avapritinib (Ayvakit™)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO181

Description

Avapritinib (Ayvakit) is an orally administered tyrosine kinase inhibitor that acts on platelet-derived growth factor receptor alpha (PDGFRA) and v-kit Hardy Zukerman 4 feline sarcoma viral oncogene homolog (KIT) mutants.

Length of Authorization

- N/A

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
avapritinib (Ayvakit)	300 mg tablets	Unresectable or metastatic Gastrointestinal Stromal Tumor with a PDGFRA exon 18 mutation	30 tablets/30 days
	200 mg tablets		
	100 mg tablets		

Initial Evaluation

I. Avapritinib (Ayvakit) is considered investigational when used for all conditions, **including** but not limited to gastrointestinal stromal tumor (GIST).

Renewal Evaluation

I. N/A

Supporting Evidence

I. The National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology guidelines state most PDGFRA mutations respond to imatinib (Gleevec), with the exception of PDGFRA D842V mutants, which do not respond to current TKI therapies [e.g. imatinib (Gleevec), sunitinib (Sutent), regorafenib (Stivarga)]. NCCN recommendations as of March 2020 were to treat patients with a PDGFRA mutation with avapritinib (Ayvakit) which is considered category 2A; however, is based on ongoing Phase I trial data.

II. GIST tumors have the following mutation prevalence: 75%-80% are KIT mutated, 5%-10% are PDGFRA mutated, and 10%-15% do not express KIT or PDGFRA. PDGFRA D842V mutants make up 60% of all PDGFRA mutations.

III. In an international survey, imatinib (Gleevec) had a median progression free survival (PFS) of 2.8 months for patients with a D842V substitution and 28.5 months for patients with other PDGFRA mutations. In 46 months of follow-up, median overall survival was 14.7 months for patients with D842V substitutions and was not reached for patients with other PDGFRA mutations.

IV. Avapritinib (Ayvakit) was FDA-approved off one on-going, Phase 1, open-label, single-arm trial (NAVIGATOR) in 43 patients with unresectable or metastatic GIST that is PDGFRA positive. Patients included had previously tried and failed one or more previous TKIs. The primary efficacy outcome is overall response rate (ORR), which is 84% (95% CI 69, 93), and 89% (95% CI 75, 97) for the PDGFRA exon 18 group, and PDGFRA D842V group, respectively. Secondary outcomes included duration of response (DOR), and PFS, which were only reported for the PDGFRA D842V group. DOR was 27.6 months (95% CI 14.3, 27.6), and median PFS was 29.5 months (95% CI not reported).

V. Clinical trials initially started avapritinib (Ayvakit) at 400 mg daily but reduced the dose to 300 mg due to toxicity. Of the patients receiving 400 mg and 300 mg, 97% and 72% experienced AEs of grade ≥3 severity, respectively. There was no noted difference in efficacy between the 400 mg and 300 mg doses.

VI. Avapritinib (Ayvakit) has not been compared against other treatments [e.g. imatinib (Gleevec), sunitinib (Sutent)] FDA-approved for unresectable or metastatic GIST. Avapritinib (Ayvakit) has notable serious side effects for anemia (9%), abdominal pain (3%), pleural effusion (3%), sepsis (3%), gastrointestinal hemorrhage (2%), vomiting (2%), acute kidney injury (2%), pneumonia (1%), and tumor hemorrhage (1%). Almost all patients experienced one AE (99%), with the most common AEs >20% being: edema, nausea, fatigue, cognitive impairment, vomiting, decreased appetite, diarrhea, increased lacrimation, abdominal pain, constipation, rash, dizziness, and hair color changes. There are no specific contraindications to using avapritinib (Ayvakit); however, warnings and precautions include: intracranial hemorrhage, central nervous system effects (e.g. cognitive impairment, dizziness, sleep disorders), and embryo-fetal toxicity.

VII. Avapritinib (Ayvakit) showed a 49% dose reduction rate, a 57% dose interruption rate, and a 16% permanent discontinuation rate due to intolerable adverse events.

Investigational or Not Medically Necessary Uses

I. Avapritinib (Ayvakit) has not been FDA-approved, OR sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Gastrointestinal Stromal Tumor
      i. The quality of the current evidence for avapritinib (Ayvakit) is considered low. The primary outcome, ORR, has not yet been correlated to clinically meaningful outcomes such as overall survival or quality of life parameters in GIST. The PFS result has unknown value due to the small sample size as well as the single arm, open-label design, and the medication has a significant safety profile. There is a

lack of evidence indicated that avapritinib (Ayvakit) would provide a net health benefit for members. Trials evaluating for treatment of GIST were underway as of February 2020, further clinical evaluation of safety and efficacy are needed to confirm a net health benefit and place in therapy for this medication.

B. Systemic mastocytosis (e.g. AdvSM, ASM, ISM, SSM)
C. Mast cell leukemia (MCL)

References

1. Ayvakit [Prescribing Information]. Blueprint Medicines: Cambridge, MA. January 2020.
2. Ayvakit [Manufacturer e-dossier]. Blueprint Medicines: Cambridge, MA. January 2020.
3. National Comprehensive Cancer Network. NCCN Guidelines: Soft Tissue Sarcoma. Available at: https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. Updated 01/23/2020.
4. Casali PG, Abecassis N, Aro HT, et al. Gastrointestinal stromal tumours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):iv68-iv78.
5. Heinrich M, Jones RL, von Mehren M, et al. Clinical Response to Avapritinib by RECIST and Choi Criteria in ≥4th Line and PDGFRA Exon 18 Gastrointestinal Stromal Tumors (GIST). Presented at: Connective Tissue Oncology Society 2019 Annual Meeting. November 15, 2019; Tokyo, Japan.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2020