BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

FRUZAQLA™ (fruquintinib) Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and/or Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**

Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Medical Necessity Requirements for FRUZAQLA (fruquintinib)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a physician specializing in the diagnosis or in consultation with an Oncologist

Indication
- Metastatic colorectal cancer previously treated with **ALL** of the following: (see Definitions section)
  - Fluoropyrimidine based chemotherapy
  - Oxaliplatin based chemotherapy

  - Irinotecan based chemotherapy
  - Anti vascular endothelial growth factor (VEGF) therapy
  - If RAS wild type and medically appropriate: anti epidermal growth factor receptor (EGFR) therapy
  - Trifluridine/tipiracil, regorafenib, or both
  - Immune checkpoint inhibitor if appropriate for microsatellite instability high (MSI H) or mismatch repair deficient (dMMR) tumor
  - BRAF inhibitor if appropriate for BRAF mutant tumor
- Other oncologic direct treatment use listed in National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

Age Requirement

- 18 years or older

Baseline Clinical Evaluation

- Blood pressure is adequately controlled
- Liver function tests: alanine transaminase (ALT), aspartate transaminase (AST), and bilirubin
- Urine protein for proteinuria
- Negative pregnancy test for individuals of childbearing potential
- Eastern Cooperative Oncology Group (ECOG) status 0 to 2

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No concomitant use with strong cytochrome P450 3A (CYP3A) inducers (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John's wort)

Additional Requirements

- No moderate hepatic impairment (total bilirubin greater than 1.5 times to less than 3 times upper limit of normal and any aspartate aminotransferase)
- No severe hepatic impairment (total bilirubin greater than 3 times upper limit of normal and any aspartate aminotransferase)
- Does not have left ventricular fraction less than or equal to 50 percent, systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg, urine protein greater than or equal to 1 gram/24 hours, or untreated brain metastases

Documentation Requirements

- A completed request form must be submitted including:
  - Chart notes
  - Lab results (blood pressure, liver function tests, urine protein, pregnancy test, ECOG status)

- Supporting clinical documentation

Initial Therapy Criteria Approval Duration

- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy.

Prescriber Qualification

- Continues to be seen by a physician specializing in or in consultation with an Oncologist

Clinical Response

- No documentation of disease progression
- No documentation of unacceptable drug toxicity

Adherence

- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No development of significant adverse drug effects such as:
  - Life threatening uncontrolled hypertension
  - Severe or life threatening hemorrhage
  - Active infection
  - Gastrointestinal perforation or fistula
  - Liver toxicity (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 3 times upper limit of normal and total bilirubin greater than 2 times upper limit of normal, or ALT or AST greater than 20 times upper limit of normal or bilirubin greater than 10 times upper limit of normal)
  - Nephrotic syndrome or unresolved proteinuria greater than 1 gram/24 hours
  - Palmar Plantar Erythrodysesthesia
  - Posterior Reversible Encephalopathy Syndrome
  - Arterial thromboembolic event
  - Allergic reactions to FD&C Yellow No. 5 (Tartrazine) and No. 6 (Sunset Yellow FCF)
  - Bronchial asthma
- No concomitant use with strong CYP3A inducers (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John's wort)

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Generic Equivalent (if available)

Additional Requirements

- Requested dose is at least 3 mg once daily
- No moderate hepatic impairment (total bilirubin greater than 1.5 times to less than 3 times upper limit of normal and any aspartate aminotransferase)
- No severe hepatic impairment (total bilirubin greater than 3 times upper limit of normal and any aspartate aminotransferase)
- Does not have left ventricular fraction less than or equal to 50 percent, systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg, urine protein greater than or equal to 1 gram/24 hours, or untreated brain metastases

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement in given indication
- Lab values confirming safe use

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Off-Label Use Requests:

Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. Off-Label Use of Non-Cancer Medications

2. Off-Label Use of Cancer Medications

Description:

Fruzaqla (fruquintinib), 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.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Some examples of chemotherapies:

- Fluoropyrimidine-based chemotherapy (e.g., capecitabine, 5-FU)
- Oxaliplatin-based chemotherapy (e.g., CAPEOX, FOLFOX)

- Irinotecan-based chemotherapy (e.g., FOLFIRI, FOLFIRINOX)
- Anti-VEGF therapy (e.g., aflibercept, bevacizumab, ramucirumab)
- Anti-EGFR therapy (e.g., cetuximab, panitumumab)
- Trifluridine/tipiracil, regorafenib, or both
- Immune checkpoint inhibitor if deemed appropriate for MSI-H/MMR deficient tumors (e.g. nivolumab, pembrolizumab)
- BRAF inhibitor if deemed appropriate for BRAF-mutant tumors (e.g., encorafenib)

Resources:

Fruzaqla (fruquintinib) product information, revised by Takeda Pharmaceuticals America, Inc. 02-2025. Available at FDA https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217564s000lbl.pdf. Accessed October 24, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Colon Cancer Version 5.2025 – Updated October 30, 2025. Available at https://www.nccn.org. Accessed November 13, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Rectal Cancer Version 4.2025 – Updated October 31, 2025. Available at https://www.nccn.org. Accessed November 13, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT04322539: A Global Multicenter Randomized Placebo-Controlled Phase 3 Trial To Compare The Efficacy And Safety Of Fruquintinib Plus Best Supportive Care To Placebo Plus Best Supportive Care In Patients With Refractory Metastatic Colorectal Cancer. Available from: http://clinicaltrials.gov. Last update posted September 09, 2023. Last verified September 2023. Accessed January 29, 2025. Re-evaluated November 13, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT02314819: A Randomized, Double-blind and Placebo-controlled Phase III Trial Comparing Fruquintinib Efficacy and Safety vs Best Support Care (BSC) in Advanced Colorectal Cancer Patients Who Have Failed at Least Second Lines of Chemotherapies. Available from: http://clinicaltrials.gov. Last update posted February 13, 2020. Last verified February 2019. Accessed January 29, 2025. Re-evaluated November 13, 2025.

Dasari A, Sobrero DA, Yao J, et al.: FRESCO-2: A Global Phase III Study Investigating the Efficacy and Safety of Fruquintinib in Metastatic Colorectal Cancer. Future Oncology 2021 Aug;17 (24): 3151-3162. Re-evaluated November 13, 2025.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.