avutometinib and defactinib (Avmapki Fakzynja Co-Pack)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO329

Description

Avutometinib (Avmapki) is a RAF/MEK clamp that inhibits MEK kinase activity and inhibits MEK1/2 and ERK1/2 and subsequent proliferation of KRAS-mutated tumor cell lines. Defactinib (Fakzynja) is an orally administered selective FAK inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
avutometinib (Avmapki) and defactinib (Fakzynja) Co-Pack	Adult patients with *KRAS*-mutated recurrent low-grade serous ovarian cancer (LGSOC) who have received prior systemic therapy.	0.8 mg capsules/ 200 mg tablets	66 capsules and tablets/28 days

Initial Evaluation

I. **Avutometinib (Avmapki) and defactinib (Fakzynja) Co-Pack** may be considered medically necessary when the following criteria are met:
   A. The member is 18 years of age or older; **AND**
   B. The medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. The medication will not be used in combination with other oncology therapy; **AND**
   D. A diagnosis of **low-grade serous ovarian cancer (LGSOC)** when the following are met:
      1. The member has advanced or metastatic (FIGO stage II-IV) low-grade serious ovarian cancer; **AND**
      2. Documentation of a *KRAS* mutation; **AND**
      3. The member has had disease progression on platinum-based chemotherapy, unless not tolerated or contraindicated; **AND**
      4. The member has had disease progression on a second line of chemotherapy, unless not tolerated or contraindicated; **AND**
      5. The member has had disease progression on hormonal therapy (i.e., aromatase inhibitors, goserelin, leuprolide, megestrol, fulvestrant), unless not tolerated or contraindicated; **AND**
      6. The member has had disease progression on bevacizumab, unless not tolerated or contraindicated; **AND**

7. The member has had disease progression on trametinib (Mekinist)*, unless not tolerated or contraindicated; **AND**
8. Provider attestation that member is not a candidate for treatment with additional lines of chemotherapy due to tolerability concerns; **AND**
9. Provider attestation that member is not a candidate for clinical trial participation

II. Avutometinib (Avmapki) and defactinib (Fakzynja) Co-Pack is considered investigational when used for all other conditions, including but not limited to:
   A. Avutometinib (Avmapki) and defactinib (Fakzynja) Co-Pack is used in combination with another oncology therapy
   B. Mesonephric gynecologic cancer
   C. Non-small cell lung cancer
   D. Pancreatic cancer
   E. Metastatic uveal melanoma
   F. Diffuse gastric cancer
   G. Brain tumors
   H. Thyroid cancer
   I. Neurofibromatosis type 1 (NF1)

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. The medication will not be used in combination with other oncology therapy; **AND**
IV. Member has exhibited improvement or stability of disease symptoms **OR**
V. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread

Supporting Evidence

I. Avutometinib (Avmapki) and defactinib (Fakzynja) is available as a Co-Pack and is the first FDA approved combination for the treatment of adults with *KRAS*-mutated recurrent low-grade serous ovarian cancer who have received prior systemic therapy. The drug was FDA-approved via the accelerated approval pathway and continued approval is contingent upon verification and description of clinical benefit in confirmatory trials.
II. Low grade serous ovarian cancer (LGSOC) is a rare tumor, comprising <10% of all epithelial ovarian cancers, with approximately 2,000 new cases diagnosed in the U.S. each year. Until

recently, the treatment paradigm of LGSOC was similar to a more common high grade serous ovarian cancer (HGSOC); however, it's now considered a distinct entity. Low grade serous ovarian cancer patients are typically younger (median age 45 years), experience prolonged survival time, typically around 10 years but with high recurrence rates. Frontline chemotherapy is known to have a poor response in LGSOC, which is frequently identified in its later stages. Most common molecular aberrations include estrogen and progesterone expression and the MAPK-pathway aberrations, including mutations in *KRAS*, *NRAS*, and *BRAF*. *KRAS* mutation represents approximately 30% of the total patient population with LGSOC.

III. Avutometinib (Avmapki) and defactinib (Fakzynja) Co-Pack was studied and is FDA-approved in adult patients only at this time. Treatment of patients less than 18 years of age is not supported by clinical trials and safety and efficacy in this population has not been established.

IV. Due to complex nature of treating LGSOC, avutometinib (Avmapki) and defactinib (Fakzynja) Co-Pack should be prescribed by, or in consultation with, an oncologist.

V. Avutometinib (Avmapki) and defactinib (Fakzynja) Co-Pack had not been sufficiently evaluated for efficacy and safety in combination with any other oncolytic medication at this time. Safety and efficacy in combination with other oncology drugs is unknown.

VI. A diagnosis of advanced or metastatic (FIGO stage II-IV) LGSOC is required as all patients were required to have this diagnosis as part of the inclusion criteria of the clinical trial studying avutometinib (Avmapki) and defactinib (Fakzynja) Co-Pack in the pivotal RAMP-201 Study. Efficacy and safety in non-LGSOC or related cancers or in earlier stages of disease has not been well studied and remains unknown.

VII. Confirmation of *KRAS* mutation is required as this is where the drug is FDA approved and has shown the most promising clinical benefit in the RAMP-201 study. Efficacy in *KRAS* wild type tumors was substantially lower than in the *KRAS* mutated cohort, therefore, *KRAS* mutation confirmation is required.

VIII. The member is required to have LGSOC that is relapsed or refractory to prior systemic therapy. In the pivotal study, RAMP-201, all patients (100%) received prior platinum-based chemotherapy, 81% received hormonal therapy as maintenance or treatment and 40% received prior bevacizumab previously. Safety and efficacy of avutometinib (Avmapki) and defactinib (Fakzynja) Co-Pack in treatment naïve patients is not established.

   a. In the primary treatment setting with systemic therapy, chemotherapy, hormonal therapy, and bevacizumab in combination with paclitaxel and carboplatin are all recommended as preferred regimens in the NCCN guidelines. Specifically, this recommendation is found in the primary systemic therapy regimens for low-grade serous/Grade 1 endometrioid for stage II-IV disease. The preferred regimens include paclitaxel/carboplatin (category 2A) +/- maintenance letrozole (category 2B) or other hormonal therapy (category 2B), paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab (category 2A), and hormone therapy (aromatase inhibitors: anastrozole, letrozole, exemestane) (category 2B).

b. In the recurrent treatment setting, chemotherapy (if not previously used), hormonal therapy, systemic therapy and observation are all listed with a category 2A recommendation. Chemotherapy in this case is referred to as preferred regimens for primary therapy. Systemic therapy is split according to platinum sensitive and platinum resistant disease. In platinum sensitive disease, preferred regimens include carboplatin/gemcitabine +/- bevacizumab, carboplatin/liposomal doxorubicin +/- bevacizumab, carboplatin/paclitaxel +/- bevacizumab, cisplatin/gemcitabine and bevacizumab monotherapy. In platinum resistant disease, preferred regimens include cyclophosphamide (oral)/bevacizumab, docetaxel, etoposide, gemcitabine, liposomal doxorubicin, liposomal doxorubicin/bevacizumab, paclitaxel, paclitaxel/bevacizumab, topotecan, topotecan/bevacizumab, and bevacizumab monotherapy.

c. Policy criteria requires trial of primary therapy with a platinum-based regimen, unless contraindicated or not tolerated, followed by a second round of chemotherapy according to platinum disease status. Additionally, bevacizumab and hormone therapy are also required as either combination treatment or monotherapy, or maintenance treatment, as either primary or recurrent treatment. Trametinib (Mekinist) is also required as this treatment option is supported by NCCN guidelines with a category 2A recommendation and has data from a randomized controlled trial against standard of care which shows superior progression free survival in favor of trametinib (Mekinist) (GOG281/LGOS). This stepwise approach aligns with the NCCN guidelines for LGSOC and the population studied in the Avutometinib (Avmapki) and defactinib (Fakzynja) clinical trial. Lastly, provider attestation that member is not a candidate for ongoing treatment with chemotherapy and clinical trial participation is also required. NCCN guidelines list various chemotherapy regimens and do not specify a limit to the number of chemotherapy regimens that can be attempted. According to NCCN guidelines all patients with ovarian cancer should be encouraged to participate in clinical trials during all aspects of their diagnosis and treatment. Clinical trials may represent the most suitable approach to treatment of rare cancers such as LGSOC at this time.

IX. Avutometinib (Avmapki) and defactinib (Fakzynja) Co-Pack was studied in one open-label, single arm, Phase 2 clinical trial in 199 total patients with metastatic LGSOC of whom 58 carried the *KRAS* mutation. At baseline patients were 60 years old, mainly White, had a median of three prior systemic therapies including platinum-based chemotherapy (100%), hormonal therapy (85%), bevacizumab (40%), and MEK inhibitors (21%). The primary efficacy outcome was overall response rate (ORR) which was 44% (95% CI 31-58). Secondary endpoints included duration of response (DOR) which was 3.3-31.1 months (range), and progression free survival (PFS) which was 22 months (95% CI 11.1-36.6).

X. In the recurrent setting, standard treatment sequencing has not yet been determined. National Comprehensive Cancer Network (NCCN) guidelines for the treatment of Ovarian Cancer (Version 3. 2025 – July 16, 2025) list recommendations for LGSOC in the LGSOC-specific section (LCOC-7)

and include hormonal therapy, chemotherapy (if not previously used), systemic therapy, or observation, all with a category 2A recommendation. Systemic therapy is split between platinum-sensitive and resistant disease. LGSOC is considered platinum-sensitive if recurrence occurred more than six months after platinum chemotherapy. In first relapses and when disease is platinum-sensitive, NCCN recommend re-treating with a platinum agent with or without bevacizumab as the preferred regimen. In platinum-resistant disease, other cytotoxic therapies are preferred which include cyclophosphamide with or without bevacizumab, docetaxel, paclitaxel, topotecan, and doxorubicin. Bevacizumab monotherapy is another preferred option in both platinum-resistant and sensitive-disease. Hormonal therapy (i.e., aromatase inhibitors, goserelin, leuprolide,) is listed as an option in both platinum-resistant and sensitive diseases. The majority of data for hormonal therapy comes from retrospective studies, with letrozole used most commonly. Prospective data for letrozole is available from a trial evaluating trametinib, study called GOG-281. Another option in LGSOC are MEK inhibitors (i.e., trametinib, binimetinib, and avutometinib/defactinib), all with a category 2A recommendation, except binimetinib (category 2B). Lastly, observation is also listed as an option under recurrent LGSOC.

Investigational or Not Medically Necessary Uses

I. Avutometinib (Avmapki) and defactinib (Fakzynja) Co-Pack has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Avutometinib (Avmapki) and defactinib (Fakzynja) Co-Pack is used in combination with another oncology therapy
      i. The medication has not been sufficiently studied in combination with any other oncology therapy at this time and is considered experimental and investigational for this reason.
      ii. Avutometinib (Avmapki) and defactinib (Fakzynja) Co-Pack is being studied in combination with letrozole in patients with low-grade serous ovarian cancer (CHAMELEON) (NCT06394804), a Phase 2 study. This study is not yet complete (estimated completion date: 04/2027) and the results are not available at this time. The safety and efficacy of this therapy in combination with letrozole remains undetermined.
   B. Mesonephric gynecologic cancer
      i. Avutometinib (Avmapki) and defactinib (Fakzynja) Co-Pack is being studied in the treatment of advanced or recurrent mesonephric gynecologic cancer in a Phase 2 study (NCT05787561). This study is not yet complete (estimated completion date: 03/2026) and the results are not available at this time. The safety and efficacy of this therapy in this condition remains undetermined.
   C. Non-small cell lung cancer

i. Avutometinib (Avmapki) and sotorasib with or without defactinib (Fakzynja) is being studied in KRAS G12C non-small cell lung cancer (RAMP 203) (NCT05074810), a Phase 1/2 study. This study is not yet complete (estimated completion date: 04/2027) and the results are not available at this time. The safety and efficacy of this therapy in this condition remains undetermined.

D. Pancreatic cancer
   i. Avutometinib (Avmapki) and defactinib (Fakzynja) Co-Pack is being studied with gemcitabine and Nab-paclitaxel in patients with pancreatic cancer (NCT05669482), a Phase 1/2 study. This study is not yet complete (estimated completion date: 08/2026) and the results are not available at this time. The safety and efficacy of this therapy in this condition remains undetermined.
E. Metastatic uveal melanoma
   i. Defactinib (Fakzynja) was studied in combination with VS-6766 for the treatment of metastatic melanoma. However, this study is terminated as of 08/2025. Trial enrollment was stopped early by the study sponsors due to no patients having significant reduction in disease. The safety and efficacy of this therapy in this condition remains undetermined.
F. Diffuse gastric cancer
   i. Avutometinib (Avmapki) and defactinib (Fakzynja) Co-Pack is studied in diffuse gastric cancer in a Phase 2 trial (NCT06487221). This study is not yet complete (estimated completion date: 05/2029) and the results are not available at this time. The safety and efficacy of this therapy in this condition remains undetermined.
G. Brain tumors
   i. Defactinib (Fakzynja) is being studied in the treatment of glioblastoma in an early Phase 1 trial (NCT05798507). This study is not yet complete (estimated completion date: 10/2026) and the results are not available at this time. The safety and efficacy of this therapy in this condition remains undetermined.
   ii. Avutometinib (Avmapki) and defactinib (Fakzynja) Co-Pack is being studied in a Phase 1 and Phase 2 trial (NCT06630260) in patients with glioblastoma. This study is not yet complete (estimated completion date: 09/2030) and the results are not available at this time. The safety and efficacy of this therapy in this condition remains undetermined.
H. Thyroid cancer
   i. Avutometinib (Avmapki) and defactinib (Fakzynja) Co-Pack is being studied in people with thyroid cancer in a Phase 2 study (NCT06007924). This study is not yet complete (estimated completion date: 08/2027) and the results are not available at this time. The safety and efficacy of this therapy in this condition remains undetermined.

I. Neurofibromatosis type 1 (NF1)
    i. There are no planned studies for this indication at this time. The safety and efficacy in this condition remains underdetermined.

References

1. Avmapki Fakzynja Co-Pack. Package Insert. Verastem Inc. May 2025.
2. Food and Drug Administration. Avmapki Fakzyna Co-Pack Multi-Discipline Review. Accessed August 21, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2025/219616Orig1s000MultidisciplineR.pdf
3. National Comprehensive Cancer Network. Ovarian Cancer Continue Including Fallopian Tube Cancer and Primary Peritoneal Cancer. NCCN. July 16, 2025. Accessed August 21, 2025. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf
4. Banerjee SN, Van Nieuwenhuysen E, Aghajanian C, et al. Efficacy and Safety of Avutometinib ± Defactinib in Recurrent Low-Grade Serous Ovarian Cancer: Primary Analysis of ENGOT-OV60/GOG-3052/RAMP 201. J Clin Oncol. Published online July 11, 2025. doi:10.1200/JCO-25-00112
5. Gershenson DM, Miller A, Brady WE, et al. Trametinib versus standard of care in patients with recurrent low-grade serous ovarian cancer (GOG 281/LOGS): an international, randomised, open-label, multicentre, phase 2/3 trial. Lancet. 2022;399(10324):541-553. doi:10.1016/S0140-6736(21)02175-9
6. Monk BJ, Grisham RN, Banerjee S, et al. MILO/ENGOT-ov11: Binimetinib Versus Physician's Choice Chemotherapy in Recurrent or Persistent Low-Grade Serous Carcinomas of the Ovary, Fallopian Tube, or Primary Peritoneum. J Clin Oncol. 2020;38(32):3753-3762. doi:10.1200/JCO.20.01164
7. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol*. 2012;30(17):2039-2045.
8. Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JI. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. J Clin Oncol. 2007;25(33):5165-5171. doi:10.1200/JCO.2007.11.5345

Related Policies

Policy Name	Disease state
cobimetinib (Cotellic®), vemurafenib (Zelboraf®) Policy	Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation
	Histiocytic neoplasms in adults
encorafenib (Braftovi®), binimetinib (Mektovi®) Policy	Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therapy
	Metastatic non-small cell lung cancer, with BRAF V600E mutation, combination therapy
trametinib (Mekinist®), dabrafenib (Tafinlar®) Policy	Melanoma, adjuvant therapy for malignant disease, BRAF V600E or K mutated, combination therapy
	Anaplastic thyroid carcinoma, advanced or metastatic, BRAF V600E mutated, combination therapy
	Melanoma, malignant unresectable or metastatic disease, BRAF V600E or K mutated, combination therapy
	Melanoma, malignant unresectable or metastatic disease, BRAF V600E or K mutated, monotherapy in BRAF treatment naïve patients

	Non-small cell lung cancer, metastatic, BRAF V600E mutated, combination therapy
	Unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options
	Pediatric low-grade glioma (LGG) with a BRAF V600E mutation, combination therapy

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2025