CLINICAL UPDATE

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

Clinical Update

TYPE OF CLINICAL UPDATE

New Indication (Advanced Systemic Mastocytosis) and Strengths (25 mg, 50 mg)

FDA APPROVAL DATE

June 16, 2021

LAUNCH DATE

June 23, 2021

REVIEW DESIGNATION

Priority; Orphan

TYPE OF REVIEW

Type 1 - New Molecular Entity, New Drug Application (NDA): 212608

DISPENSING RESTRICTIONS

Specialty Pharmacy

Overview

INDICATION(S) FOR USE

- Gastrointestinal Stromal Tumor (GIST) – For the treatment of adults with unresectable or metastatic GIST harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations.
- Advanced Systemic Mastocytosis (AdvSM) – For the treatment of adult patients with AdvSM. AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SMAHN), and mast cell leukemia (MCL).
    - Limitations of Use: Not recommended for the treatment of patients with AdvSM with platelet counts of less than 50 X 10^9/L.

MECHANISMS OF ACTION

Avapritinib is a tyrosine kinase inhibitor that targets KIT D816V, PDGFRA and PDGFRA D842 mutants as well as multiple KIT exon 11, 11/17 and 17 mutants with half maximal inhibitory concentrations (IC_{50s}) less than 25 nM in biochemical assays. Certain mutations in PDGFRA and KIT can result in the autophosphorylation and constitutive activation of these receptors which can contribute to tumor and mast cell proliferation. Other potential targets for avapritinib include wild type KIT, PDGFRB, and CSFR1. In cellular assays, avapritinib inhibited the autophosphorylation of KIT D816V with an IC_{50} of 4 nM, approximately 48-fold lower concentration than wild-type KIT. In cellular assays, avapritinib inhibited the proliferation in KIT mutant cell lines, including a murine

mastocytoma cell line and a human mast cell leukemia cell line. Avapritinib also showed growth inhibitory activity in a xenograft model of murine mastocytoma with KIT exon 17 mutation.

Avapritinib inhibited the autophosphorylation of PDGFRA D842V, a mutation associated with resistance to approved kinase inhibitors, with an IC_{50} of 30 nM. Avapritinib also had anti-tumor activity in mice implanted with an imatinib-resistant patient-derived xenograft model of human GIST with activating KIT exon 11/17 mutations.

DOSAGE FORM(S) AND STRENGTH(S)

Tablets: 25 mg, 50 mg, 100 mg, 200 mg, and 300 mg

DOSE & ADMINISTRATION

- GIST: Select patients for treatment with Ayvakit™ based on the presence of a PDGFRA exon 18 mutation.
- GIST: The recommended dosage is 300 mg orally once daily.
- AdvSM: The recommended dosage is 200 mg orally once daily.

EFFICACY

Efficacy of new strengths is consistent with existing strengths.

Gastrointestinal Stromal Tumors:

The efficacy of Ayvakit™ was demonstrated in NAVIGATOR (NCT02508532), a multi-center, singlearm, open-label clinical trial. Eligible patients were required to have a confirmed diagnosis of GIST and an ECOG performance status (PS) of 0 to 2. Patients received Ayvakit™ 300 mg or 400 mg (1.33 times the recommended dose) orally once daily until disease progression or unacceptable toxicity. The trial initially enrolled patients at a starting dose of 400 mg, which was later reduced to the recommended dose of 300 mg due to toxicity. As there was no apparent difference in overall response rate (ORR) between patients who received 300 mg daily compared to those who received 400 mg daily, these patients were pooled for the efficacy evaluation. The major efficacy outcome measure was ORR based on disease assessment by independent radiological review using modified RECIST v1.1 criteria, 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. An additional efficacy outcome measure was duration of response (DOR).

Patients with GIST Harboring a PDGFRA Exon 18 Mutation

Patients with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation were identified by local or central assessment using a PCR- or NGS-based assay. The assessment of efficacy was based on a total of 43 patients, including 38 patients with PDGFRA D842V mutations. The median duration of follow up for patients with PDGFRA exon 18 mutations was 10.6 months (range: 0.3 to 24.9 months). The study population characteristics were median age of 64 years (range: 29 to 90 years), 67% were male, 67% were White, 93% had an ECOG PS of 0-1, 98% had metastatic disease, 53% had largest target lesion >5 cm, and 86% had prior surgical resection. 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 enrolled in NAVIGATOR are summarized in Table 8.

Table 8. Efficacy Results for Patients with GIST Harboring PDGFRA Exon 18 Mutations in NAVIGATOR

Efficacy Parameter	PDGFRA exon 18[1] N = 43	PDGFRA D842V N = 38
Overall Response Rate (95% CI)	84% (69%, 93%)	89% (75%, 97%)
Complete Response, n (%)	3 (7%)	3 (8%)
Partial Response, n (%)	33 (77%)	31 (82%)
Duration of Response	n=36	n=34
Median in months (range)	NR (1.9+, 20.3+)	NR (1.9+, 20.3+)
Patients with DOR ≥ 6-months, n (%)*	22 (61%)	20 (59%)

Abbreviations: CI=confidence interval; NR=not reached; NE=not estimable
+ Denotes ongoing response
[1] Exon 18 mutations other than D842V included in this population are: deletion of D842_H845 (n=3); D842Y (n=1); and deletion of D842_H845 with insertion of V (n=1).
* 11 patients with an ongoing response were followed < 6 months from onset of response.

Advanced Systemic Mastocytosis:

The efficacy of Ayvakit™ was demonstrated in EXPLORER (NCT02561988) and PATHFINDER (NCT03580655), two multi-center, single-arm, open-label clinical trials. Response-evaluable patients include those with a confirmed diagnosis of AdvSM per World Health Organization (WHO) and deemed evaluable by modified international working group-myeloproliferative neoplasms research and treatment European competence network on mastocytosis (IWG-MRT-ECNM) criteria at baseline as adjudicated by an independent central committee, who received at least 1 dose of Ayvakit™, had at least 2 post-baseline bone marrow assessments, and had been on study for at least 24 weeks, or had an end of study visit. All enrolled patients had an ECOG performance status (PS) of 0 to 3 and 91% had a platelet count of ≥ 50 X 109 /L prior to initiation of therapy.

Patients enrolled in EXPLORER received a starting dose of Ayvakit™ ranging from 30 mg to 400 mg (0.15 – 2 times the recommended dose) orally once daily. In PATHFINDER, patients were enrolled at a starting dose of 200 mg orally once daily. The efficacy of AYVAKIT in the treatment of AdvSM was based on overall response rate (ORR) in 53 patients with AdvSM dosed at up to 200 mg daily per modified IWG-MRT-ECNM criteria as adjudicated by the central committee. Additional efficacy outcome measures were duration of response (DOR), time to response, and changes in individual measures of mast cell burden.

The median duration of follow up for these patients was 11.6 months (95% confidence interval: 9.9, 16.3).

The study population characteristics were median age of 67 years (range: 37 to 85 years), 58% were male, 98% were White, 68% had an ECOG PS of 0-1, 32% had an ECOG PS of 2-3, 40% had ongoing corticosteroid therapy use for AdvSM at baseline, 66% had prior antineoplastic therapy, 47% had received prior midostaurin, and 94% had a D816V mutation. The median bone marrow mast cell infiltrate was 50%, the median serum tryptase level was 255.8 ng/mL, and the median KIT D816V mutant allele fraction was 12.2%.

Table 9. Efficacy Results for Patients with AdvSM in EXPLORER and PATHFINDER

	All evaluable patients	ASM	SM-AHN	MCL
Overall Response Rate[1], %	**N=53**	**N=2**	**N=40**	**N=11**
per modified IWG-MRT-ECNM	57	100	58	45
(95% CI[2])	(42, 70)	(16, 100)	(41, 73)	(17, 77)
Complete Remission with full or partial hematologic recovery, %	28	50	33	9
Partial Remission, %	28	50	25	36
Clinical Improvement, %	15	0	20	0
Stable Disease, %	19	0	13	45

Abbreviations: CI=confidence interval; CR=complete remission; CRh=complete remission with partial recovery of peripheral blood counts; PR=partial remission

[1] Overall Response Rate (ORR) per modified IWG-MRT-ECNM is defined as patients who achieved a CR, CRh or PR (CR + CRh + PR)

[2] Clopper–Pearson confidence interval

For all evaluable patients, the median duration of response was 38.3 months (95% confidence interval: 19, not estimable) and the median time to response was 2.1 months.

In the subgroup of patients with MCL, the efficacy of AYVAKIT was based on complete remission (CR).