DOSING AND SAFETY

GUIDE



A clinical tool for dose modifications for adverse events to help patients remain on treatment

AVMAPKI® FAKZYNJA® CO-PACK
(avutometinib capsules; defactinib tablets)
0.8 mg; 200 mg

INDICATION

Avmapki Fakzynja Co-Pack is indicated for the 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. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- **Ocular Toxicities:** Ocular toxicities, including visual impairment and vitreoretinal disorders, occurred. Perform comprehensive ophthalmic evaluation at baseline, prior to cycle 2, every three cycles thereafter, and as clinically indicated. Withhold Avmapki Fakzynja Co-Pack for ocular toxicities until improvement at the same or reduced dose. Permanently discontinue Avmapki Fakzynja Co-Pack for any grade 4 toxicity.

Please see additional Important Safety Information throughout and click here for full Prescribing Information.

Avmapki Fakzynja Co-Pack dosing schedule: A 4-week cycle

The dosing schedule of 3 weeks on and 1 week off may help mitigate the accumulation of toxicities and contribute to a low discontinuation rate[1,2]

Avmapki Fakzynja Co-Pack is taken during the first 3 weeks, as follows[1]:

Avmapki



3.2 mg (4 capsules) = 1 DOSE

- One dose on **Day 1** and **Day 4** of **Weeks 1, 2, and 3**
- At the same time **with food***

Fakzynja



200 mg (1 tablet) = 1 DOSE

- One dose, **2 times a day,** on **Weeks 1, 2, and 3**
- **With food***

Medications should be refrigerated between 36°F and 46°F (2°C to 8°C) in the original bottles

Week 4
No medication

This completes 1 treatment cycle

Continue 4-week cycle until disease progression or unacceptable toxicity

Product images shown are not actual size.

*Capsules and tablets should be swallowed whole. Capsules and tablets should not be chewed, broken, opened, or crushed.

IMPORTANT SAFETY INFORMATION (CONT'D)

Warnings and Precautions (cont'd)

- **Serious Skin Toxicities:** Skin toxicities, including photosensitivity and severe cutaneous adverse reactions (SCARs), occurred. Adhere to concomitant medications. Monitor for skin toxicities and interrupt, reduce or permanently discontinue Avmapki Fakzynja Co-Pack based on severity, tolerability and duration.

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Additional dosing guidance[1]

If your patient...	They should...
Misses a dose (Avmapki by >24 hours or Fakzynja by >6 hours)	• Skip the missed dose and take the next scheduled dose as prescribed • Not take two doses at the same time to make up for a missed dose
Vomits after taking Avmapki or Fakzynja	• Not take an additional dose • Take the next scheduled dose as prescribed
Takes antacids or H2 receptor antagonists	• Avoid concomitant use with Avmapki Fakzynja Co-Pack • Take Fakzynja 2 hours before or 2 hours after the administration of a locally acting antacid if use of an acid reducing agent cannot be avoided

H2, histamine-2 (as in H2 receptor antagonists).

IMPORTANT SAFETY INFORMATION (CONT'D)

Warnings and Precautions (cont'd)

- **Hepatotoxicity:** Monitor liver function tests prior to each cycle, on day 15 of the first 4 cycles, and as clinically indicated. Withhold, reduce or discontinue Avmapki Fakzynja Co-Pack based on severity and persistence of abnormality.

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The safety of Avmapki Fakzynja Co-Pack was evaluated in RAMP 201, an open-label multicenter study that included 57 adult patients with measurable *KRAS*-mutated recurrent LGSOC[1]

- **Serious AEs** occurred in 32% of patients who received Avmapki Fakzynja Co-Pack
  - The most common (≥2%) serious AEs were sepsis (9.0%), intestinal obstruction (3.6%), pyelonephritis (3.6%), and hydronephrosis (3.6%)
- **Fatal AEs** occurred in 3.6% of patients who received Avmapki Fakzynja Co-Pack including intestinal obstruction (1.8%) and perforation (1.8%)



IMPORTANT SAFETY INFORMATION (CONT'D)

Warnings and Precautions (cont'd)

- **Rhabdomyolysis:** Monitor creatine phosphokinase prior to the start of each cycle, on day 15 of the first four cycles, and as clinically indicated. If increased CPK occurs, evaluate patients for rhabdomyolysis or other causes. Withhold, reduce or permanently discontinue Avmapki Fakzynja Co-Pack based on severity and duration of the adverse reaction.

AE, adverse event.

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No Grade 4 treatment-emergent AEs occurred[1]

Most non-laboratory AEs were Grade 1 or 2[2]

The most common (≥25%) AEs, including laboratory abnormalities, were:

- increased CPK
- nausea
- fatigue
- increased AST
- rash
- diarrhea
- musculoskeletal pain
- edema
- decreased hemoglobin
- increased ALT
- vomiting
- increased blood bilirubin
- increased triglycerides
- decreased lymphocyte count
- abdominal pain
- dyspepsia
- dermatitis acneiform
- vitreoretinal disorders
- increased ALP
- stomatitis
- pruritus
- visual impairment
- decreased platelet count
- constipation
- dry skin
- dyspnea
- cough
- urinary tract infection
- decreased neutrophil count

Please refer to the prescribing information for additional details on AEs.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase.

IMPORTANT SAFETY INFORMATION (CONT'D)

Warnings and Precautions (cont'd)

- **Embryo-Fetal Toxicity:** Avmapki Fakzynja Co-Pack can cause fetal harm. Advise patients of the potential risk to a fetus and to use effective contraception.

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AEs were manageable, mainly with dose holds or reductions, which allowed most patients to stay on therapy[2]

Dosage interruptions occurred in **84%** of patients[1]

- AEs that required dosage interruptions in ≥5% of patients included elevations in CPK (25%), hyperbilirubinemia (25%), diarrhea (12%), edema (11%), fatigue (9%), vision blurred (9%), vitreoretinal disorders (7%), transaminitis (7%), paronychia (5%), nausea (5%), abdominal pain (5%), vomiting (5%), dyspnea (5%), sepsis (5%), and rash (5%)

Following dose interruption, treatment may be resumed at the same or reduced dose depending on the severity and resolution of the AE[1]

Dose reductions occurred in **44%** of patients[1]

- AEs that required dose reductions in ≥5% of patients included elevations in CPK (9%), fatigue (5%), hyperbilirubinemia (5%), and dermatitis acneiform (5%)

Recommended dose reductions for AEs[1]

Avmapki capsule	Fakzynja tablet
	
Reduced dose of Avmapki 2.4 mg (3 capsules) = 1 DOSE	**Reduced dose of Fakzynja** 200 mg (1 tablet) = 1 DOSE
2.4 mg twice weekly for first 3 weeks of each 4-week cycle	200 mg once daily for first 3 weeks of each 4-week cycle

Product images shown are not actual size.

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AEs were manageable, mainly with dose holds or reductions, which allowed most patients to stay on therapy (cont'd)[2]

Permanent discontinuation occurred in **14%** of patients[1]

- The AEs leading to permanent discontinuation included elevations in CPK, dyspnea, malaise, decreased glomerular filtration rate, hyperbilirubinemia, increased ALT, and abdominal pain (1.8% each)

Permanent discontinuation for AEs[1]

- Permanently discontinue both Avmapki and Fakzynja in patients unable to tolerate after one dose reduction of both products

Patients maintained a high relative dose intensity (mean actual/planned cumulative dose) for both Avmapki (0.82) and Fakzynja (0.75)[3]

- AEs were manageable mainly with dose holds or reductions, allowing most patients to have prolonged exposure and remain on treatment until disease progression. This was demonstrated by the high relative dose intensity (mean, 0.8) and the 14% discontinuation rate due to AEs[1,2]

View the reduced dosing calendar
A downloadable resource to help patients on a modified dosing schedule track their treatment

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Avmapki Fakzynja Co-Pack can cause ocular AEs, including visual impairment and vitreoretinal disorders[1]

Incidence

- Ocular toxicities occurred in 68% of patients
- 26% experienced vitreoretinal disorders, including retinal detachment (9%) and retinal vein occlusion (0.7%)
- 29% had ongoing ocular events at last follow-up

Common ocular AEs (≥5%)

- Visual impairment (38%)
- Dry eye (13%)
- Orbital/periorbital edema (8%)
- Vitreous floaters (5%)

Median time to onset

- 5 days (range, 1 to 943 days) for symptomatic ocular AEs
- 27 days (range, 2 to 535 days) for retinal detachment
- 112 days (range, 23 to 943 days) for asymptomatic ocular AEs

Dose modifications due to AEs

- 13% required dose interruption
- One patient had a dose reduction

Recommended monitoring strategies

- Conduct a comprehensive ophthalmic exam
  - At baseline
  - Prior to cycle 2 and every 3 cycles thereafter
  - As clinically indicated
- Promptly refer to an eye care professional for any new or worsening ocular signs or symptoms

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Monitor for ocular AEs and withhold, reduce, or permanently discontinue Avmapki Fakzynja Co-Pack based on severity and persistence[1]

AE severity	Dose action	Dose upon resumption
Keratitis		
Confluent superficial keratitis, a cornea epithelial defect, or 3-line or more loss in best corrected distance visual acuity	Withhold dose until resolved to nonconfluent superficial keratitis	Resume at **same dose**
Corneal ulcer or stromal opacity or best corrected distance visual acuity 20/200 or worse		Resume at **reduced dose**
Corneal perforation	Permanently discontinue	
Blurred vision		
BCVA worse than baseline but no worse than 20/200	Withhold dose until resolution to baseline or 20/40, whichever is worse	Resume at **same dose**
BCVA 20/200 or worse		Resume at **reduced dose**
Conjunctivitis		
Confluent superficial punctate staining, moderate to severe vasodilation	Withhold dose until resolution to nonconfluent superficial keratitis	Resume at **same dose**
Conjunctival ulcer or neovascularization		Resume at **reduced dose**

AE severity	Dose action	Follow-up
Retinal pigment epithelial (RPE) detachment		
First occurrence	None	Repeat OCT examination in 2 weeks
First follow-up OCT examination and RPE present	Reduce dose	
Second follow-up OCT examination and RPE present and/or loss of 1 line in BCVA	Withhold dose	
Third follow-up OCT examination	Resume at reduced dose if RPE resolving/resolved Permanently discontinue if no resolution	–

BCVA, best corrected visual acuity;
OCT, optical coherence tomography.

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Avmapki Fakzynja Co-Pack can cause serious skin toxicities, including SCARs[1]

Cases of acute generalized exanthematous pustulosis, erythema multiforme, and drug reaction with eosinophilia and systemic symptoms have been reported in clinical trials of avutometinib (a drug in Avmapki Fakzynja Co-Pack)

Incidence

- Skin toxicities occurred in 94% of patients
- 12% of patients had Grade 3 skin reactions, including dermatitis acneiform (7%), rash (7%), and pruritus (1.5%)
- 10% of patients developed bacterial skin infections
- 66% of patients had ongoing skin toxicity at last follow-up

Common skin AEs (≥10%)

- Rash (67%)
- Dermatitis acneiform (43%)
- Dry skin (43%)
- Pruritus (32%)
- Photosensitivity (13%)

Median time to onset

- 14 days (range, 1 to 500 days) for first skin toxicity

Dose modifications due to AEs

- 10% required dose interruption
- 7% required dose reduction
- 0.7% required permanent discontinuation

SCARs, severe cutaneous adverse reactions.

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Recommended prophylactic strategies

- Administer topical corticosteroids (applied to the face, scalp, neck, upper chest, and upper back) and systemic oral antibiotics at initiation of Avmapki Fakzynja Co-Pack and during at least the first 2 cycles
- Limit unnecessary exposure to sunlight and apply daily sunscreen (SPF ≥30)

Monitor for skin toxicity and withhold, reduce dose, or permanently discontinue Avmapki Fakzynja Co-Pack based on severity and persistence[1]

AE Severity*	Dose action	Dose upon resumption
Rash		
Grade ≤2: Not responsive to supportive care or recurs after resolution to Grade ≤1	Consider withholding dose	–
Grade ≤2: Intolerable	Reduce dose	–
Grade 3	Withhold dose until resolved to Grade 2	Resume at **reduced dose** Resume at **same dose** if resolved to Grade ≤1
Grade 3: Recurrent despite dose reduction	Permanently discontinue	
Grade 4		

*Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.
SPF, sun protection factor.

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Avmapki Fakzynja Co-Pack can cause hepatotoxicity[1]

Incidence

- Increased AST (73%), bilirubin (51%), ALT (49%), and ALP (46%) occurred
- Grade 3-4 elevations in ALT was 3%, AST was 3%, bilirubin was 2.3%, and ALP was 0.8%

Mechanism

- Defactinib (a component of Avmapki Fakzynja Co-Pack) may increase bilirubin by inhibiting enzymes responsible for metabolizing (uridine diphosphate-glucuronosyltransferase [UGT] 1A1) and transporting (organic anion transporting polypeptides [OATP] 1B1/1B3) bilirubin

Dose modifications due to AEs

- Elevations in one or more liver-related laboratory values led to dose interruption for 20%, dose reduction for 2.2%, and permanent discontinuation for 0.7%

Recommended monitoring strategies

- Monitor liver-related laboratory values
  - Prior to the start of each cycle
  - On Day 15 of the first 4 cycles
  - As clinically indicated

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Monitor for AEs related to hepatotoxicity and withhold or reduce Avmapki Fakzynja Co-Pack based on severity and duration[1]

AE Severity*	Dose action	Dose upon resumption
Hepatotoxicity		
Grade 2 hyperbilirubinemia (without Gilbert's syndrome) with **Grade ≤1 increase in AST and/or ALT**	Withhold dose until hyperbilirubinemia Grade ≤1	Resume at **same dose**
Grade 2 hyperbilirubinemia with **Grade 2 increase in AST and/or ALT**	Withhold dose until hyperbilirubinemia Grade ≤1 or baseline	
Grade 3 hyperbilirubinemia associated with **Grade ≤1 increase in AST and/or ALT**		
Recurrent Grade 3 hyperbilirubinemia associated with **Grade ≤1 increase in AST and/or ALT**	Withhold dose until hyperbilirubinemia Grade ≤2 or at baseline	Resume at **reduced dose**
Grade 3 increased AST and/or ALT not associated with hyperbilirubinemia	Withhold dose until Grade ≤2 or baseline	
Grade 4 hyperbilirubinemia associated with **Grade ≤1 increase in AST and/or ALT**	Withhold dose	Resume at **reduced dose** if resolved within one week

Permanently discontinue Avmapki Fakzynja Co-Pack if the following AEs related to hepatotoxicity occur[1]

AE Severity*	Dose action	Dose upon resumption
Hepatotoxicity		
Grade 2 hyperbilirubinemia associated with **Grade >2 increase in AST and/or ALT**	Permanently discontinue	
Grade 3 hyperbilirubinemia associated with **Grade ≥2 increase in AST and/or ALT**		
Grade 4 increase in AST and/or ALT		
Grade 4 hyperbilirubinemia associated with **Grade ≤1 increase in AST and/or ALT** that does not resolve within 1 week		
Grade 4 hyperbilirubinemia associated with **Grade ≥2 increase in AST and/or ALT**		

*Severity as defined by NCI CTCAE version 5.0.

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Avmapki Fakzynja Co-Pack can cause increased CPK[1]

Rhabdomyolysis has occurred in a patient treated with Avmapki Fakzynja Co-Pack at the recommended dosage

Incidence

- Increased CPK occurred in 75% of patients, including Grade 3-4 elevations in 18% of patients
  - Among those with elevated CPK, 19% had concurrent creatinine increase and 10% experienced myalgia
- Elevation of CPK >10 times the baseline value with a concurrent increase in serum creatinine of ≥1.5 times the baseline value occurred in 0.7% of patients

Dose modifications due to AEs

- Increased CPK resulted in
  - Dose interruption for 22% of patients
  - Dose reduction for 7% of patients
  - Discontinuation for 2.9% of patients

Recommended monitoring strategies

- Monitor CPK levels
  - Prior to the start of each cycle
  - On Day 15 of the first four cycles
  - As clinically indicated
- If increased CPK occurs, evaluate patients for rhabdomyolysis or other causes

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Monitor for AEs related to rhabdomyolysis and withhold, reduce dose, or permanently discontinue Avmapki Fakzynja Co-Pack based on severity and duration[1]

AE Severity*	Dose action	Dose upon resumption
Increased creatine phosphokinase (CPK)		
Grade 3	Withhold dose	Resume at **same dose** if improves to Grade ≤1 within 3 weeks **Permanently discontinue** for CPK elevation longer than 3 weeks
Grade 4	Withhold dose until resolved to Grade 2	Resume at **reduced dose** if improves to Grade ≤1 within 3 weeks **Permanently discontinue** for CPK elevation longer than 3 weeks
Any grade CPK elevation with rhabdomyolysis or other event related to CPK elevation	Permanently discontinue	

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Embryo-fetal toxicity[1]

Based on the mechanisms of action, Avmapki Fakzynja Co-Pack can cause fetal harm when administered to a pregnant woman. Inhibition of either molecular pathway has been associated with embryo-fetal anomalies and lethality in animals

- Advise patients of the potential risk to a fetus
- Advise lactating women not to breastfeed
- Inform patients that Avmapki Fakzynja Co-Pack may impair fertility in males and females

Recommended management strategies

- Advise **females** of reproductive potential to use effective contraception during treatment with Avmapki Fakzynja Co-Pack and for 1 month after the last dose
- Advise **males** with female partners of reproductive potential to use effective contraception during treatment with Avmapki Fakzynja Co-Pack and for 4 months after the last dose

IMPORTANT SAFETY INFORMATION (CONT'D)

Drug Interactions

- **Strong and moderate CYP3A4 inhibitors:** Avoid concomitant use with Avmapki Fakzynja Co-Pack.
- **Strong and moderate CYP3A4 inducers:** Avoid concomitant use with Avmapki Fakzynja Co-Pack.
- **Warfarin:** Avoid concomitant use of Avmapki Fakzynja Co-Pack with warfarin and use an alternative to warfarin.
- **Gastric acid reducing agents:** Avoid concomitant use of Avmapki Fakzynja Co-Pack with proton pump inhibitors (PPIs) or H2 receptor antagonists. If use of an acid-reducing agent cannot be avoided, administer Fakzynja 2 hours before or 2 hours after the administration of a locally acting antacid.

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Other AEs: Dosing modifications of Avmapki Fakzynja Co-Pack[1]

AE Severity*	Dose action	Dose upon resumption
Grade 2	Consider withholding dose if AE does not respond to supportive care or recurs after resolution to Grade ≤1	–
Grade 3: First occurrence	Withhold dose until resolved to baseline or Grade ≤1	Resume at **same dose**
Grade 3: Second occurrence		Resume at **reduced dose**
Grade 3: Recurrent despite dose reduction	Permanently discontinue	
Grade 4		

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A recommended approach to help your patients remain on treatment[1,2]

- **Initiate treatment** using the standard dosing schedule for the 4-week cycle
- **Monitor for AEs** taking into consideration the warnings and precautions including ocular toxicities, serious skin toxicities, hepatotoxicity, rhabdomyolysis, and embryo-fetal toxicity
- **Manage AEs** with dose modifications based on severity and persistence (dose interruptions, 84% of patients; dose reductions, 44%; and, permanent discontinuation, 14%)
- **Continue treatment** until disease progression or unacceptable toxicity



References: 1. Avmapki Fakzynja Co-Pack. Prescribing Information. Verastem, Inc; 2025. **2.** Banerjee SN, et al. *J Clin Oncol*. 2025;43(25):2782-2792. **3.** Data on file, Verastem Inc. 2025.

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