Iowa PDL New Drug Review

Proprietary Name: Avmapki Fakzynja® Co-pack
Common Name: avutometinib & defactinib
PDL Category: Antineoplastic Agents

Pharmacology/Usage: Avmapki Fakzynja® co-pack contains Avmapki® capsules (avutometinib) co-packaged with Fakzynja® tablets (defactinib). Avmapki® and Fakzynja® are both kinase inhibitors.

Specifically, avutometinib is a MEK1 inhibitor and induces the formation of inactive RAF/MEK complexes and prevents phosphorylation of MEK1/2 by RAF. RAF and MEK proteins are regulators of the RAS/RAF/MEK/ERK (MAPK) pathway. Avutometinib inhibited MEK1/2 and ERK1/2 phosphorylation and proliferation of tumor cell lines harboring KRAS mutations. Treatment of cancer cells with avutometinib increased the level of phosphorylated focal adhesion kinase (FAK).

Defactinib is an inhibitor of FAK and proline-rich tyrosine kinase-2 (Pyk2), the two members of the FAK family of nonreceptor tyrosine kinases. Defactinib inhibited FAK autophosphorylation in cancer cells in vitro and in mouse models.

Avutometinib in combination with defactinib enhanced inhibition of cell proliferation *in vitro* and anti-tumor activity in mouse tumor models.

Indication: 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.

There is no pregnancy category for this medication; however, the risk summary indicates that based on the mechanisms of action, this product can cause fetal harm when given to a pregnant woman. There are no available data with use in pregnant women to inform a drug-associated risk. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify the pregnancy status of females of reproductive potential prior to starting treatment. In addition, advise females of reproductive potential to use effective contraception during treatment and for 1 month after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the last dose. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Co-pack includes Avmapki® (avutometinib) capsules co-packaged with Fakzynja® (defactinib) tablets.

- Avmapki® capsules contain 0.8mg avutometinib
  - Swallow capsules whole; do not chew, break, or open the capsules.
- Fakzynja® tablets contain 200mg defactinib
  - Swallow tablets whole; do not chew, break, or crush the tablets.

Recommended Dosage: Select patients for the treatment of recurrent LGSOC with Avmapki Fakzynja® co-pack based on the presence of a *KRAS* mutation in tumor specimens. 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.

Conduct a comprehensive ophthalmic exam at baseline, prior to cycle 2, and every 3 cycles thereafter regardless of baseline exam findings, and as clinically indicated.

With initiation of and during at least the first 2 cycles of Avmapki Fakzynja® co-pack administer:

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

The recommended dosage of *Avmapki® capsules* is 3.2mg (four 0.8mg capsules) taken PO twice weekly (day 1 and day 4) for the first 3 weeks of each 4-week cycle until disease progression or unacceptable toxicity. Take at the same time with each dose and take with food.

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.

The recommended dosage of *Fakzynja® tablets* is 200mg (one tablet) taken PO twice daily for the first 3 weeks of each 4-week cycle until disease progression or unacceptable toxicity. Take each dose with food.

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.

Information regarding dose modifications due to adverse reactions, such as keratitis, blurred vision, conjunctivitis, retinal pigment epithelial (RPE) detachment, rash, hepatotoxicity, increased blood creatine phosphokinase (CPK), or other adverse reactions, can be found in the prescribing information.

Drug Interactions: Defactinib is a CYP3A4 substrate. Avoid concomitant use of Avmapki Fakzynja® co-pack with strong or moderate CYP3A4 inhibitors.

Avoid concomitant use of Avmapki Fakzynja® co-pack with strong or moderate CYP3A4 inducers.

Concomitant use of Fakzynja® with gastric acid reducing agents decreases defactinib exposure, which may reduce the efficacy of Avmapki Fakzynja® co-pack. Avoid concomitant use of Avmapki Fakzynja® co-pack with proton pump inhibitors (PPIs) or H2 receptor antagonists (H2RAs). 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.

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

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Avmapki Fakzynja® co-pack) for all grades. Please note that there was no placebo data to compare with in the prescribing information.* The most frequently reported adverse events included nausea (74%), diarrhea (68%), vomiting (49%), abdominal pain (39%), dyspepsia (37%), stomatitis (35%), constipation (30%), dry mouth (18%), decreased weight (11%), fatigue (72%), edema (67%), rash (72%), dermatitis acneiform (37%), pruritus (35%), dry skin (30%), alopecia (23%), photosensitivity (16%), musculoskeletal pain (68%), joint swelling (11%), vitreoretinal disorders (37%), visual impairment (35%), dry eye (12%), dyspnea (26%), cough (25%), dizziness (23%), headache

(16%), neuropathy peripheral (14%), dysgeusia (11%), hemorrhage (23%), hypertension (16%), venous thromboembolism (14%), decreased appetite (18%), urinary tract infection (25%), paronychia (14%), and upper respiratory tract infection (11%).

Laboratory abnormalities for all grades included increased creatine phosphokinase (82%), increased aspartate aminotransferase (70%), decreased albumin (70%), increased alanine aminotransferase (58%), increased blood bilirubin (48%), increased triglycerides (46%), increased alkaline phosphatase (37%), decreased potassium (23%), decreased hemoglobin (65%), decreased lymphocyte count (40%), decreased platelet count (35%), decreased neutrophil count (25%), and proteinuria (22%).

Avmapki Fakzynja® co-pack can cause ocular adverse reactions, including visual impairment and vitreoretinal disorders. 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 3 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 adverse reactions and withhold, reduce, or permanently discontinue Avmapki Fakzynja® co-pack based on severity and persistence of ocular adverse reactions.

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. 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 the phase 3 study used topical corticosteroids and systemic oral antibiotics for prophylaxis of skin adverse reactions. Limit unnecessary exposure to sunlight and apply daily sunscreen. Monitor for skin toxicity and withhold, reduce the dose, or permanently discontinue Avmapki Fakzynja® co-pack based on severity and persistence.

Avmapki Fakzynja® co-pack can cause hepatotoxicity. 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 the dose, or permanently discontinue Avmapki Fakzynja® co-pack based on severity and duration of these adverse reaction.

Avmapki Fakzynja® co-pack can cause increased creatine phosphokinase (CPK). 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, assess patients for rhabdomyolysis or other causes. Withhold, reduce, or permanently discontinue Avmapki Fakzynja® co-pack based on severity and duration of the adverse reactions.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Verastem Inc.

Analysis: The efficacy of Avmapki Fakzynja® co-pack was assessed in an open-label, multicenter study (RAMP-201) that included adult patients with measurable *KRAS*-mutated recurrent LGSOC (N=57). 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. Furthermore, 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 Fakzynja® co-pack until disease progression or unacceptable toxicity. The median age of included patients was 60 years (range 29 to 87), while 75% were white, 72% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 28% had an ECOG performance status of 1. In addition, 14% of patients

had received 1 prior line of systemic therapy, 25% 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.

The major efficacy outcome measure was overall response rate (ORR) assessed by blinded independent review committee (BIRC) per 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. Efficacy results are presented in the table below, which was adapted from the prescribing information.

Efficacy Outcome	Avmapki Fakzynja® co-pack (N=57)
Confirmed Overall Response Rate	44%
Complete Response	3.5%
Partial Response	40%
Duration of Response, range (months)	3.3, 31.1

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

Place in Therapy: 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. Select patients for the treatment of recurrent LGSOC with Avmapki Fakzynja® co-pack based on the presence of a *KRAS* mutation in tumor specimens. Conduct a comprehensive ophthalmic exam at baseline, prior to cycle 2, and every 3 cycles thereafter regardless of baseline exam findings, and as clinically indicated. In addition, with initiation of and during at least the first 2 cycles of Avmapki Fakzynja® co-pack administer topical corticosteroids and systemic oral antibiotics. The efficacy of Avmapki Fakzynja® co-pack was assessed in an open-label multicenter study that included adults with measurable *KRAS*-mutated recurrent LGSOC. The main efficacy outcome measure was overall response rate (ORR), and the confirmed ORR was 44% with patients taking Avmapki Fakzynja® co-pack.

Summary

It is recommended that Avmapki Fakzynja® co-pack should be non-recommended in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Avmapki Fakzynja® co-pack [package insert]. Needham, MA: Verastem, Inc; 2025.