RXADVANCE
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NEW DRUG APPROVAL

Brand Name	Ayvakit™
Generic Name	avapritinib
Drug Manufacturer	Blueprint Medicines Corporation

New Drug Approval

FDA Approval Date: January 9, 2020
Review Designation: Priority, Orphan
Type of Review: New Drug Application 212608

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Stromal or mesenchymal neoplasms affecting the gastrointestinal (GI) tract present as subepithelial neoplasms, which are divided into two groups. The most common group consists of GISTs, often located in the stomach and proximal small intestine; however, GISTs can occur in the alimentary tract and occasionally in the omentum, mesentery and peritoneum. GISTs are mainly by expression of the KIT protein and frequently harbour mutations in the KIT or PDGFRA genes.

GISTs are the most common nonepithelial neoplasm involving the GI tract, yet mesenchymal tumors only constitute approximately 1% of primary GI cancers. GISTs occur predominantly in middle-aged and older individuals.

- Familial GIST – Approximately 5% of patients have one of several familial autosomal dominant syndromes, including primary familial GIST syndrome, neurofibromatosis type 1 (NF1) and Carney-Stratakis syndrome. Phenotypic, histologic and molecular features of the GIST appear to be indistinguishable in familial and sporadic cases.

- Pediatric GIST – GISTs are rare in children or young adults, yet GISTS in this population have distinct clinical as well as molecular and pathologic features. Chronic GI bleeding is the most common presentation and present more common in females in this age group. 85% of pediatric GISTs lack KIT or PDGFRA mutations.

Annual incidence of GIST is approximately 4000-6000 cases in the United States per year. Approximately 80% of GIST tumors have a mutation in KIT, and 10% of patients with GIST have mutations in PDGFRA, predominantly D842V. Overall 5-year survival rate for GIST is 76%, but this drops to 48% in patients with unresectable or metastatic GIST.

Efficacy

Avapritinib demonstrated efficacy in patients with primary GIST harbouring a PDGFRA exon 18 mutation in an open-label, single-arm study (the NAVIGATOR trial). The assessment of efficacy was based on a total of 43 patients. Median duration of follow-up was 10.6 months. Avapritinib provided an overall response rate (ORR) of 84% (complete response [CR] in 7% and partial response [PR] in 77%) in patients with unresectable or metastatic GIST harbouring a PDGFRA exon mutation (n=43) with 61% maintaining response for at least 6 months. Similar results were found in the cohort with PDGFRA D842V mutation (n=38) including an ORR of 89% (CR in 8% and PR

in 82%) with 59% maintaining response for at least 6 months. Patient median age was 69 years of age (range=29-90 years of age); 98% had metastatic disease, 53% with largest target lesion exceeding 5cm; 86% had prior surgical resection and median prior kinase inhibitor use was 1.

NAVIGATOR Clinical Trial: Efficacy Results for Patients with GIST Harboring *PDGFRA* Exon 18 Mutations		
Efficacy Parameter	***PDGFRA* Exon 18**	***PDGFRA* D842V**
Overall Response Rate	84% (69%, 93%)	89% (75%, 97%)
Complete Response, n (%)	3 (7%)	3 (8%)
Partial Response, n (%)	33 (77%)	31 (82%)
Duration of Response	N=6	N=34
Median in months	Not reached	Not reached
Patients with DOR ≥ 6-months, n (%) *	22 (61%)	20 (59%)

Avapritinib is not approved for use in fourth-line therapy for GIST. A phase 3 trial (the VOYAGER trial) is currently ongoing for use as a fourth-line GIST therapy.

Evidence of tumor response or stabilization is indicative of efficacy.

Safety

ADVERSE EVENTS

Adverse reactions listed occurred in 10% or more of patients.

- Cardiovascular: edema
- Dermatologic: alopecia, hair color change, rash
- Endocrine/Metabolic: decreased weight
- Gastrointestinal: abdominal pain, constipation, decreased appetite, diarrhea, disorder of taste, indigestion, nausea, vomiting
- Neurologic: asthenia, fatigue, dizziness, headache, impaired cognition, sleep disorder
- Ophthalmic: excessive tear production
- Psychiatric: mood disorder
- Respiratory: dyspnea, pleural effusion
- Other: fever

WARNINGS & PRECAUTIONS

Intracranial hemorrhage

Withhold AYVAKIT for grade 1 or 2 reactions until resolution; resume at a reduced dose. Permanently discontinue for recurrent grade 1 or 2 reactions or first occurrences of grade 3 or 4 reactions. Events of intracranial haemorrhage occurred from 1.7 to 19.3 months after avapritinib initiation.

Central nervous system (CNS) effects

Adverse reactions include cognitive impairment, dizziness, sleep disorders, mood disorders, speech disorders and hallucinations. Depending on severity, avapritinib may continue at same dose, withhold or permanently discontinue. If resumed, dose may be at same dose or reduced dose upon improvement.

Embryo-fetal toxicity
Can cause fetal harm. Females of reproductive potential should be appropriately counseled and use effective contraception.

CONTRAINDICATIONS

None

Clinical Pharmacology

Avapritinib is a tyrosine kinase inhibitor that targets PDGFRA and PDGFRA D842 mutants as well as KIT exon 11, 11/17 and 17 mutants. Certain mutations in PDGFRA and KIT result in autophosphorylation and constitutive activation of these receptors which contribute to tumor cell proliferation. Other potential targets of avapritinib include wild type KIT, PDGFRB and CSFR1.

Dose & Administration

ADULTS

300mg orally once daily, on an empty stomach (1 hour before or 2 hours after meals). Continue treatment until disease progression or unacceptable toxicity. Do not make up missed doses within 8 hours of the next scheduled dose.
For grade 1 adverse reactions: Reduce dose to 200mg once daily
For grade 2 adverse reactions: Reduce dose to 100mg once daily

PEDIATRICS

Safety and effectiveness of avapritinib in pediatric patients has not been established.

GERIATRICS

No overall differences in safety and efficacy were observed.

RENAL IMPAIRMENT

No dosage adjustment required for mild or moderate impairment; no dose adjustments have been established for severe renal impairment or end-stage renal disease (ESRD).

HEPATIC IMPAIRMENT

No dosage adjustment required for mild or moderate impairment; no dose adjustments have been established for severe hepatic impairment.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 100mg, 200mg and 300mg