HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AVMAPKI™ FAKZYNJA™ CO-PACK safely and effectively. See full prescribing information for AVMAPKI™ FAKZYNJA™ CO-PACK.

AVMAPKI™ FAKZYNJA™ CO-PACK (avutometinib capsules; defactinib tablets), co-packaged for oral use

Initial U.S. Approval: 2025

----------INDICATIONS AND USAGE----------
AVMAPKI FAKZYNJA CO-PACK, a combination of avutometinib and defactinib, each kinase inhibitors, 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. (1,14)

----------DOSAGE AND ADMINISTRATION----------
- AVMAPKI 3.2 mg administered orally twice weekly (Day 1 and Day 4) for the first 3 weeks of each 4-week cycle. (2.3)
- FAKZYNJA 200 mg administered orally twice daily for the first 3 weeks of each 4-week cycle. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
- AVMAPKI Capsules: 0.8 mg of avutometinib (3)
- FAKZYNJA Tablets: 200 mg of defactinib (3)

----------CONTRAINDICATIONS----------
None. (4)

----------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. (2.4, 5.1)
- 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. (2.4, 5.2)
- 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. (2.4, 5.3)
- 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. (2.4, 5.4)
- 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. (5.5, 8.1, 8.3)

----------ADVERSE REACTIONS----------
The most common (≥ 25%) adverse reactions, including laboratory abnormalities, were increased creatine phosphokinase, nausea, fatigue, increased aspartate aminotransferase, rash, diarrhea, musculoskeletal pain, edema, decreased hemoglobin, increased alanine aminotransferase, vomiting, increased blood bilirubin, increased triglycerides, decreased lymphocyte count, abdominal pain, dyspepsia, dermatitis acneiform, vitreoretinal disorders, increased alkaline phosphatase, stomatitis, pruritus, visual impairment, decreased platelet count, constipation, dry skin, dyspnea, cough, urinary tract infection, and decreased neutrophil count. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Verastem at 1-833-633-8786 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Strong and moderate CYP3A4 inhibitors: Avoid concomitant use with AVMAPKI FAKZYNJA CO-PACK. (7.1)
- Strong and moderate CYP3A4 inducers: Avoid concomitant use with AVMAPKI FAKZYNJA CO-PACK. (7.1)
- Warfarin: Avoid concomitant use of AVMAPKI FAKZYNJA CO-PACK with warfarin and use an alternative to warfarin. (7.2)
- 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. (7.1)

----------USE IN SPECIFIC POPULATIONS----------
Lactation: Advise not to breastfeed. (8.2)
Infertility: May impair fertility in males and females. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 05/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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 *[see Clinical Studies (14)].* Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of recurrent LGSOC with AVMAPKI FAKZYNJA CO-PACK based on the presence of a *KRAS* mutation in tumor specimens *[see Clinical Studies (14)]*.

An FDA-approved test for the detection of a *KRAS* mutation in LGSOC for selecting patients for treatment with AVMAPKI FAKZYNJA CO-PACK is not available.

2.2 Eye Exams and Prophylactic Skin Medications

Ophthalmic Exams

Conduct a comprehensive ophthalmic exam at baseline, prior to cycle 2, and every three cycles thereafter regardless of baseline exam findings, and as clinically indicated *[see Warnings and Precautions (5.1)].*

Prophylactic Medications for Skin Reactions

With initiation of and during at least the first 2 cycles of AVMAPKI FAKZYNJA CO-PACK administer *[see Warnings and Precautions (5.2)]*:

- Topical corticosteroid (applied to the face, scalp, neck, upper chest and upper back)
- Systemic oral antibiotics

2.3 Recommended Dosage and Administration

AVMAPKI Capsules
The recommended dosage of AVMAPKI capsules is 3.2 mg (four 0.8 mg capsules) taken orally twice weekly (Day 1 and Day 4) for the first 3 weeks of each 4-week cycle until disease progression or unacceptable toxicity.

Take AVMAPKI at the same time with each dose. AVMAPKI should be taken with food *[see Clinical Pharmacology (12.3)]*. Swallow capsules whole. Do not chew, break, or open the capsules.

If a dose of AVMAPKI is missed by more than 24 hours, skip the missed dose and take the next scheduled dose as prescribed. Do not take two doses at the same time to make up for a missed dose. If vomiting occurs after taking AVMAPKI, do not take an additional dose. Take the next scheduled dose as prescribed.

FAKZYNJA Tablets
The recommended dosage of FAKZYNJA tablets is 200 mg (one tablet) taken orally twice daily for the first 3 weeks of each 4-week cycle until disease progression or unacceptable toxicity.

Take each dose of FAKZYNJA with food *[see Clinical Pharmacology (12.3)]*. Swallow tablets whole. Do not chew, break or crush the tablets.

If a dose of FAKZYNJA is missed by more than 6 hours, skip the missed dose and take the next scheduled dose as prescribed. Do not take two tablets at the same time to make up for a missed dose. If vomiting occurs after taking FAKZYNJA, do not take an additional dose. Take the next scheduled dose as prescribed.

2.4 Dosage Modifications for Adverse Reactions

Dose reductions due to adverse reactions due to AVMAPKI FAKZYNJA CO-PACK are summarized in Table 1.

Table 1 Recommended Dose Reductions for Adverse Reactions

Dose Level	**AVMAPKI Capsule**	**FAKZYNJA Tablet**
Starting dose	3.2 mg twice weekly for first 3 weeks of each 4-week cycle	200 mg twice daily for first 3 weeks of each 4-week cycle
Dose reduction	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
Permanently discontinue both AVMAPKI and FAKZYNJA in patients unable to tolerate after one dose reduction of both products.		

Dosage modifications for adverse reactions to AVMAPKI FAKZYNJA CO-PACK are summarized in Table 2.

Table 2 AVMAPKI FAKZYNJA CO-PACK Dosage Modifications

Adverse Reaction	**Severity[1]**	**Dose Modification**
Keratitis *[see Warnings and Precautions (5.1)]*	Confluent superficial keratitis, a cornea epithelial defect, or 3-line or more loss in best corrected distance visual acuity	Withhold AVMAPKI FAKZYNJA CO-PACK until resolved to nonconfluent superficial keratitis, then resume at same dose.
	Corneal ulcer or stromal opacity or best corrected distance visual acuity 20/200 or worse	Withhold AVMAPKI FAKZYNJA CO-PACK until resolved to nonconfluence superficial keratitis, then resume at reduced dose.

	Corneal perforation	Permanently discontinue AVMAPKI FAKZYNJA CO-PACK.
Blurred vision *[see Warnings and Precautions (5.1)]*	BCVA worse than baseline but no worse than 20/200	Withhold AVMAPKI FAKZYNJA CO-PACK until resolution to baseline or 20/40, whichever is worse, then resume treatment at same dose.
	BCVA 20/200 or worse	Withhold AVMAPKI FAKZYNJA CO-PACK until resolution to baseline or 20/40, whichever is worse, then resume at reduced dose.
Conjunctivitis *[see Warnings and Precautions (5.1)]*	Confluent superficial punctate staining, moderate to severe vasodilation	Withhold AVMAPKI FAKZYNJA CO-PACK until resolution to nonconfluent superficial keratitis, then resume at same dose.
	Conjunctival ulcer or neovascularization	Withhold AVMAPKI FAKZYNJA CO-PACK until resolution to nonconfluent superficial keratitis, then resume at reduced dose.
Retinal Pigment Epithelial (RPE) Detachment *[see Warnings and Precautions (5.1)]*	N/A	First occurrence • Repeat Optical Coherence Tomography (OCT) examination in two weeks. First follow-up OCT examination and RPE present • Reduce dose of AVMAPKI FAKZYNJA CO-PACK • Repeat OCT examination in two weeks. Second follow-up OCT examination and RPE present and/or loss of 1 line in BCVA: • Withhold AVMAPKI FAKZYNJA CO-PACK • Repeat OCT examination in two weeks. Third follow-up OCT examination • RPE resolving/resolved, resume at reduced dose. • No resolution, permanently discontinue AVMAPKI FAKZYNJA CO-PACK

Rash *[see Warnings and Precautions (5.2)]*	Grade ≤ 2	Consider withholding AVMAPKI FAKZYNJA CO-PACK if rash does not respond to supportive care or recurs after resolution to Grade ≤1. Dose reduce AVMAPKI FAKZYNJA CO-PACK for intolerable Grade 2.
	Grade 3	Withhold AVMAPKI FAKZYNJA CO-PACK until resolved to Grade 2 then resume at reduced dose. Resume at same dose if resolved to Grade ≤1. Permanently discontinue AVMAPKI FAKZYNJA CO-PACK for recurrent Grade 3 despite dose reduction.
	Grade 4	Permanently discontinue AVMAPKI FAKZYNJA CO-PACK.
Hepatotoxicity *[see Warnings and Precautions (5.3)]*	Grade 2	Withhold AVMAPKI FAKZYNJA CO-PACK for • Grade 2 hyperbilirubinemia (without Gilbert's syndrome) with Grade ≤1 increase in AST and/or ALT until hyperbilirubinemia Grade ≤1, then resume at same dose. • Grade 2 hyperbilirubinemia with Grade 2 increase in AST and/or ALT until hyperbilirubinemia Grade ≤1 or baseline, then resume at same dose. Permanently discontinue AVMAPKI FAKZYNJA CO-PACK for Grade 2 hyperbilirubinemia associated with Grade >2 increase in AST and/or ALT.
	Grade 3	Withhold AVMAPKI FAKZYNJA CO-PACK • if Grade 3 hyperbilirubinemia is associated with Grade ≤1 increase in AST and/or ALT until hyperbilirubinemia Grade

		≤1 or at baseline, then resume at same dose. • if recurrent Grade 3 hyperbilirubinemia is associated with Grade ≤1 increase in AST and/or ALT until hyperbilirubinemia Grade ≤2 or at baseline, then resume at reduced dose. • if Grade 3 increased AST and/or ALT is not associated with hyperbilirubinemia until Grade ≤2 or at baseline, then resume at reduced dose. Permanently discontinue AVMAPKI FAKZYNJA CO-PACK for Grade 3 hyperbilirubinemia associated with Grade ≥2 increase in AST and/or ALT.
	Grade 4	Withhold AVMAPKI FAKZYNJA CO-PACK for • Grade 4 hyperbilirubinemia associated with Grade ≤1 increase in AST and/or ALT and if resolves within one week resume at reduced dose. Permanently discontinue AVMAPKI FAKZYNJA CO-PACK for • 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.
Increased Blood Creatine Phosphokinase (CPK) *[see Warnings and Precautions (5.4)]*	Grade 3	Withhold AVMAPKI FAKZYNJA CO-PACK, if improves to Grade ≤1 within three weeks resume at same dose. Permanently discontinue AVMAPKI FAKZYNJA CO-PACK

		for CPK elevation longer than three weeks.
	Grade 4	Withhold AVMAPKI FAKZYNJA CO-PACK, if improves to Grade ≤1 within three weeks resume at reduced dose. Permanently discontinue AVMAPKI FAKZYNJA CO-PACK for CPK elevation longer than three weeks.
	Any grade CPK elevation with rhabdomyolysis or other event related to CPK elevation	Permanently discontinue AVMAPKI FAKZYNJA CO-PACK
Other Adverse Reactions	Grade 2	Consider withholding AVMAPKI FAKZYNJA CO-PACK if adverse reaction does not respond to supportive care or recurs after resolution to Grade ≤1.
	Grade 3	First occurrence: Withhold AVMAPKI FAKZYNJA CO-PACK until resolved to baseline or Grade ≤1 then resume at same dose. Second occurrence: Withhold AVMAPKI FAKZYNJA CO-PACK until resolved to baseline or Grade ≤1 then resume at reduced dose. Permanently discontinue AVMAPKI FAKZYNJA CO-PACK for recurrent Grade 3 despite dose reduction.
	Grade 4	Permanently discontinue AVMAPKI FAKZYNJA CO-PACK.

N/A: Not applicable
[1] Severity as defined by National Center Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0

3 DOSAGE FORMS AND STRENGTHS

AVMAPKI FAKZYNJA CO-PACK is AVMAPKI (avutometinib) capsules co-packaged with FAKZYNJA (defactinib) tablets.

- AVMAPKI capsules contain 0.8 mg avutometinib and are white capsules with “6766” printed on the cap and the strength “0.8 mg” printed on the body in black ink.
- FAKZYNJA tablets contain 200 mg defactinib and are white to off-white tablets, oval and debossed with “VS2” on one side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Ocular Toxicities

AVMAPKI FAKZYNJA CO-PACK can cause ocular adverse reactions, including visual impairment and vitreoretinal disorders.

Ocular adverse reactions occurred in 68% of patients with recurrent LGSOC treated with AVMAPKI FAKZYNJA CO-PACK. Common ocular adverse reactions (≥ 5%) were visual impairment (38%), dry eye (13%), orbital/periorbital edema (8%), and vitreous floaters (5%). Thirty-five patients (26%) experienced vitreoretinal disorders, including retinal detachment (9%), and retinal vein occlusion (0.7%). Eighteen patients (13%) experienced an ocular adverse reaction that resulted in dose interruption of AVMAPKI FAKZYNJA CO-PACK and one patient experienced an ocular adverse reaction that resulted in dose reduction.

The median time to onset of symptomatic ocular adverse reactions was 5 days (range 1 to 943 days) and to onset of asymptomatic ocular adverse reactions was 112 days (range 23 to 943 days). The median time to onset of retinal detachment was 27 days (range 2 to 535 days). Of the patients who experienced ocular adverse reactions, 29% had ongoing ocular events at last follow-up.

Refer patients to a qualified eye care professional for a comprehensive ophthalmic exam at baseline, prior to cycle 2, every three cycles thereafter, and as clinically indicated. Promptly refer patients to an eye care professional for any new or worsening ocular signs or symptoms.

Monitor for ocular adverse reactions and withhold, reduce, or permanently discontinue AVMAPKI FAKZYNJA CO-PACK based on severity and persistence of ocular adverse reactions *[see Dosage and Administration (2.4)].*

5.2 Serious Skin Toxicities

AVMAPKI FAKZYNJA CO-PACK can cause serious skin toxicities, including Severe Cutaneous Adverse Reactions (SCARs). 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).

Skin toxicities occurred in 94% of patients with recurrent LGSOC treated with AVMAPKI FAKZYNJA CO-PACK. The most common skin toxicities (≥ 10%) were rash (67%), dermatitis acneiform (43%), dry skin (43%), pruritus (32%), and photosensitivity (13%). Grade 3 skin reactions occurred in 12% of patients including dermatitis acneiform (7%), rash (7%), and pruritus (1.5%). Thirteen patients (10%) developed bacterial skin infections. Skin toxicity led to dose interruption of AVMAPKI FAKZYNJA CO-PACK in 10%, to dose reduction in 7%, and to permanent discontinuation in 0.7% of patients. The median time to onset of the first skin toxicity was 14 days (range 1 to 500 days). At last follow-up, 66% of patients had ongoing skin toxicity.

Patients in RAMP-201 used topical corticosteroids (applied to the face, scalp, neck, upper chest and upper back) and systemic oral antibiotics for prophylaxis of skin adverse reactions. These medications were initiated at the start of AVMAPKI FAKZYNJA CO-PACK and administered during at least the first two cycles of treatment.

Limit unnecessary exposure to sunlight and apply daily sunscreen (sun protection factor [SPF] ≥ 30). Monitor for skin toxicity and withhold, reduce dose, or permanently discontinue AVMAPKI FAKZYNJA CO-PACK based on severity and persistence *[see Dosage and Administration (2.4)].*

5.3 Hepatotoxicity

AVMAPKI FAKZYNJA CO-PACK can cause hepatotoxicity.

In patients with recurrent LGSOC who received AVMAPKI FAKZYNJA CO-PACK, increased AST (73%), bilirubin (51%), ALT (49%), and alkaline phosphatase (46%) occurred. Grade 3-4 elevations in ALT was 3%, AST was 3%, bilirubin was 2.3% and alkaline phosphatase was 0.8%. 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% of patients.

Increased blood bilirubin may be attributed to defactinib (a component of AVMAPKI FAKZYNJA CO-PACK) due to the inhibition of enzymes responsible for metabolizing (uridine diphosphate-glucuronosyltransferase (UGT)1A1) and transporting (Organic Anion Transporting Polypeptides (OATP)1B1/1B3) bilirubin *[see Clinical Pharmacology (12.3)].*

Monitor liver related laboratory values prior to the start of each cycle, on day 15 of the first four cycles, and as clinically indicated. Withhold, reduce dose, or permanently discontinue AVMAPKI FAKZYNJA CO-PACK based on severity and duration of these adverse reactions *[see Dosage and Administration (2.4)].*

5.4 Rhabdomyolysis

AVMAPKI FAKZYNJA CO-PACK can cause increased creatine phosphokinase (CPK). Increased CPK occurred in 75% of patients with recurrent LGSOC treated with AVMAPKI FAKZYNJA CO-PACK, including Grade 3-4 elevations in 18% of patients. Among the patients who experienced an elevation in CPK, concurrent increase in creatinine occurred in 19% (n=19/102) and myalgia occurred in 10% (n=10/102). 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. Increased CPK resulted in dose interruption for 22%, in dose reduction for 7%, and in discontinuation for 2.9% of patients. Rhabdomyolysis has occurred in a patient with LGSOC treated with AVMAPKI FAKZYNJA CO-PACK at the recommended dosage in a clinical trial.

Monitor CPK 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 reactions *[see Dose Modifications (2.4)]*.

5.5 Embryo-Fetal Toxicity

Based on the mechanisms of action, AVMAPKI FAKZYNJA CO-PACK can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. Inhibition of either molecular pathway has been associated with embryo-fetal anomalies and lethality in animals.

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. 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 male patients 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 *[see Use in Specific Populations (8.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Ocular Toxicities *[see Warnings and Precautions (5.1)]*
- Serious Skin Toxicities *[see Warnings and Precautions (5.2)]*
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*
- Rhabdomyolysis *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in Warnings and Precautions reflect exposure to the AVMAPKI FAKZYNJA CO-PACK (combination of AVMAPKI 3.2 mg twice weekly and FAKZYNJA 200 mg twice daily) for the first 3 weeks in a 4-week cycle until disease progression or unacceptable toxicity in 136 adult patients with recurrent LGSOC treated on RAMP-201 and FRAME (NCT03875820). The median duration of treatment was 10 months (range 0 to 51 months).

RAMP-201

The safety of AVMAPKI FAKZYNJA CO-PACK was evaluated in RAMP-201, a single-arm multicenter trial in 57 patients with *KRAS*-mutated recurrent LGSOC *[see Clinical Studies (14)]*. Patients received AVMAPKI FAKZYNJA CO-PACK (AVMAPKI 3.2 mg twice weekly and FAKZYNJA 200 mg twice daily) for the first 3 weeks in a 4-week cycle until disease progression or unacceptable toxicity. The median duration of treatment was 12 months (range 0.03-40).

Serious adverse reactions occurred in 32% of patients who received AVMAPKI FAKZYNJA CO-PACK. The most common (≥2%) serious adverse reactions were sepsis (9%), intestinal obstruction (3.6%), pyelonephritis (3.6%), and hydronephrosis (3.6%). Fatal adverse reactions occurred in 3.6% of patients who received AVMAPKI FAKZYNJA CO-PACK, including intestinal obstruction (1.8%) and perforation (1.8%).

Permanent discontinuation of AVMAPKI FAKZYNJA CO-PACK due to an adverse reaction occurred in 14% of patients. The adverse reactions leading to permanent discontinuation included elevations in creatine phosphokinase, dyspnea, malaise, decreased glomerular filtration rate, hyperbilirubinemia, increased alanine aminotransferase, and abdominal pain (1.8% each).

Dosage interruptions of AVMAPKI FAKZYNJA CO-PACK due to an adverse reaction occurred in 84% of patients. Adverse reactions which required dosage interruptions in ≥ 5% of patients included elevations in creatine phosphokinase (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%).

Dose reductions of AVMAPKI FAKZYNJA CO-PACK due to an adverse reaction occurred in 44% of patients. Adverse reactions which required dose reductions in ≥ 5% of patients were elevations in creatine phosphokinase (9%), fatigue (5%), hyperbilirubinemia (5%), and dermatitis acneiform (5%).

The most common (≥25%) adverse reactions, including laboratory abnormalities, were increased creatine phosphokinase, nausea, fatigue, increased aspartate aminotransferase, rash, diarrhea, musculoskeletal pain, edema, decreased hemoglobin, increased alanine aminotransferase, vomiting, increased blood bilirubin, increased triglycerides, decreased lymphocyte count, abdominal pain, dyspepsia, dermatitis acneiform, vitreoretinal disorders, increased alkaline phosphatase, stomatitis, pruritus, visual impairment, decreased platelet count, constipation, dry skin, dyspnea, cough, urinary tract infection, and decreased neutrophil count.

Table 3 summarizes the adverse reactions in RAMP-201.

Table 3 Adverse Reactions (≥10%) in Patients with *KRAS*-Mutated Recurrent LGSOC who Received AVMAPKI FAKZYNJA CO-PACK in RAMP-201[1]

Adverse Reaction	**AVMAPKI FAKZYNJA CO-PACK N = 57**	
	All Grades %	**Grade 3 or 4[7] %**
Gastrointestinal disorders		
Nausea	74	1.8
Diarrhea	68	7
Vomiting	49	3.5
Abdominal pain[2]	39	1.8
Dyspepsia[2]	37	0
Stomatitis[2]	35	3.5
Constipation	30	0
Dry mouth	18	0
Decreased Weight	11	0
General disorders and administration site condition		
Fatigue[2]	72	3.5
Edema[2]	67	1.8
Skin and subcutaneous tissue disorders		
Rash[3]	72	3.5
Dermatitis acneiform[4]	37	5.3
Pruritus[2]	35	1.8
Dry skin[2]	30	0
Alopecia[2]	23	0
Photosensitivity[2]	16	0
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[2]	68	1.8
Joint swelling	11	0
Eye disorders		
Vitreoretinal disorders[5]	37	3.5
Visual impairment[6]	35	0
Dry eye	12	0
Respiratory disorders		

Dyspnea[2]	26	5.3
Cough	25	0
Nervous system disorders		
Dizziness	23	1.8
Headache	16	0
Neuropathy peripheral[2]	14	0
Dysgeusia	11	0
Vascular disorders		
Hemorrhage[2]	23	0
Hypertension	16	5.3
Venous thromboembolism[2]	14	5.3
Metabolism and nutrition disorders		
Decreased appetite	18	1.8
Infections and infestations		
Urinary tract infection	25	3.5
Paronychia	14	1.8
Upper respiratory tract infection	11	0

[1] Severity as defined by National Center Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.
[2] Includes multiple terms
[3] Includes: butterfly rash, dermatitis, drug eruption, erythema, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, and rash pruritic
[4] Includes: acne, dermatitis acneiform, folliculitis, perioral dermatitis, and rash pustular
[5] Includes: chorioretinopathy, detachment of retinal pigment epithelium, macular fibrosis, macular hole, maculopathy, retinal detachment, retinal drusen, retinal vein occlusion, retinopathy, serous retinal detachment, serous retinopathy, subretinal fluid, vitreous detachment, and vitreous floaters
[6] Includes: asthenopia, astigmatism, halo vision, metamorphopsia, photophobia, photopsia, vision blurred, visual field defect, and visual impairment
[7] No Grade 4 treatment-emergent adverse events occurred.

Clinically relevant adverse reactions in < 10% of patients who received AVMAPKI FAKZYNJA CO-PACK included urticaria and decreased ejection fraction.

Table 4 summarizes the laboratory abnormalities in RAMP-201.

Table 4 Select Laboratory Abnormalities (≥ 10%) in Patients with *KRAS*-Mutated Recurrent LGSOC who Received AVMAPKI FAKZYNJA CO-PACK in RAMP-201

Laboratory Abnormality	AVMAPKI FAKZYNJA CO-PACK	
	All Grades (%)[1]	Grade 3 or 4 (%)[1]
Chemistry		
Increased creatine phosphokinase	82	19
Increased aspartate aminotransferase	70	3.5
Decreased albumin	70	0
Increased alanine aminotransferase	58	3.5
Increased blood bilirubin	48	3.5
Increased triglycerides	46	3.5
Increased alkaline phosphatase	37	1.8
Decreased potassium	23	9
Hematology		
Decreased hemoglobin	65	5
Decreased lymphocyte count	40	1.8
Decreased platelet count	35	0
Decreased neutrophil count	25	1.8
Urine		
Proteinuria	22	4.4

[1]The denominator used to calculate the rate varied from 45 to 57 based on the number of patients with a baseline value and at least one post-treatment value.

Clinically relevant laboratory abnormalities in < 10% of patients who received AVMAPKI FAKZYNJA CO-PACK included increased INR and prolonged activated partial thromboplastin time.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on AVMAPKI FAKZYNJA CO-PACK

Strong and Moderate CYP3A4 Inhibitors

Avoid concomitant use of AVMAPKI FAKZYNJA CO-PACK with strong or moderate CYP3A4 inhibitors.

Defactinib is a CYP3A4 substrate. Concomitant use of defactinib with a strong CYP3A4 inhibitor increases defactinib exposure *[see Clinical Pharmacology (12.3)],* which may increase the risk of AVMAPKI FAKZYNJA CO-PACK adverse reactions.

Strong and Moderate CYP3A4 Inducers

Avoid concomitant use of AVMAPKI FAKZYNJA CO-PACK with strong or moderate CYP3A4 inducers.

Defactinib is a CYP3A4 substrate. Concomitant use of defactinib with a strong CYP3A4 inducer decreases defactinib exposure, which may reduce the effectiveness of FAKZYNJA *[see Clinical Pharmacology (12.3)]*.

Gastric Acid Reducing Agents
Avoid concomitant use of AVMAPKI FAKZYNJA CO-PACK with proton pump inhibitors (PPIs) or H2 receptor antagonists. If concomitant 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.

Concomitant use of FAKZYNJA with gastric acid reducing agents decreases defactinib exposure, which may reduce the effectiveness of AVMAPKI FAKZYNJA CO-PACK *[see Clinical Pharmacology (12.3)]*.

7.2 Effect of AVMAPKI FAKZYNJA CO-PACK on Other Drugs

Warfarin
Avoid concomitant use of AVMAPKI FAKZYNJA CO-PACK with warfarin. For patients requiring anticoagulation, an alternative to warfarin is recommended. If concomitant use is unavoidable, monitor INR frequently during treatment with AVMAPKI FAKZYNJA CO-PACK.

Cases of bleeding and increased INR occurred in patients taking FAKZYNJA concomitantly with warfarin in clinical trials.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on the mechanisms of action, AVMAPKI FAKZYNJA CO-PACK can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data on the use of AVMAPKI FAKZYNJA CO-PACK in pregnant women to inform a drug-associated risk. Animal reproductive and developmental toxicity studies have not been conducted with avutometinib or defactinib; however, inhibition of either molecular pathway has been associated with embryo-fetal anomalies and lethality in animals. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of avutometinib, defactinib, or their metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise lactating women not to breastfeed during treatment with AVMAPKI FAKZYNJA CO-PACK and for 2 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

AVMAPKI FAKZYNJA CO-PACK can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating treatment with AVMAPKI FAKZYNJA CO-PACK.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with AVMAPKI FAKZYNJA CO-PACK and for 1 month after the last dose.

Males

Advise male patients 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.

Infertility

Based on animal studies, AVMAPKI FAKZYNJA CO-PACK may impair fertility in females and males of reproductive potential. The effects on fertility were not reversible in animals *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of AVMAPKI FAKZYNJA CO-PACK in pediatric patients has not been established.

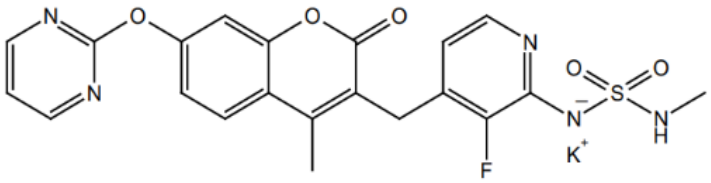
8.5 Geriatric Use

Of the 136 patients in clinical studies of AVMAPKI FAKZYNJA CO-PACK, 29% were age 65 years or older. No overall differences in safety were observed between patients age 65 years or older and younger patients. Clinical studies of AVMAPKI FAKZYNJA CO-PACK did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

11 DESCRIPTION

AVMAPKI FAKZYNJA CO-PACK contains AVMAPKI (avutometinib) capsules co-packaged with FAKZYNJA (defactinib) tablets.

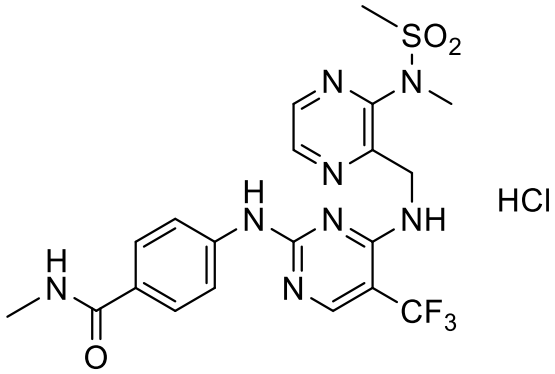
AVMAPKI capsules contain avutometinib, a kinase inhibitor. The chemical name of avutometinib is N-(3-Fluoro-4-{[4-methyl-7-(2-pyrimidinyloxy)-2H-chromen-2-on-3-yl]methyl}-2-pyridyl)-N'-methylsulfamide potassium salt. The molecular formula for avutometinib is $C_{21}H_{17}FN_5O_5S$ (as potassium salt) and its molecular weight is 509.55. The chemical structure of avutometinib is shown below:



Avutometinib potassium is a white to pale yellow powder. It is practically insoluble in the pH range of 1 to 7 in aqueous media. The pKa is 7.02.

AVMAPKI capsules for oral administration contain 0.8 mg of avutometinib (equivalent to 0.864 mg as the avutometinib potassium salt) with the following inactive ingredients: magnesium stearate and mannitol in a hypromellose capsule shell (carrageenan, hypromellose, potassium chloride, purified water, and titanium oxide) printed with black ink (black iron oxide, butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, and strong ammonia solution).

FAKZYNJA tablets contain defactinib, a kinase inhibitor. The chemical name of defactinib is N-methyl-4-({4-[({3-methyl(methylsulfonyl)aminopyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide hydrochloride. The molecular formula for defactinib is $C_{20}ClH_{22}F_3N_8O_3S$ (as hydrochloride [HCl] salt) and its molecular weight is 546.96. The chemical structure of defactinib is shown below:



Defactinib hydrochloride is a white to pale yellow powder. It is very slightly soluble at pH 1 and practically insoluble in the pH range of 4.5 to 6.8 in aqueous media. The pKa is 3.81.

FAKZYNJA tablets are available for oral administration. Each FAKZYNJA tablet contains 200 mg defactinib (equivalent to 214.36 mg as the defactinib hydrochloride salt) and the following inactive

ingredients: lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Avutometinib

Avutometinib is a 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

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 in mouse tumor models including LGSOC.

12.2 Pharmacodynamics

Avutometinib exposure-response relationships and the time course of pharmacodynamic response have not been fully characterized.

Defactinib exposure-response relationships and the time course of pharmacodynamic response have not been fully characterized.

Cardiac Electrophysiology

At the recommended doses for AVMAPKI FAKZYNJA CO-PACK, a mean increase in the QTc interval >20 msec was not observed. For the 88 patients with PR interval measured in RAMP-201, the mean PR interval increased by 16 msec from baseline to Cycle 1 Day 15 4-hours post dose.

12.3 Pharmacokinetics

The pharmacokinetics of avutometinib and defactinib were studied in healthy subjects and in patients with advanced solid tumors and are presented as mean (%CV) unless otherwise specified.

Avutometinib

Avutometinib exhibits dose proportional increases peak plasma concentrations (C_{max}) and area under the concentration time curve (AUC) with a single dose ranging from 0.1 mg to 5 mg (0.03 to 1.6 times the approved recommended dose). No significant accumulation of avutometinib was observed at the recommended dosage.

Defactinib

Defactinib exhibits dose proportional increases in C_{max} and AUC with twice daily dosing ranging from 12.5 mg to 450 mg (0.06 to 2.25 times the approved recommended dosage). Defactinib steady-state plasma concentrations are reached in approximately 15 days. Defactinib accumulation is approximately 1.5-fold at the approved recommended dosage.

Absorption

The median time to avutometinib peak plasma concentration (T_{max}) under fasted conditions is approximately 2 hours.

The median time to defactinib T_{max} under fed conditions is approximately 4 hours.

Effect of Food

No clinically significant differences in avutometinib AUC were observed following administration with a high-fat meal. Avutometinib C_{max} was decreased by 29% following administration with a high-fat meal (approximately 900 to 1000 calories, 50% fat).

Defactinib AUC increased by 2.7-fold and C_{max} increased by 1.9-fold following administration with a high-fat meal (approximately 900 to 1000 calories, 50% fat).

Distribution

Avutometinib steady state apparent volume of distribution (V_d) is 25 L (19%). Avutometinib human plasma protein binding is 99% *in vitro*.

Defactinib steady state apparent V_d is 1,560 L (59%). Defactinib human plasma protein binding is 90% *in vitro*.

Elimination

Avutometinib estimated elimination half-life is 51 hours (28%) and the apparent oral clearance (CL/F) is 0.3 L/h (30%).

Defactinib estimated elimination half-life is 9 hours (171%) and the CL/F is 69 L/h (173%).

Metabolism

Avutometinib is primarily metabolized by CYP3A4 and nonenzymatic degradation.

Defactinib is metabolized primarily by CYP3A4 and CYP2C9. Two major metabolites, N-desmethyl sulfonamide (M2) and N-desmethyl amide (M4), were identified in plasma. M2 and M4 AUCs represent 92% and 28% of defactinib exposure, respectively. M2 is inactive and M4 is equipotent when compared to defactinib.

Excretion

After a single dose of radiolabeled avutometinib 2.4 mg (0.8 times the approved recommended dose), 39% (9.5% unchanged) of the dose was recovered in feces and 52% (3.2% unchanged) in urine.

After a single dose of radiolabeled defactinib 400 mg (2 times the approved recommended dose), 87% (52% unchanged) of the dose was recovered in feces and 7.6% (0.8% unchanged) in urine.

Specific Populations

No clinically significant differences in the pharmacokinetics of avutometinib were observed based on age (21 to 87 years), sex, race (84% White, 3% Black and 2% Asian), body weight (40 to 169 kg), mild and moderate renal impairment (CLcr 30 to 89 mL/min, estimated by Cockcroft-Gault), or mild hepatic impairment (AST > ULN or total bilirubin >1 x ULN to 1.5 x ULN). The effect of severe renal impairment (CLcr < 30 mL/min) or moderate to severe hepatic impairment (AST or ALT ≥ 2.5 x ULN or total bilirubin ≥ 1.5 x ULN) on avutometinib pharmacokinetics is unknown.

No clinically meaningful differences in the pharmacokinetics of defactinib were observed based on age (21 to 87 years), sex, race (82% White, 3% Black and 2% Asian), body weight (40 to 169 kg), mild and moderate renal impairment (CLcr 30 to 89 mL/min), or mild hepatic impairment (AST > ULN or total bilirubin >1 x ULN to 1.5 x ULN). The effect of severe renal impairment (CLcr < 30 mL/min) or moderate to severe hepatic impairment (AST or ALT ≥ 2.5 x ULN or total bilirubin ≥ 1.5 x ULN) on defactinib pharmacokinetics is unknown.

Drug Interaction Studies

Clinical Studies

Strong CYP3A4 Inhibitors:
No clinically significant differences in avutometinib pharmacokinetics were observed when used concomitantly with itraconazole (strong CYP3A4 inhibitor).

Defactinib C_{max} increased by 2.2-fold and AUC by 3.9-fold following concomitant use with itraconazole (strong CYP3A4 inhibitor) 200 mg daily for 10 days. M4 AUC increased by 2.2-fold and C_{max} decreased by 6.8%.

Strong CYP3A4 Inducers:
Avutometinib AUC decreased by 34% with no clinically significant change in C_{max} following coadministration with phenytoin (strong CYP3A4 inducer) three times daily for 23 days and a single dose of avutometinib 2.4 mg (0.8 times the approved recommended dose) on Day 17.

Defactinib C_{max} decreased by 83% and AUC by 87% following coadministration with phenytoin (strong CYP3A4 inducer) three times daily for 23 days and a single dose of defactinib 200 mg (1.0 times the approved recommended dose) on Day 14. M4 AUC decreased by 79% and C_{max} decreased by 70%.

Proton Pump Inhibitors (PPIs):
Defactinib displayed pH-dependent aqueous solubility *[see Description (11)]*. Defactinib AUC decreased by 79% and C_{max} decreased by 85% following concomitant use of multiple doses of omeprazole (PPI) 40 mg daily. M4 AUC decreased by 83% and C_{max} decreased by 88%.

In Vitro Studies

CYP450 Enzymes:
Avutometinib is a CYP3A4 substrate, but not a substrate of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. Avutometinib is not an inhibitor of CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. Avutometinib is not an inducer of CYP3A4, CYP2B6, and CYP1A2.

Defactinib is a CYP3A4 and CYP2C9 substrate, but not a substrate of CYP1A2, CYP2B6, CYP2C8, CYP2C19, and CYP2D6. Defactinib is a reversible inhibitor of CYP3A4 and CYP2C9, but not CYP1A2, CYP2B6, CYP2C8, CYP2C19, and CYP2D6. Defactinib is a time-dependent inhibitor of CYP3A4. Defactinib is an inducer of CYP2B6, and CYP1A2, but not CYP3A4.

UGT Enzymes:
Defactinib may inhibit UGT1A1 at clinically relevant concentrations.

Transporter Systems:
Avutometinib is a substrate of P-gp and BCRP, but not a substrate of MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2. Avutometinib is not an inhibitor of P-gp, BCRP, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2.

Defactinib is a BCRP and P-gp substrate, but not a substrate of MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2. Defactinib is an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, and MATE2-K, but not an inhibitor of MATE1, OAT1, OAT3, OCT1, and OCT2.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Avutometinib

Carcinogenesis
Carcinogenicity studies have not been conducted with avutometinib.

Mutagenesis
Avutometinib was not mutagenic in the bacterial reverse mutagenesis (Ames) assay and was not clastogenic in an *in vitro* Chinese hamster lung chromosome aberration assay or an *in vivo* rat bone marrow micronucleus assay.

Impairment of Fertility
Dedicated fertility studies have not been conducted with avutometinib. In repeat dose toxicity studies, avutometinib was administered orally once daily for up to 13-weeks duration in rats and monkeys. In female rats, atrophy of the ovary was observed at doses ≥ 0.04 mg/kg/day (approximately ≥ 0.25 times the human exposure at the recommended dose based on AUC). Atrophy of the uterus and thinning of the mucosa and increased single cell necrosis of the mucosal epithelium in the vagina were observed at 0.16 mg/kg/day (0.5 times the human exposure at the recommended dose based on AUC). In female monkeys, thinning of the vaginal mucosa was observed at doses ≥ 0.02 mg/kg/day (≥ 0.7 times the human exposure at the recommended dose based on AUC). All findings were reversible.

Defactinib

Carcinogenesis
Carcinogenicity studies have not been conducted with defactinib.

Mutagenesis
Defactinib was not mutagenic in the bacterial reverse mutagenesis (Ames) assay and was not clastogenic in an *in vitro* Chinese hamster lung cell chromosome aberration assay. Defactinib was positive in the *in vitro* micronucleus assay through an aneugenic mechanism and in the *in vivo* rat bone marrow micronucleus assay.

Impairment of Fertility
Dedicated fertility studies have not been conducted with defactinib. In male rats administered defactinib for up to 13 weeks, small prostate, seminal vesicle, and testes, decreased prostate weight, diffuse tubule degeneration/atrophy of the testes and sperm granuloma of the epididymis were observed at doses ≥ 125 mg/kg/day (below the human exposure at the recommended dose based on AUC). At the end of the recovery period, findings in the testes were observed.

In male dogs administered defactinib for up to 13 weeks, increased prostate and testes weights and testicular degeneration and cellular debris in the epididymis were observed at doses ≥ 1 mg/kg/day (below the human exposure at the recommended dose based on AUC). At the end of the recovery period, findings in the testes and epididymis that included cellular debris, duct dilation, and hypospermia were observed.

13.2 Animal Toxicology and/or Pharmacology

Avutometinib

In repeat-dose toxicity studies up to 13-weeks duration in rats and monkeys, tissue mineralization in multiple organs was observed at doses ≥ 0.01 mg/kg/day and 0.03 mg/kg/day, respectively (≥ 0.06 and 1.4 times the human exposure at the recommended dose based on AUC, respectively) as well as increased inorganic phosphorus in rats.

In a cardiovascular telemetry study in monkeys, a single oral dose of avutometinib increased systolic, diastolic, and mean blood pressure at 1 mg/kg (approximately 15 times the human C_{max} at the recommended dose). In the repeat-dose toxicology studies up to 13-weeks duration in rats, myocardial degeneration and necrosis were observed at doses ≥ 0.01 mg/kg/day (below the human exposure at the recommended dose based on AUC).

Defactinib

In a cardiovascular telemetry study in dogs, a single oral dose of defactinib decreased myocardial contractility at doses ≥ 5 mg/kg (approximately the human exposure at the recommended dose based on AUC) and increased ventricular systolic, diastolic and mean blood pressure at doses ≥ 25 mg/kg/day (≥ 2.7 times the human exposure at the recommended dose based on AUC). In the 13-week repeat-dose toxicology study in dogs, myocardium hypertrophy was observed at doses ≥ 1 mg/kg/day (below the human exposure at the recommended dose based on AUC) at the end of the dosing and recovery periods.

14 CLINICAL STUDIES

The efficacy of AVMAPKI FAKZYNJA CO-PACK was evaluated in RAMP-201 (NCT04625270), an open-label, multicenter study that included 57 adult patients with measurable *KRAS*-mutated recurrent LGSOC. Patients were required to have received at least one prior systemic therapy, including a platinum-based regimen. *KRAS* mutation status was determined by prospective local testing using next generation sequencing (NGS) or polymerase chain reaction of tumor tissue specimens. Patients were excluded if they were candidates for debulking surgery, were on treatment with warfarin, had an active skin disorder requiring systemic therapy within the past year, or had an ocular disorder (including a history of retinal pathology, an active or chronic visually significant corneal disorder, or a history of glaucoma).

Patients received AVMAPKI 3.2 mg orally twice weekly for the first 3 weeks out of a 4-week cycle and FAKZYNJA 200 mg orally twice daily for the first 3 weeks out of a 4-week cycle until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall response rate (ORR) assessed by blinded independent review committee (BIRC) according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. An additional efficacy outcome measure was duration of response (DoR). Tumor response assessments occurred every 8 weeks for the first 72 weeks and every 12 weeks thereafter.

The median age was 60 years (range: 29 to 87); 75% were White, 3.5% were Asian, 3.5% were Black or African American, and 18% did not have race reported; 3.5% of patients were Hispanic or Latino; 72% had an ECOG PS of 0 and 28% had ECOG PS of 1. The *KRAS* mutations identified by local testing were G12V (53%), G12D (35%), Q61H (3.5%), G12C (1.8%), G12R (1.8%), A146V (1.8%), and mutations not otherwise specified at G12x (1.8%) and on codon 12/13 (1.8%). Fourteen percent of patients had received 1 prior line of systemic therapy, 25% of patients had received 2 prior lines, 18% had received 3 prior lines and 40% had received more than 3 prior lines of systemic therapy. All patients had received prior platinum-based chemotherapy, 84% received prior hormonal therapy (as maintenance or treatment), 40% received prior bevacizumab and 21% received a prior MEK inhibitor.

Efficacy results are presented in Table 5.

Table 5 Efficacy Results in RAMP-201

	AVMAPKI FAKZYNJA CO-PACK **N = 57**
Confirmed Overall Response Rate (95% CI)[1]	44% (31,58)
Complete response	3.5%
Partial response	40%
Duration of Response (DoR)	
Range (months)	3.3, 31.1

[1] ORR 95% CI calculated using Clopper-Pearson method

The tumor *KRAS* mutations observed in the 25 responders were A146V, G12D, G12R, G12V, and Q61H.

16 HOW SUPPLIED/STORAGE AND HANDLING

AVMAPKI FAKZYNJA CO-PACK is supplied in a carton that contains:

AVMAPKI capsules in a 24-count bottle with child-resistant closure (NDC 71779-660-02)	NDC 71779-623-01
FAKZYNJA tablets in a 42-count bottle with child-resistant closure (NDC 71779-630-01)	

- AVMAPKI (avutometinib) 0.8 mg capsules are supplied as white capsules with “6766” printed on the cap and the strength “0.8 mg” printed on the body in black ink in a bottle containing 24 capsules. The bottle contains a desiccant that should not be discarded.

- FAKZYNJA (defactinib) 200 mg tablets are supplied as white to off-white, oval and debossed with “VS2” on one side of the tablet in a bottle containing 42 tablets.

Store AVMAPKI capsules and FAKZYNJA tablets refrigerated at 2°C to 8°C (36°F to 46°F) in their original bottles.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Ocular Toxicities

Inform patients of the need for eye exams before and during treatment with AVMAPKI FAKZYNJA CO-PACK.

Advise patients to contact their healthcare provider if they experience any visual changes, pain, or inflammation around their eye(s) *[see Warnings and Precautions (5.1)]*.

Serious Skin Toxicities

Inform patients that skin reactions have occurred during treatment with AVMAPKI FAKZYNJA CO-PACK.

Advise patients to use prophylactic topical steroids and oral antibiotics *[see Dosage and Administration (2.2)]* and to limit unnecessary exposure to sunlight with application of daily sunscreen (sun protection factor [SPF] ≥ 30) *[see Warnings and Precautions (5.2)]*.

Advise patients to contact their healthcare provider if they develop a rash, progressively worsening skin reactions, or blistering of the skin or mouth *[see Warnings and Precautions (5.2)]*.

Hepatotoxicity

Advise patients that they will need to undergo laboratory testing to monitor their liver function.

Advise patients to contact their healthcare provider for signs or symptoms of liver dysfunction *[see Warnings and Precautions (5.3)].*

Rhabdomyolysis

Inform patients that they will need to undergo laboratory testing to monitor CPK levels.

Advise patients to contact their healthcare provider for signs or symptoms of rhabdomyolysis *[see Warnings and Precautions (5.4)].*

Drug Interactions

Inform patients to avoid concomitant use of AVMAPKI FAKZYNJA CO-PACK with PPIs or H2 receptor antagonists.

Advise patients that if use of an acid reducing agent cannot be avoided, to take FAKZYNJA 2 hours prior to, or 2 hours after, the administration of a locally acting antacid *[see Drug Interactions (7.1)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

Advise females to inform their healthcare providers of a known or suspected pregnancy. 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 male patients 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 *[see Warnings and Precautions (5.5) and Use in Specific Population (8.1, 8.3)]*.

Lactation

Advise women not to breastfeed during treatment with AVMAPKI FAKZYNJA CO-PACK and for 2 weeks after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males and females of reproductive potential that AVMAPKI FAKZYNJA CO-PACK may impair fertility *[see Use in Specific Populations (8.3)]*.

Manufactured for and Distributed by:
Verastem, Inc.
Needham, Massachusetts 02494
1-877-878-6662

PATIENT INFORMATION

AVMAPKI™ FAKZYNJA™ CO-PACK (ave-MAP-kee Fak-zin-jah koh-pak)
(avutometinib capsules; defactinib tablets)
co-packaged for oral use

What is AVMAPKI FAKZYNJA CO-PACK?

AVMAPKI FAKZYNJA CO-PACK is a prescription medicine used to treat adults who have:

- low-grade serous ovarian cancer (LGSOC) that has come back (recurrent), **and**
- LGSOC with an abnormal *KRAS* gene, **and**
- previously been treated with medicine for their cancer.

It is not known if AVMAPKI FAKZYNJA CO-PACK is safe and effective in children.

Before taking AVMAPKI FAKZYNJA CO-PACK, tell your healthcare provider about all of your medical conditions, including if you:

- have a history of eye or vision problems
- have had severe skin reactions
- have liver problems
- are pregnant or plan to become pregnant. AVMAPKI FAKZYNJA CO-PACK can harm your unborn baby.
  Females who are able to become pregnant:
  - Your healthcare provider should do a pregnancy test before you start treatment with AVMAPKI FAKZYNJA CO-PACK.
  - You should use effective birth control (contraception) during treatment and for 1 month after the last dose of AVMAPKI FAKZYNJA CO-PACK.
  - Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with AVMAPKI FAKZYNJA CO-PACK.

  Males with a female partner who is able to become pregnant:
  - You should use effective birth control (contraception) during treatment and for 4 months after the last dose of AVMAPKI FAKZYNJA CO-PACK.
- are breastfeeding or plan to breastfeed. It is not known if AVMAPKI FAKZYNJA CO-PACK passes into your breast milk. Do not breastfeed during treatment and for 2 weeks after the last dose of AVMAPKI FAKZYNJA CO-PACK.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. AVMAPKI FAKZYNJA CO-PACK may affect the way other medicines work, and other medicines may affect how AVMAPKI FAKZYNJA CO-PACK works.

Especially tell your healthcare provider if you take:

- proton pump inhibitors (PPIs) or H2 receptor antagonists
- a blood thinner called warfarin

Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist when you get a new medicine.

How should I take AVMAPKI FAKZYNJA CO-PACK?

- Take AVMAPKI FAKZYNJA CO-PACK exactly as directed by your healthcare provider.
- Do not change your dose or stop taking AVMAPKI FAKZYNJA CO-PACK without talking to your healthcare provider.
- If you develop certain side effects your healthcare provider may change your dose, temporarily stop, or completely stop your treatment with AVMAPKI FAKZYNJA CO-PACK.

Take AVMAPKI capsules and FAKZYNJA tablets with food.

- If you vomit after taking AVMAPKI capsules or FAKZYNJA tablets, do not take an additional dose. Take the next scheduled dose as prescribed by your healthcare provider.

AVMAPKI capsules:

- Take each dose at the same time.
- Swallow the capsules whole. Do not chew, break, or open the capsules.
- If you miss a dose of AVMAPKI by more than 24 hours, skip the missed dose and take the next scheduled dose as prescribed by your healthcare provider. Do not take two doses at the same time to make up for a missed dose.

FAKZYNJA tablets:

- Swallow the tablets whole. Do not chew, break, or crush the tablets.
- If you take antacids, take FAKZYNJA tablets 2 hours before or 2 hours after taking the antacid.
- If you miss a dose of FAKZYNJA by more than 6 hours, skip the missed dose and take the next scheduled dose as prescribed by your healthcare provider. Do not take two doses at the same time to make up for a missed dose.

Before and during treatment with AVMAPKI FAKZYNJA CO-PACK, your health care provider will give you medicines to apply to your face, scalp, neck, upper chest and upper back, and antibiotic medicines to take by mouth to help prevent skin reactions.

What should I avoid while taking AVMAPKI FAKZYNJA CO-PACK?

- Limit your time in the sun. AVMAPKI FAKZYNJA CO-PACK can make your skin sensitive to the sun (photosensitivity) and the light from sunlamps and tanning beds. You may burn more easily and get a severe sunburn. Apply daily sunscreen with a Sun Protection Factor (SPF) of 30 or greater and wear a hat and clothes that cover your skin to protect against sunburn. Talk to your healthcare provider if you get a sunburn.

What are the possible side effects of AVMAPKI FAKZYNJA CO-PACK?
AVMAPKI FAKZYNJA CO-PACK may cause serious side effects, including:

- **eye problems.** Eye problems are common with AVMAPKI FAKZYNJA CO-PACK and can be severe. Your healthcare provider will send you to see an eye care professional before starting treatment, during treatment, and for any new or worsening eye problems. Tell your healthcare provider if you get any new or worsening eye problems including:
  - changes in vision, such as blurred vision, double vision, or vision loss
  - dry eye(s)
  - eye and eyelid inflammation, including redness, swelling, and itching
  - eye pain
  - new or increased floaters (small dark spots or squiggly lines that float across your vision)
  - light hurting eyes or seeing flashes of light

- **severe skin reactions**. Skin reactions are common with AVMAPKI FAKZYNJA CO-PACK and can be severe or life threatening. Tell your healthcare provider if you develop any new or worsening skin reactions including:
  - skin rash or acne
  - dry skin
  - itching
  - blisters on your skin
  - redness or swelling of your face, hands, or soles of your feet
  - blisters or sores in your mouth
  - peeling of your skin
  - skin infection

- **liver problems.** Liver problems are common with AVMAPKI FAKZYNJA CO-PACK and can be severe. Treatment with AVMAPKI FAKZYNJA CO-PACK can increase the level of aspartate aminotransferase, alanine aminotransferase, and bilirubin in your blood. Your healthcare provider will do blood tests before starting each treatment cycle and during treatment to check your liver function. Tell your healthcare provider if you get any signs or symptoms of severe liver problems including:
  - yellowing of your skin or the white part of your eyes
  - itchy skin
  - feeling very tired
  - flu-like symptoms
  - nausea or vomiting
  - upper right side stomach pain
  - dark or tea colored urine
  - bleeding or bruising more easily than normal

- **muscle problems (rhabdomyolysis).** AVMAPKI FAKZYNJA CO-PACK may cause muscle problems that can be severe. Treatment with AVMAPKI FAKZYNJA CO-PACK can increase the level of an enzyme in your blood called creatine phosphokinase (CPK) and can be a sign of muscle damage. Your healthcare provider will perform blood tests to check your levels of CPK before starting each treatment cycle and during treatment. Tell your healthcare provider if you get any signs or symptoms of increased CPK including:
  - weakness or difficulty moving arms and legs
  - muscle or bone aches or pain that does not go away
  - dark, red colored urine or decreased urine output

The most common side effects of AVMAPKI FAKZYNJA CO-PACK include:

- nausea
- tiredness
- increased aspartate aminotransferase
- diarrhea
- swelling in the body (edema)
- decreased hemoglobin
- increased alanine aminotransferase
- vomiting
- increased blood bilirubin
- increased triglycerides
- stomach-area pain
- acid reflux
- increased alkaline phosphatase
- decreased platelets
- constipation
- shortness of breath
- cough
- urinary tract infection
- decreased lymphocytes
- decreased neutrophils
- proteinuria

AVMAPKI FAKZYNJA CO-PACK may cause fertility problems in females and males, which may affect your ability to have children. Talk to your healthcare provider if this is a concern for you.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of AVMAPKI FAKZYNJA CO-PACK. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AVMAPKI FAKZYNJA CO-PACK?

- Store AVMAPKI capsules and FAKZYNJA tablets in the refrigerator between 36°F to 46°F (2°C to 8°C) in the original bottles.
- The AVMAPKI capsules and FAKZYNJA tablets come in child-resistant bottles.

Keep AVMAPKI FAKZYNJA CO-PACK and all medicines out of the reach of children.

General information about the safe and effective use of AVMAPKI FAKZYNJA CO-PACK.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use AVMAPKI FAKZYNJA CO-PACK for a condition for which it was not prescribed. Do not give AVMAPKI FAKZYNJA CO-PACK to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about AVMAPKI FAKZYNJA CO-PACK that is written for health professionals.

What are the ingredients in AVMAPKI FAKZYNJA CO-PACK?

AVMAPKI (avutometinib) capsules:
Active ingredient: avutometinib
Inactive ingredients: magnesium stearate, mannitol, black iron oxide, butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, and strong ammonia solution. The capsule shell contains carrageenan, hypromellose, potassium chloride, purified water, and titanium oxide.

FAKZYNJA (defactinib) tablets:
Active ingredient: defactinib
Inactive ingredients: lactose monohydrate, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

Manufactured for and Distributed by: Verastem, Inc., Needham, Massachusetts 02494

For more information, go to www.AvmapkiFakzynjaCo-Pack.com or call 1-877-878-6662.

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 05/2025