Avutometinib and Defactinib (AVMAPKI FAKZYNJA CO-PACK)
National Drug Monograph
July 2026
VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: AC, active-controlled; BRAF, v-RAF murine sarcoma viral oncogene homolog B1; CO, crossover; DB, double-blind; FAK, focal adhesion kinase; KRAS Kristen rat sarcoma viral oncogene homolog; MAPK, mitogen-activated protein kinase; MC, multicenter; MEK, mitogen-activated extracellular signal-regulated kinase; NRAS, neuroblastoma rat sarcoma viral oncogene homolog; ORR, objective response rate; PC, placebo-controlled; Pyk2, proline-rich tyrosine kinase-2; Q, RAF, rapidly accelerated fibrosarcoma; RCT, randomized clinical trial

FDA PRESCRIBING INFORMATION[1]

Description / MOA	KRAS-mutated recurrent low-grade serous ovarian cancer (LGSOC) is an uncommon life-threatening subtype of ovarian cancer with previously limited options for therapy or palliation. Avutometinib, a dual RAF/MEK inhibitor, combined with defactinib, a FAK/Pyk2 inhibitor, represents the first targeted therapy for this disease. Avutometinib provides MAPK pathway inhibition while avoiding feedback reactivation, and defactinib blocks the compensatory FAK signaling that tumors often upregulate to resist MAPK blockade. This novel, synergistic combination was designed to achieve deeper and longer-lasting pathway inhibition in tumors driven by dysregulated MAPK signaling from KRAS, NRAS, or BRAF mutations.
Indication Under Review	Treatment of adult patients 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.
Dosage Regimen	Avutometinib 3.2 mg (four 0.8-mg caps) PO twice **weekly** (Day 1 and Day 4) for the first 3 weeks of each 4-week cycle. Defactinib 200 mg (one tab) PO twice **daily** for the first 3 weeks of each 4-week cycle until disease progression or unacceptable toxicity.
Dosage Forms Under Review	Avutometinib 0.8-mg capsules Defactinib 200-mg tablets
Boxed Warnings	□ none
Contraindications	□ none
Other Warnings	□ Ocular toxicities □ Serious skin toxicities □ Hepatotoxicity □ Rhabdomyolysis □ Embryo-fetal toxicity
Most common AEs (≥ 25%)	□ Increased creatine phosphokinase (CPK), nausea, fatigue, increased aspartate aminotransferase, rash
Drug Interactions	**Strong and moderate CYP3A4 inhibitors:** Avoid; may increase effects of defactinib and toxicity **Strong and moderate CYP3A4 inducers:** Avoid; may decrease effects of defactinib and efficacy **Warfarin:** Avoid; if concomitant use is unavoidable, monitor INR frequently **Gastric acid reducing agents:** Avoid; may decrease effects of defactinib; if proton pump inhibitor or H2 receptor antagonist cannot be avoided, separate doses by 2 hours.
Pregnancy	□ Advise pregnant women and females of reproductive potential of the potential risk to a fetus
Lactation	□ Advise not to breastfeed
Renal impairment	**Mild and Moderate:** No clinically significant differences were observed in the PK of either avutometinib or defactinib. **Severe:** Effects on the PK of either avutometinib or defactinib are unknown.
Hepatic impairment	**Mild (AST > ULN or total bilirubin >1 to 1.5 x ULN):** No clinically significant differences were observed in the PK of either avutometinib or defactinib. **Moderate to Severe (AST or ALT ≥ 2.5 x ULN or total bilirubin ≥ 1.5 x ULN):** Effects on the PK of either avutometinib or defactinib are unknown.

CLINICAL EVIDENCE SUMMARY

RAMP-201 Study	**Efficacy and Safety of Avutometinib ± Defactinib in Recurrent Low-Grade Serous Ovarian Cancer: Primary Analysis of ENGOT-OV60/GOG-3052/RAMP 201[2]**
Design	Adaptive, four-part, phase 2, OL, MC RCT with stratified randomization by *KRAS* mutant (mt) and *KRAS* wild-type (wt) tumors and blinded assessment of objective response rate (ORR) by an independent review committee
Primary Endpoint	Objective response rate (ORR); Overall survival was a secondary endpoint

Population	Adult women with measurable, histologically confirmed ovarian or peritoneal LGSOC who received at least one prior platinum-based regimen. Patients were allowed to have one line of prior MEKi or RAFi therapy. *Baseline Characteristics (N = 115 women):* Median age 54 years (range, 21–87 years); Median of 3 (range, 1–9) prior lines of systemic therapy; 99% had received prior platinum-based chemotherapy; 22% a prior MEKi.
Interventions	Part A: Avutometinib 3.2 mg orally twice **weekly** plus defactinib 200 mg twice **daily**, on a 3-weeks-on/1-week-off schedule vs. Avutometinib 4 mg orally twice **weekly** for 3 weeks Part B: expanded enrollment Part C: go forward with Avutometinib plus defactinib
Results	**Primary Efficacy Results Part B: avutometinib/defactinib vs. avutometinib:** ORR 44 vs. 23% KRASm; 17 vs. 13% KRASwt **Primary Efficacy Results in All Patients in RAMP-201 Part C: avutometinib/defactinib**

Outcome	All patients (N=109)	KRAS mutant (N=57)
ORR, n/N (%)	34/109 (31)	25/57 (44)
PFS, median (95% CI), mos	12.9 (10.9, 20.2)	22.0 (11.1, 36.6)
DOR, median (95% CI), mos	31.1 (14.8, 31.1)	31.1 (14.8, 31.1)

ORR, objective response rate; PFS, progression-free survival; DOR duration of response

Authors' Conclusions	The combination of avutometinib + defactinib at the doses studied produced clinically meaningful ORRs, DOR, and PFS; results support the use of avutometinib + defactinib as a new standard therapy for women with recurrent LGSOC.
Limitations	Small study population (rare disease) and even smaller *KRAS* mt subgroup (for which treatment is FDA approved); open-label, avutometinib monotherapy has not been compared with placebo (thus, it is uncertain whether the monotherapy comparator is better than placebo); various prior therapies may complicate assessment of the effects of study treatment
Trial Safety Results	All adverse events, including serious skin toxicity, reflect use of prophylactic topical corticosteroids and oral antibiotics. **RAMP-201 Adverse Events** • Fatal adverse reactions included gastrointestinal hemorrhage, intestinal obstruction and large intestine perforation. • Serious adverse reactions most commonly included abdominal pain. • Discontinuations due to adverse reactions most commonly included increased CPK. **Cardiomyopathy Safety Signal.** In consultation with cardiology experts, the FDA review team concluded that there is a safety signal for cardiomyopathy and it has been insufficiently evaluated. Cardiomyopathy was not added to the US Prescribing Information because the risk has not been fully characterized. More data to follow in RAMP-301

THERAPEUTIC ALTERNATIVES AND THEIR PLACE-IN-THERAPY

Drug	VANF	VA Restrictions	FDA Labeling	Supportive evidence[5]	Guidelines and Pathways[3, 4]
Trametinib	PA-F	Restrict to Hematology/ Oncology	Glioma, melanoma, NSCLC, solid tumors with *BRAF V600Em*, anaplastic thyroid cancer	**P2/3 GOG281/LOGS (KRASm, N=30)** PC vs. Trametinib ORR 6 vs. 26% PFS 7.2 vs. 13 mos; HR 0.48; p<0.0001 DOR 5.9 vs. 13.6 mos	**VA Oncology Pathway, LGSOC v3.2025** Recurrent disease, after prior chemotherapy, if no *KRAS*-mutation **NCCN Guidelines (v.2.2026)** Trametinib (category 2A; off-label) or binimetinib (category 2B, ≥ 50% but < 85% consensus; off-label)
Avutometinib + Defactinib	TBD	Non-formulary	Low-grade, serous, recurrent, *KRAS*-mutated ovarian cancer	**RAMP-201 (KRASm, N=57)** Avutometinib/defactinib ORR 44% PFS 22 mos DOR 31.1 mos	**VA Oncology Pathway, LGSOC v3.2025** Recurrent disease, after prior chemotherapy, if *KRAS* mutation positive, recommends avutometinib + defactinib; Alternative is trametinib **NCCN Guidelines (v.2.2026)** Avutometinib + Defactinib is Category 2A in recurrent setting in KRAS-mutation positive disease

DOR, median duration of response in months; PC, physician's choice chemotherapy or hormonal therapy; PFS, median progression-free survival in months

SUMMARY

Background

- LGSOC is a rare tumor, representing < 10% of new epithelial ovarian cancers. Relative to high-grade serous ovarian cancer, LGSOC affects a younger population and tends to be less responsive to chemotherapy. In 30% of patients the driver is the *KRAS* mutation, the most common type of mitogen-activated protein kinase (*MAPK*) mutation.
- Recurrent LGSOC responds poorly to chemotherapy (ORR 0% to 13%), whereas MEKis have produced ORRs of 16% with binimetinib and 26% with trametinib. Discontinuations due to adverse reactions occurred in about one third of study populations with these treatments.

Summary of Evidence	• The phase 2 OL RAMP-201 RCT showed that, relative to avutometinib 4 mg BIW, the combination of oral avutometinib 3.2 mg BIW + defactinib 200 mg BID was numerically better in ORR and numerically comparable/inferior in PFS. • Combination therapy is more toxic than avutometinib monotherapy, but overall the adverse reactions were manageable with dose adjustments or holds. • Indirect historical comparisons between avutometinib + defactinib and other targeted therapies for recurrent LGSOC (binimetinib and trametinib) are limited by the use of different comparators (avutometinib monotherapy for combination avutometinib + defactinib vs chemotherapy for binimetinib and trametinib). The ongoing phase 3 RCT may provide data on the effects of avutometinib + defactinib relative to chemotherapy. • FDA concluded that the ORR of 43.9% (95% CI 30.7%, 57.6%) based on an early analysis of 57 patients enrolled in the noncomparative phase of the RAMP-201 study (evaluating combination avutometinib and defactinib) improved upon the ORR (range, 9% to 28%) observed with other available therapies for a population with a high unmet need and limited treatment options. • Differences to note when indirectly comparing trials: RAMP-201 allowed prior MEKi therapy (22% included) whereas GOG281 did not; RAMP-201 did not have a control arm whereas GOG281 had a comparator arm • Trametinib and avutometinib/defactinib have both demonstrated activity in KRASm, recurrent LGSOC population; ORR appear to be comparable; PFS is notably different and although the DOR is impressive, it was not reported for trametinib.

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References

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