BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

AVMAPKI™ FAKZYNJA™ CO-PACK (avutometinib & defactinib) oral 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 AVMAPKI FAKZYNJA CO-PACK (avutometinib and defactinib)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by an Oncologist or in consultation with an Oncologist

Indication
- KRAS mutated recurrent low grade serous ovarian cancer (LGSOC) with prior systemic therapy including a platinum based regimen

ORIGINAL EFFECTIVE DATE: 08/21/2025 | ARCHIVE DATE: | LAST REVIEW DATE: | LAST CRITERIA REVISION DATE:

- Other oncologic treatment uses listed in the 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

- Documentation of **ONE** of the following responsive KRAS mutation in tumor specimens:
  - A146V
  - G12D
  - G12R
  - G12V
  - Q61H
- Comprehensive ophthalmic evaluation
- Liver function tests
- Creatine phosphokinase (CPK)
- Negative pregnancy test (if applicable)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (when 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

- **NONE** of the following:
  - Concomitant use of strong or moderate CYP3A4 inhibitors or inducers
  - Concomitant use with gastric acid reducing agents (e.g., PPIs or H2 receptor antagonists)
  - Coexisting high grade ovarian cancer or another histology
  - Severe renal impairment (CrCl less than 30 mL/min)
  - Moderate to severe hepatic impairment (AST or ALT 2.5 times ULN or greater or total bilirubin 1.5 times ULN or greater)
  - Symptomatic brain metastases requiring steroids or other interventions
  - Active skin disorder requiring systemic therapy within the past year
  - History of rhabdomyolysis
  - Concurrent ocular disorders

Documentation Requirements

- A completed request form must be submitted, including:
  - Chart notes
  - Lab results (KRAS mutation, liver function, CPK, 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 disease progression or unacceptable drug toxicity

Adherence

- Adherence to the prescribed therapy regimen has been documented
- No more than **ONE** dose reduction of both products due to intolerance

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (when 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:
  - Severe ocular toxicities (visual impairment, vitreoretinal disorders)
  - Serious skin toxicities (photosensitivity, severe cutaneous adverse reactions)
  - Hepatotoxicity
  - Rhabdomyolysis
  - Other moderate recurring or severe adverse reactions
- **NONE** of the following:
  - Concomitant use of strong or moderate CYP3A4 inhibitors or inducers
  - Concomitant use with gastric acid reducing agents (e.g., PPIs or H2 receptor antagonists)
  - Coexisting high grade ovarian cancer or another histology
  - Severe renal impairment (CrCl less than 30 mL/min)
  - Moderate to severe hepatic impairment (AST or ALT 2.5 times ULN or greater or total bilirubin 1.5 times ULN or greater)
  - Symptomatic brain metastases requiring steroids or other interventions
  - Active skin disorder requiring systemic therapy within the past year
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Additional Requirements

- ANY **ONE** of the following responsive KRAS mutations:
  - A146V
  - G12D
  - G12R
  - G12V
  - Q61H

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement in given indication
- Lab values confirming safe use (as listed above)

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:

Avmapki-Fakzynja Co-Pack (avutometinib capsules; defactinib tablets) a combination of kinase inhibitors, is indicated for the treatment of adult individuals with *KRAS*-mutated recurrent low-grade serous ovarian cancer (LGSOC) who have received prior systemic therapy. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Avutometinib is an MEK1 inhibitor. Avutometinib induces the formation of inactive RAF/MEK complexes and prevents phosphorylation of MEK1/2 by RAF. RAF and MEK proteins are regulators of the RAS/RAF/MEK/ERK (MAPK) pathway. Avutometinib inhibited MEK1/2 and ERK1/2 phosphorylation and proliferation of tumor cell lines harboring KRAS mutations. Treatment of cancer cells with avutometinib increased the level of phosphorylated focal adhesion kinase (FAK). Defactinib is an inhibitor of FAK and proline-rich tyrosine kinase-2 (Pyk2), the two members of the FAK family of nonreceptor tyrosine kinases. Defactinib inhibited FAK autophosphorylation in cancer cells *in vitro* and in mouse xenograft models. Avutometinib in combination with defactinib enhanced inhibition of cell proliferation *in vitro* and anti-tumor activity mouse tumor models including LGSOC.

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Definitions:

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

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Version 2.2025 – Updated May 23, 2025.

PRINCIPLES OF SYSTEMIC THERAPY
Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)/Fallopian Tube/Primary Peritoneal Cancer
Recurrence Therapy for Platinum-Sensitive Disease (alphabetical order)
Useful in Certain Circumstances
For low-grade serous carcinoma:
• Avutometinib/defactinib (for *KRAS*-mutated tumors)
• Trametinib (off-label)
• Binimetinib (category 2B)

PRINCIPLES OF SYSTEMIC THERAPY
Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)/Fallopian Tube/Primary Peritoneal Cancer
Recurrence Therapy for Platinum-Resistant Disease (alphabetical order)
Useful in Certain Circumstances
For low-grade serous carcinoma:
• Avutometinib/defactinib (for *KRAS*-mutated tumors)
• Trametinib (off-label)
• Binimetinib (category 2B)

Resources:

Avmapki Fakzynja Co-Pack (avutometinib capsules; defactinib tablets) product information, revised by Verastem, Inc. 05-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 21, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Version 2.2025 – Updated May 23, 2025. Available at https://www.nccn.org. Accessed June 21, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT04625270: A Phase 2 Study of Avutometinib (VS-6766) (Dual RAF/MEK Inhibitor) Alone and In Combination With Defactinib (FAK Inhibitor) in Recurrent Low-Grade Serous Ovarian Cancer (LGSOC). Available from: http://clinicaltrials.gov. Last update posted January 29, 2025. Last verified March 2024. Accessed June 21, 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.