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 Advanced Systemic Mastocytosis, including aggressive systemic mastocytosis, systemic mastocytosis with an associated hematological neoplasm and mast cell leukemia	30 tablets/30 days
	200 mg tablets		
	100 mg tablets		
	50 mg tablets		
	25 mg tablets		

Initial Evaluation

I. **Avapritinib (Ayvakit)** is considered investigational when used for all conditions, including but not limited to gastrointestinal stromal tumor (GIST) and advanced systemic mastocytosis (AdvSM) [e.g., aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), mast cell leukemia (MCL)].

Renewal Evaluation

I. N/A

Supporting Evidence

I. **Gastrointestinal Stromal Tumors (GIST)**

- 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 January 2021 were to treat patients with a PDGFRA mutation with avapritinib (Ayvakit) which is considered category 2A.
- 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.
- 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.
- Avapritinib (Ayvakit) was FDA-approved off interim analysis of one 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 was overall response rate (ORR), and at interim analysis, it was 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).
    1. At trial completion, the ORR in the *PDGFRA* D842V population (n = 56), 91% (51/56 patients). The DOR was 27.6 months (95% CI: 17.6 – not reached [NR]); the median PFS was 34.0 months (95% CI: 22.9 – NR); median OS was not reached.
- Single-arm, open-label clinical trials may provide indicators of primary efficacy. However, data from these trials are insufficient to determine causal relationship between drug use and patient outcomes and may not be clinically meaningful to make healthcare decisions. Additionally, the primary endpoint, ORR, despite being considered an optimal marker for a single-arm study design, is not a strong surrogate marker. Overall Response Rate (ORR) is not a direct measure of benefit and cannot be used as a comprehensive measure of drug activity.
- 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 medications significant safety profile. There is a lack of evidence indicated that avapritinib (Ayvakit) would provide a net health benefit for members.

- 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.
- 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.
- Avapritinib (Ayvakit) showed a 49% dose reduction rate, a 57% dose interruption rate, and a 22% permanent discontinuation rate due to intolerable adverse events.
- There is one ongoing randomized, open-label, phase 3 clinical trial studying avapritinib (Ayvakit) against regorafenib (Stivarga) in patients with locally advanced unresectable or metastatic GIST (VOYAGER). The primary endpoint is progression-free survival (PFS), notable secondary endpoints of objective response rate (ORR), and overall survival (OS). Preliminary results indicate the primary endpoint of statistically significant improvement in PFS was not met, and therefore patients are not being followed for OS. As of October 2021, the mature clinical trial data is not available.

II. **Advanced Systemic Mastocytosis (AdvSM)**

- Systemic mastocytosis (SM) is a rare, clonal neoplastic proliferation of mast cells driven by the *KIT*D816V mutation, resulting in uncontrolled proliferation and activation of abnormal mast cells in various tissues, including skin, bone marrow, gastrointestinal tract, liver, spleen, and lymph nodes. Advanced systemic mastocytosis (AdvSM) accounts for approximately 5% of all SM cases and includes aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL).

- According to NCCN guidelines, as of March 2021, treatment options for all forms of AdvSM include midostaurin, cladribine, and enrollment in clinical trial. Peginterferon alfa-2a ± prednisone may also be considered as another treatment option for patients diagnosed with ASM or SM-ANH. All therapies carry a category 2A recommendation.
- Avapritinib (Ayvakit) was FDA-approved based on the data from one phase 1 (EXPLORER) and one ongoing phase 2 (PATHFINDER) multicenter, single-arm, open-label clinical trials. Patients were considered evaluable if they had a confirmed diagnosis of AdvSM per World Health Organization (WHO) and met modified international working group-myeloproliferative neoplasms research and treatment-European competence network on mastocytosis (IWG-MRT-ECNM) criteria at baseline. There were 48 evaluable patients in the EXPLORER trial and 32 patients in the PATHFINDER trial at interim analysis. The primary efficacy endpoint in the PATHFINDER trial was overall response rate (ORR), which was 75%. A favorable ORR was observed in the EXPLORER trial, which was 75% (95% CI, 62 – 86). Additional efficacy outcome measures included duration of response (DOR) and time to response; the median DOR for all evaluable patients was 38.3 months (95% CI, 19, not estimable) and time to response was 2.1 months.
- Single-arm, open-label clinical trials may provide indicators of primary efficacy. However, data from these trials are insufficient to determine causal relationship between the drug use with patient outcomes and may not be clinically meaningful to make healthcare decisions. Additionally, the primary endpoint, ORR, despite being considered an optimal marker for a single-arm study design, is not a strong surrogate marker. Overall Response Rate (ORR) is not a direct measure of benefit and cannot be used as a comprehensive measure of drug activity.
- Based on information from the EXPLORER and PATHFINDER trials, the quality of evidence is considered low at this time given the single-arm, open-label trial design and use of surrogate marker as the primary efficacy outcome. At this time, there is no correlation between ORR and clinically meaningful outcomes of morbidity and mortality or quality of life parameters. Therefore, the true efficacy of the medication remains unknown. The medication also has a significant safety profile that is under post-marketing review by the FDA. There is a lack of evidence indicating that avapritinib (Ayvakit) would provide a net health benefit for members.
- Avapritinib (Ayvakit) is associated with notable serious side effects, including anemia (5%), subdural hematoma (4%), pleural effusion, ascites and pneumonia (3% each), acute kidney injury, gastrointestinal hemorrhage, intracranial hemorrhage, encephalopathy, gastric hemorrhage, large intestine perforation, pyrexia, and vomiting (2% each). No new safety signals were observed during the clinical trials for AdvSM.

- The FDA has issued a post-marketing requirement to provide additional evaluation of the safety signals of intracranial hemorrhage and cognitive adverse reactions associated with avapritinib (Ayvakit), which can only be adequately assessed in clinical trials. This trial is anticipated to be submitted by 12/2021. The FDA has also issued a second post-marketing requirement to submit the completed phase 2 PATHFINDER trial data, which is anticipated to be completed 1/2026.

Investigational or Not Medically Necessary Uses

I. Avapritinib (Ayvakit) has not been FDA-approved, OR sufficiently studied for safety and efficacy for any condition or setting to date, including those listed below:
   A. Gastrointestinal Stromal Tumor
   B. Advanced Systemic mastocytosis (e.g., AdvSM, ASM, SM-ANH, MCL)
   C. Non-advanced systemic mastocytosis (e.g., ISM, SSM)
   D. Soft Tissue Sarcoma

References

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3. National Comprehensive Cancer Network. NCCN Guidelines: Systemic Mastocytosis. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mastocytosis.pdf. Updated 07/09/2021.
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5. 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.
6. 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.
7. Jones RL, et al. Avapritinib in unresectable or metastatic PDGFRA D842V-mutant gastrointestinal stromal tumors: Long-term efficacy and safety data from the NAVIGATOR phase 1 trial. European Journal of Cancer. 145(2021); 132-142.
8. DeAngelo DJ, et al. PATHFINDER: Interim Analysis of Avapritinib in Patients with Advanced Systemic Mastocytosis (AdvSM). Presented at the American Association for Cancer Research Annual Meeting. May 2021.
9. Radia DH, et al. Avapritinib induces responses in patients with advanced systemic mastocytosis (AdvSM), regardless of prior midostaurin therapy. Poster Presentation at BSH 2021 Virtual ASM. April 2021.

Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of new indication advanced systemic mastocytosis (AdvSM) and updated trial information for gastrointestinal stromal tumors (GIST)	10/2021
Policy created	05/2020