PDL DRUG REVIEW

Proprietary Name: Ayvakit®
Common Name: avapritinib
PDL Category: Antineoplastics

Summary

Pharmacology/Usage: Avapritinib, the active ingredient of Ayvakit®, is a kinase inhibitor that targets platelet-derived growth factor receptor alpha (PDGFRA) and PDGFRA D842 mutants as well as multiple KIT exon 11, 11/17, and 17 mutants.

Indication: For the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations.

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings from animal studies and its mechanism of action, Ayvakit® can cause fetal harm when given to a pregnant woman. There are no available data on use in pregnant women. Advise pregnant women of the potential risk to a fetus. In addition, verify the pregnancy status of females of reproductive potential prior to starting treatment. In this same population as well as with males with female partners of reproductive potential, use effective contraception during treatment and for 6 weeks after the final dose. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets: 100mg, 200mg, 300mg

Recommended Dosage: Select patients for treatment with Ayvakit® based on the presence of a PDGFRA exon 18 mutation. An FDA-approved test for the detection of exon 18 mutations is not currently available.

Take 300mg PO QD on an empty stomach, at least 1 hour before and 2 hours after a meal. Continue until disease progression or unacceptable toxicity. Do not make up for a missed dose within 8 hours of the next scheduled dose. Dose reductions and dosage modifications are recommended based on adverse reactions (such as intracranial hemorrhage, CNS effects, and others) and further information can be found in the prescribing information.

Dose adjustments are not required with mild or moderate renal impairment as well as with mild or moderate hepatic impairment. The recommended dose has not been established for patients with severe renal impairment, severe hepatic impairment, or end-stage renal disease.

Drug Interactions: Coadministration of Ayvakit® with a strong or moderate CYP3A inducer decreased avapritinib concentrations. Avoid the coadministration of Ayvakit® with strong or moderate CYP3A inducers.

Coadministration of Ayvakit® with a strong or moderate CYP3A inhibitor increased avapritinib concentrations, which may increase the incidence and severity of adverse reactions of Ayvakit®. Avoid coadministration of

Ayvakit® with strong or moderate CYP3A inhibitors. If coadministration of Ayvakit® with a moderate CYP3A inhibitor cannot be avoided, reduce the dose of Ayvakit® from 300mg to 100mg QD.

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

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Ayvakit®) for all grades. There was no placebo data in the prescribing information to compare with.* The most frequently reported adverse events included edema (72%), fatigue/asthenia (61%), pyrexia (14%), nausea (64%), vomiting (38%), diarrhea (37%), abdominal pain (31%), constipation (23%), dyspepsia (16%), cognitive impairment (48%), dizziness (22%), headache (17%), sleep disorders (16%), taste effects (15%), mood disorders (13%), decreased appetite (38%), increased lacrimation (33%), rash (23%), hair color changes (21%), alopecia (13%), dyspnea (17%), pleural effusion (12%), and weight decreased (13%).

Laboratory abnormalities included decreased hemoglobin (81%), decreased leukocytes (62%), decreased neutrophils (43%), decreased platelets (27%), increased INR (24%), increased activated partial thromboplastin time (13%), increased bilirubin (69%), increased aspartate aminotransferase (51%), decreased phosphate (49%), decreased potassium (34%), decreased albumin (31%), decreased magnesium (29%), increased creatinine (29%), decreased sodium (28%), increased alanine aminotransferase (19%), and increased alkaline phosphatase (14%).

Intracranial hemorrhage occurred in 1% of the 267 patients with GIST and overall in 3% of the 355 patients who received Ayvakit®, occurring in the range of 1.7 to 19.3 months after the start of Ayvakit®. Furthermore, 0.9% of patients receiving Ayvakit® required permanent discontinuation for an intracranial hemorrhage. Withhold and then resume at a reduced dose upon resolution, or permanently discontinue Ayvakit® based on severity.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Blueprint Medicines Corporation

Analysis: The safety and efficacy of Ayvakit® were assessed in a single-arm, multicenter, open-label study that included patients required to have a confirmed diagnosis of GIST and an ECOG performance status of 0 to 2. The trial initially enrolled patients at a starting dose of 400mg, which was later reduced to the recommended dose of 300mg due to toxicity. As there was no apparent difference in overall response rate (ORR) between patients who received 300mg daily compared to those who received 400mg daily, these patients were pooled for the efficacy assessment. The main outcome assessed was ORR based on disease assessment by independent radiological review using modified RECIST v1.1 criterion, in which lymph nodes and bone lesions were not target lesions and progressively growing new tumor nodules within a pre-existing tumor mass was progression. Duration of response (DOR) was also assessed.

Patients with unresectable or metastatic GIST with a PDGFRA exon 18 mutation were identified using a PCR- or NGS-based assay. The assessment of efficacy was based on 43 patients, including 38 with PDGFRA D824V mutations. The median duration of follow-up for patients with PDGFRA exon 18 mutations was 10.6 months. The included subjects had a median age of 64 years (range 29 to 90 years), while 67% were male, 67% were white, 93% had an ECOG performance status of 0 to 1, 98% had metastatic disease, and 86% had prior surgical resection. Furthermore, the median number of prior kinase inhibitors was 1 (range 0 to 5).

Efficacy results in patients with GIST harboring PDGFRA exon 18 mutations including the subgroup of patients with PDGFRA D842V mutations can be seen in the table below, which was adapted from the prescribing information.

	PDGFRA exon 18 (N=43)	PDGFRA D842V (N=38)
Overall Response Rate	84%	89%
Complete Response	3 (7%)	3 (8%)
Partial Response	33 (77%)	31 (82%)

	PDGFRA exon 18 (N=43)	PDGFRA D842V (N=38)
Duration of Response (DOR)	N=36	N=34
Median in months	Not reached	Not reached
Patients with DOR ≥6 months	22 (61%)	20 (59%)

Place in Therapy: Ayvakit® is an oral tyrosine kinase inhibitor indicated for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations. Select patients for treatment with Ayvakit® based on the presence of a PDGFRA exon 18 mutation. An FDA-approved test for the detection of exon 18 mutations is not currently available. In a small single-arm study, overall response rate was seen in 84% of patients.

It is recommended that Ayvakit® should be non-recommended with conditions in order to confirm the appropriate diagnosis and clinical parameters for use.

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

References

[1] Ayvakit [package insert]. Cambridge, MA: Blueprint Medicines Corporation; 2020.