqla) 5mg daily plus best supportive care or placebo with best supportive care. Median overall survival was significantly prolonged with fruquintinib (Fruzaqla) compared with placebo (9.3 months [95% CI, 8.2-10.5] vs 6.6 months [95% CI, 5.9-8.1]); HR 0.65 (95% CI, 0.51-0.83; P<0.001). However, at the time of the study, standard treatment practices for metastatic colorectal cancer in China were not the same as the standard treatment practices in the United States. Only one-third of the patients had received previous anti-VEGF therapy, and none had received trifluridine–tipiracil or regorafenib.

VII. The safety profile of fruquintinib (Fruzaqla) is similar to that of other FDA-approved anti-VEGF agents indicated for mCRC. Adverse events did occur more frequently in the fruquintinib (Fruzaqla) group compared to placebo. The most common adverse events were hypertension (37% vs 9%), asthenia (34% vs 23%), and hand-foot syndrome (19% vs 3%). A total of 93 (20%) patients who received fruquintinib (Fruzaqla) and 49 (21%) who received placebo discontinued treatment due to adverse events (asthenia and gastrointestinal perforation, proteinuria, and elevated LFTs).

VIII. The use of fruquintinib (Fruzaqla) has not been studied in combination with other oncology therapies, and due to lack of safety and efficacy data with a combination regimen, these agents should not be used together.

Investigational or Not Medically Necessary Uses

I. Fruquintinib (Fruzaqla) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   - A. Fruquintinib (Fruzaqla) used in combination with another oncology therapy. Fruquintinib (Fruzaqla) was studied as monotherapy in the FRESCO and FRESCO-2 trials.
   - B. Gastroesophageal junction adenocarcinoma
     - i. Fruquintinib plus paclitaxel demonstrated improvements in progression-free survival, objective response rate, disease control rate, and more, in patients with advanced gastric or gastroesophageal junction adenocarcinoma in a Phase 3 FRUTIGA study. Results are to be shared with the China National Medical Products Administration.
   - C. Breast cancer
     - i. There is an ongoing open-label study evaluating fruquintinib in HER2- breast cancer (NCT03251378)
   - D. NSCLC
     - i. There was a withdrawn trial evaluating fruquintinib in NSCLC
   - E. Soft tissue sarcoma

i. There is a recruiting trial evaluating fruquintinib in chemotherapy resistant soft tissue sarcoma in China (NCT05142631)

F. Advanced pancreatic cancer – Phase 2 trial evaluating fruquintinib in advanced pancreatic cancer in China

References

1. Dasari A, Lonardi S, Garcia-Carbonero R, et al. 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.
2. Li J, Qin S, Xu RH, 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.
3. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Versions 4.2023 – Nov 16, 2023). 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 1, 2023.
4. Fruzaqla (fruquintinib) [prescribing information]. Lexington, MA: Takeda Pharmaceuticals; November 2023.
5. UpToDate, Inc. Systemic therapy for nonoperable metastatic colorectal cancer: Approach to later lines of systemic therapy. UpToDate [database online]. Waltham, MA. Last updated October 19, 2023. Available at: http://www.uptodate.com/home/index.html.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
regorafenib (Stivara®) Policy	Gastrointestinal stromal tumor, metastatic colorectal cancer, hepatocellular carcinoma
trifluridine/tipiracil (Lonsurf®) Policy	Stomach or esophagogastric adenocarcinoma, metastatic colorectal cancer
encorafenib (Braftovi®), binimetinib (Mektovi®) Policy	Malignant melanoma (BRAF V600E mutation), metastatic colorectal cancer with BRAF V600E mutation

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2024