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	Indication	Dosage Form	Quantity Limit
avapritinib (Ayvakit)	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	300 mg tablets	30 tablets/30 days
		200 mg tablets	
		100 mg tablets	
		50 mg tablets	
		25 mg tablets	
	Indolent Systemic Mastocytosis	25 mg tablets	30 tablets/30 days

Initial Evaluation

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

Renewal Evaluation

I. N/A

Supporting Evidence

I. Avapritinib (Ayvakit) is FDA-approved 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, adult patients with advanced systemic mastocytosis (AdvSM), including patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL), and adults with indolent systemic mastocytosis (ISM) whose symptoms are not adequately controlled by best supportive care (BSC).

II. Avapritinib (Ayvakit) has not been evaluated in patients under the age of 18; therefore, its safety and efficacy in the pediatric population is unknown.

III. Avapritinib (Ayvakit) has not been sufficiently evaluated for safety and/or efficacy in combination with any other oncolytic medication. Avapritinib (Ayvakit) has been studied when used in combination with BSC therapies (e.g., antihistamines, cromolyn, anti-IgE antibody, leukotriene receptor antagonists, corticosteroids, etc.) in patients with systemic mastocytosis.

IV. Due to the complex nature of treating any of the diagnoses listed above, treatment with avapritinib (Ayvakit) should be prescribed by, or in consultation with, an oncologist. When being requested for systemic mastocytosis, treatment may be prescribed by, an oncologist, allergist, immunologist gastroenterologist, or dermatologist.

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

   a. 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)]. Avapritinib (Ayvakit) carries a category 2A recommendation as a preferred first line regimen for patients with unresectable, progressive, or metastatic GIST with a PDGFRA exon 18 mutations that are insensitive to imatinib (including PDGFRA D842V). Avapritinib (Ayvakit) is also listed under “useful in certain circumstances” as an additional treatment option after progression on approved therapies.

   b. 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.

   c. 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.

   d. 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.

e. 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.

f. 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.

g. 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.

h. Avapritinib (Ayvakit) showed a 49% dose reduction rate, a 57% dose interruption rate, and a 22% permanent discontinuation rate due to intolerable adverse events.

i. 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.

j. The VOYAGER trial was a randomized, open-label, phase 3 clinical trial evaluating PFS, ORR, and OS of avapritinib (Ayvakit) against regorafenib (Stivarga) in patients with locally advanced unresectable or metastatic GIST. There was no significant difference in median PFS between avapritinib and regorafenib in patients with molecularly unselected, late-line GIST. In May 2020, the FDA issued a complete response letter stating that it will not approve a new drug application for avapritinib for use in the treatment of adult patients with unresectable or metastatic fourth-line GIST based on data from VOYAGER.

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

a. 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 the following disease variants: aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL).

b. According to NCCN guidelines for systemic mastocytosis, as of May 2022, treatment options for AdvSM include cytoreductive therapy, allogenic HCT, and enrollment in clinical trials. Cytoreductive therapies include avapritinib, midostaurin, cladribine, imatinib, and peginterferon alfa-2a ± prednisone. The guidelines note the following treatment considerations for AdvSM, all with category 2A recommendations:

1. Preferred regimens: Avapritinib and midostaurin
2. Other recommended regimens: Cladribine for patients that may require when rapid debulking of disease. Peginterferon alfa-2a, has a cytostatic mechanism of action and may be more suitable for patients with slowly progressive disease without the need for rapid cytoreduction
3. Useful in certain circumstance: Imatinib is FDA-approved for adult patients with ASM without the KIT D816V mutation (including wild-type) or with unknown mutational status. Imatinib included as a treatment option for patients with ASM (for KIT D816V mutation negative or unknown, WDSM, or if eosinophilia is present with FIP1L1-PDGFRA fusion gene may also be considered as another treatment option for patients diagnosed with ASM or SM-ANH.

c. Avapritinib (Ayvakit) was FDA-approved based on the data from one phase 1 (EXPLORER) and a prespecified interim analysis of the 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.

d. A pooled efficacy and safety analysis from the EXPLORER and PATHFINDER trials compared avapritinib and best available therapy in patients with AdvSM who received ≥1 systemic therapy prior to avapritinib. The ORR in n=31 evaluable patients was 71% (95% CI: 52 – 86), including 19% with complete remission (CR)/CR with partial recovery of peripheral blood counts (CRh). Median OS was not reached (median follow-up 17.7 months). Median time to response was 2.3 months, median time to CR/CRh was 7.4 months. The median duration of response (DOR) was not reached. Median OS was significantly improved in patients treated with avapritinib (49.0 months [95% CI, 46.9 months–not estimable] vs. 26.8 months [95% CI, 18.2–39.7 months]; adjusted HR, 0.48; 95% CI, 0.29–0.79; P = .004). Data further demonstrated that avapritinib treatment was associated with improved OS compared to midostaurin (HR, 0.59; 95% CI, 0.36–0.97; P < .001) and cladribine (HR, 0.32; 95% CI, 0.15–0.67; P = .003). OS was also improved in patients with SM-AHN treated with avapritinib compared to best available therapy. The efficacy of avapritinib in patients with AdvSM was established irrespective of prior therapies or S/A/R mutation status.
e. 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.
f. 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.

g. 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). Grade ≥3 cytopenias occurred in up to one-quarter of patients and facial/periorbital edema (any grade) in one-half (3 percent grade ≥3 facial/periorbital edema). No new safety signals were observed during the clinical trials for AdvSM.

h. In patients with AdvSM, a platelet count must be performed prior to initiating therapy and every 2 weeks first the first 8 weeks of starting therapy. Thrombocytopenia is listed as a warning/precaution for therapy when used in patients with AdvSM. Avapritinib (Ayvakit) is not recommended for the treatment of patients with AdvSM with platelet counts of less than 50 X 10^9/L.

i. 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.

VII. **Non-advanced, indolent systemic mastocytosis (ISM)**

a. Indolent systemic mastocytosis (ISM) is defined as a rare, usually benign, chronic, form of systemic mastocytosis characterized by an abnormal accumulation of neoplastic mast cells mainly in the bone marrow, but also in other organs or tissues such as the skin. ISM accounts for more than 70% of all SM cases in published literature. One of the key diagnostic determinants that differentiates ISM from other SM subtypes includes absence of C-findings (are indicative of organ damage produced by mast cell infiltration via biopdy), no evidence of an associated hematologic neoplasm, low mast cell burden, and higher prevalence of skin lesions. Patients with ISM have a near-normal life expectancy, and ISM carries a low risk of progression with < 3% of patients progressing to a more severe form of systemic mastocytosis. The most common cause of death is disability or anaphylaxis.

b. Avapritinib (Ayvakit) is the first FDA-approved therapy for ISM. Approval was based on data from the randomized, double-blind, placebo-controlled part of the PIONEER trial, 141 patients received avapritinib (Ayvakit) 25 mg once daily + best supportive care (BSC) and 71 patients received placebo + BSC. The study included adults with an indolent SM diagnosis confirmed by central pathology review, and moderate-to-severe symptom burden despite an optimized regimen of BSC, which may include antihistamines, cromolyn, anti-IgE antibody, leukotriene receptor antagonists, corticosteroids, etc. All patients were able to continue symptom-directed therapy throughout the trial and, following completion of the 24-week treatment period, had the option to receive

avapritinib (Ayvakit) in an open-label extension study (HARBOR trial). The primary endpoint was the change in patient-reported disease symptoms as assessed by the ISM Symptom Assessment Form (ISM-SAF) total symptom score (TSS) Key secondary endpoints include mean change in individual symptom scores of ISM-SAF, change in most severe symptom score, QoL, and several biomarkers of mast cell burden. Avapritinib (Ayvakit) achieved a statistically significant improvement in TSS compared to placebo at 24 weeks (p=0.003) and demonstrated statistically significant differences all key secondary endpoints, observed with improvements in severe symptoms and across all symptoms measured by the ISM-SAF that deepened over time.

c. The most common treatment-related AEs were headache (8 %), nausea (6%), peripheral edema (6%), periorbital edema (6%), and dizziness (3%). Across treatment arms, most adverse events were mild to moderate in severity, and treatment-related AEs leading to discontinuations were low for both arms (< 2% each). No new safety signals were observed during the clinical trials for ISM.
d. Data from this trial are insufficient to determine causal relationship between the drug use with patient outcomes and may not be clinically meaningful to make healthcare decisions. It is unclear whether avapritinib (Ayvakit) provides a clinically meaningful improvement in a condition that is already indolent. Furthermore, the NCCN guideline acknowledges that the IWG-MRT-ECNM response criteria were developed mainly for use in clinical trials and may not be widely used in clinical practice. There is a lack of evidence indicating that avapritinib (Ayvakit) would provide a net health benefit for members with an already indolent form of SM.
e. The NCCN guidelines recommend observation or treating mast cell activation symptoms with best supportive care in patients with symptomatic ISM. The guidelines do not have any pharmacotherapies listed in their treatment algorithm for ISM nor have avapritinib (Ayvakit) noted as a potential therapy option for ISM. Furthermore, the NCCN guidelines encourages enrollment in well-designed clinical trials investigating novel therapeutic strategies regardless of SM type. As of May 2023, an expanded access program (EAP) (NCT04714086) for avapritinib for patients with ISM is available, which may provide access to therapy in lieu of clinical trial enrollment.

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 (GIST)
   B. Advanced systemic mastocytosis (AdvSM, ASM, SM-ANH, MCL)
   C. Non-advanced, indolent systemic mastocytosis (ISM)

D. Non-advance, smoldering systemic mastocytosis (SMM)
E. Soft tissue sarcoma
F. Solid tumors with or without CKIT or PDGFRA mutations
G. Acute myeloid leukemia (AML) with or without CKIT or PDGFRA mutations

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
regorafenib (Stivarga)	Gastrointestinal Stromal Tumors (GIST)
dasatinib (Sprycel)	Gastrointestinal Stromal Tumors (GIST)
ripretinib (Qinlock)	Gastrointestinal Stromal Tumors (GIST)
sunitinib (Sutent)	Gastrointestinal stromal tumors (GIST)
imatinib (Gleevec)	Gastrointestinal stromal tumors (GIST) Systemic mast cell disease (systemic mastocytosis)
midostaurin (Rydapt)	Systemic mast cell disease (aggressive systemic mastocytosis, systemic mastocytosis with hematological neoplasm, mast cell leukemia)
omalizumab (Xolair)	Systemic mastocytosis

Policy Implementation/Update

Action and Summary of Changes	Date
Added new indication of indolent systemic mastocytosis (ISM). Updated supporting evidence, E/I section, references for all indications. Added solid tumors and AML to E/I section. Added related policies section.	05/2023
Addition of new indication advanced systemic mastocytosis (AdvSM) and updated trial information for gastrointestinal stromal tumors (GIST)	10/2021
Policy created	05/2020