AYVAKIT® (avapritinib) **SAMPLE Clinical Policy**

Objective:

This sample prior authorization (PA) policy is provided as a courtesy from Blueprint Medicines Corporation. The purpose of this sample is to describe clinical criteria that may be considered for use in determining clinical appropriateness of care and determination of coverage as relevant to use of AYVAKIT. Disease state background and abbreviated product safety and efficacy information are included but **are not intended to substitute for your organization's clinical review.** Please refer to the AYVAKIT Important Safety Information and Prescribing Information for full safety and efficacy data or contact your Blueprint National Account Executive if you have any questions regarding AYVAKIT.

Background on Avapritinib

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*.[1]

AYVAKIT® (avapritinib) is indicated for the treatment of adult patients with[1]:

- Unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations, and

- Advanced SM (AdvSM) including patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).

  Limitations of Use: AYVAKIT is not recommended for the treatment of patients with AdvSM with platelet counts of $<50 \times 10^9$/L.

- Indolent systemic mastocytosis (ISM).

  Limitations of Use: AYVAKIT is not recommended for patients with platelet counts of $<50 \times 10^9$/L.

Background on Systemic Mastocytosis

Systemic mastocytosis (SM) is a clonal mast cell neoplasm that is driven by the *KIT* D816V mutation in ~95% of cases.[2-5] Other somatic mutations occurring in <5% of adults with SM include V560G, D815K, D816Y, insVI815-816, D816F, D816H, and D820G.[5] SM is associated with uncontrolled activation and proliferation of abnormal mast cells, resulting in a wide range of heterogeneous and unpredictable symptoms.[5-7] There are more than 20 symptoms that can occur across multiple organ systems in patients with SM; they include but are not limited to: anaphylaxis (with hypotension and syncope), abdominal pain or cramping, diarrhea, osteoporosis, brain fog, pruritus, and dyspnea.[5,6,8,9]

SM is a rare disease. The prevalence of SM is ~1 in 10,000 people.[10] It is estimated that ~32,000 people in the United States may have SM.[10,11]

Receiving an accurate diagnosis can be a prolonged and complicated experience for patients with SM. In a descriptive analysis based on the Blueprint Medicines-sponsored TouchStone survey, receiving a diagnosis on average took ~6 years from symptom onset and visits with ~6 specialists.[12*]

SM consists of non-advanced and advanced forms, and can be further classified as subtypes using the diagnostic criteria defined by the World Health Organization (WHO).[13] The WHO criteria may include some, but not necessarily all, of the following assessments: serum tryptase levels, biopsy of bone marrow or other extracutaneous tissues, mutation testing, imaging, and mast cell immunophenotyping.[5,13]

Background on Indolent Systemic Mastocytosis

Indolent systemic mastocytosis (ISM) is a non-advanced form of SM.[14] ISM is classified using the WHO criteria as meeting the criteria for SM but with absence of organ damage or associated hematologic neoplasm (AHN).[5,13] ISM represents ~75% to 90% of cases of SM.[2,10,14]

Patients with ISM can experience a wide range of chronic, potentially debilitating symptoms, such as skin lesions, abdominal pain, diarrhea, bone pain, brain fog, and fatigue.[5,6,15-17] In addition, some patients with ISM may experience an increase in symptom burden. In a retrospective, US claims-based analysis sponsored by Blueprint Medicines, 15.1% of patients with lower-symptom-burden ISM progressed to higher-symptom-burden ISM over a 24-month interval (n/N=493/3263).[11†] Disease progression has been observed in ~5% of patients with ISM.[10,11,14]

The current treatment approach involves symptomatic therapies, such as over-the-counter and prescription medications (off-label). Historically, there have been no therapies approved for the treatment of ISM.[5,18]

AYVAKIT is a TKI that targets *KIT* D816V—the underlying driver of disease in ~95% of patients with ISM.[1-4]

The safety and efficacy of AYVAKIT was evaluated in PIONEER (NCT03731260), a phase 2, double-blind, randomized, placebo-controlled study in adult patients with ISM based on WHO classification. Enrolled patients had moderate to severe symptoms despite receiving at least 2 symptom-directed therapies. AYVAKIT 25 mg QD plus best supportive care (BSC) treatment demonstrated statistically significant improvements for primary and key secondary efficacy endpoints compared with placebo plus BSC at Week 24.[1]

AYVAKIT 25 mg QD plus BSC achieved a statistically significant improvement in Indolent Systemic Mastocytosis-Symptom Assessment Form (ISM-SAF) total symptom score (TSS) compared with placebo plus BSC at Week 24 (absolute mean change in ISM-SAF TSS, -15.33 points in the AYVAKIT 25 mg QD plus BSC arm vs -9.64 points in the placebo plus BSC arm, 2-sided *P*=0.012).

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*Based on results from US adults with a self-reported SM diagnosis (N=56) who completed an online survey of 100 items including the 12-item Short-form Health Survey, the ISM Symptom Assessment Form, and the Work Productivity and Activity Impairment Questionnaire.[12]

†Based on a Blueprint Medicines–sponsored retrospective analysis using a large, nationally representative US claims database including patients with commercial, Managed Medicaid, and Medicare Advantage coverage (2015-2022). Patients were identified using a claims-based algorithm based on the WHO criteria for SM. Total study population size: N=8710. Higher-symptom-burden ISM included patients with ≥2 SM ICD-10-CM diagnosis codes (D47.02) or an SM diagnosis code (D47.02) following an ambiguous mast cell neoplasm diagnosis code, as well as any of the following: ≥2 diagnosis codes indicative of organ involvement, ≥2 prescriptions for advanced SM-directed therapies (TKIs, cytoreductive therapies including interferons, cladribine, brentuximab vedotin, omalizumab), ≥1 diagnosis code indicating compromised bone, hepatomegaly, splenomegaly or weight loss, and/or ≥4 claims of high-frequency anaphylaxis/epinephrine injector. Lower-symptom-burden ISM included remaining patient cohort excluding AdvSM.[11]

AYVAKIT 25 mg QD plus BSC also demonstrated significant improvements across objective measures of mast cell burden, including serum tryptase levels, *KIT* D816V allele frequency (VAF), and reductions in bone marrow mast cell aggregates: 53.9% of patients in the AYVAKIT 25 mg QD plus BSC arm achieved ≥50% reduction in serum tryptase compared with 0% in the placebo plus BSC arm (P <0.0001); 67.8% of patients achieved ≥50% reduction in *KIT* D816V VAF compared with 6.3% in the placebo plus BSC arm (P <0.0001); and 52.8% of patients achieved ≥50% reduction in bone marrow mast cell aggregates compared with 22.8% in the placebo plus BSC arm (P <0.0001).[1]

Improvements were observed in the 12-item Short-form Health Survey (SF-12®) physical component scores by 20% (14% to 26%) in the AYVAKIT 25 mg QD plus BSC arm and 12% (5% to 19%) in the placebo plus BSC arm; the SF-12 mental health component scores increased by 12% (8% to 17%) in the AYVAKIT 25 mg QD plus BSC arm and 6% (-1% to 13%) in the placebo plus BSC arm.[19]

AYVAKIT was generally well tolerated in PIONEER for patients with ISM. Serious adverse reactions occurred in 1 patient (0.7%) who received AYVAKIT due to pelvic hematoma. Permanent discontinuation of AYVAKIT due to an adverse reaction occurred in 1 patient (0.7%) due to dyspnea and dizziness. Dosage interruptions of AYVAKIT due to an adverse reaction occurred in 5% of patients. The most common adverse reactions (≥10%) in the AYVAKIT group were eye edema, dizziness, peripheral edema, and flushing. Of all adverse reactions, 55% were Grade 1, 38% were Grade 2, and 7% were Grade 3. Among patients with edema adverse reactions, 95% were Grade 1 and 5% were Grade 2. Among patients with hemorrhage adverse reactions, 86% were Grade 1 and 14% were Grade 2.[1]

Background on Advanced Systemic Mastocytosis

Advanced SM (AdvSM) is a subset of SM. The World Health Organization (WHO) has identified 3 subtypes of AdvSM: aggressive SM (ASM), mast cell leukemia (MCL), and SM with associated hematologic neoplasm (SM-AHN). The classification of AdvSM can be made based on a combination of major and minor criteria as established by the WHO, and organopathy resulting from mast cell infiltration ("C-findings").[8]

Advanced disease may further increase risk of multi-organ dysfunction, organ failure, and shortened overall survival (OS).[14,20*] In a retrospective study, the median OS was 3.5 years for patients with ASM, 2 years for SM-AHN, and <6 months for MCL.[20*]

Based on US claims data, the prevalence of AdvSM is estimated to be approximately 2300 people.[11†] Up to 70% of patients with AdvSM have SM-AHN.[21]

Although symptom-directed treatment should be considered in all patients with AdvSM, patients may still have debilitating symptoms that are poorly controlled or refractory; furthermore, symptom-directed treatment does not prevent organ damage or address the underlying cause of disease.[5,8]

The safety and efficacy of AYVAKIT in AdvSM were evaluated in the phase 1 EXPLORER (NCT02561988) and phase 2 PATHFINDER (NCT03580655) trials. AYVAKIT demonstrated efficacy in patients with AdvSM regardless of AdvSM subtype. Based on a total of 53 patients with AdvSM who

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CI, confidence interval; IWG-MRT-ECNM, International Working Group-Myeloproliferative Neoplasms Research and Treatment & European Competence Network on Mastocytosis.

*OS was examined in a retrospective study at the Mayo Clinic between 1976 and 2007. Median follow-up was 20.7 months.[20] A later study with 23 patients with MCL demonstrated a median OS for patients with MCL of 1.9 years, with a 10-year survival of 29.9%.[14]

†Based on the total prevalent SM patients observed in US claims data between 12/31/2017 and 5/31/2022. Patients were identified as having SM per ICD-10-CM diagnosis codes for SM. Patients were identified as prevalent if they were found to have generated any billing claim in the prior 6 months.[11]

were evaluable for response, 66% had prior antineoplastic therapy and 47% had received prior midostaurin.[1]

Overall response rate (ORR) was defined, per modified IWG-MRT-ECNM criteria, as complete remission (CR), complete remission with partial hematologic recovery (CRh) and partial response (PR); 57% (CR/CRh 28%; PR 28%) [95% CI: 42%, 70%]. With the addition of patients who had a clinical improvement, 72% ORR was achieved.* Median duration of response (DOR) was 38.3 months (95% CI: 19, NE). ORR was achieved across subtypes of AdvSM: 45% for MCL (n=11; 95% CI: 17%, 77%); 58% for SM-AHN (n=40; 95% CI: 41%, 73%); and 100% for ASM (n=2; 95% CI: 16%, 100%).[1]

AYVAKIT was generally well tolerated in EXPLORER and PATHFINDER for patients with AdvSM, as the majority of adverse reactions were Grade 1 or 2. The most common adverse reactions (≥20%) were edema, diarrhea, nausea, and fatigue/asthenia. Serious adverse reactions were seen in 34% of patients receiving the recommended starting dose of 200 mg (N=80).[1]

In AdvSM patients who received AYVAKIT at 200 mg daily, intracranial hemorrhage (ICH) occurred in 2 of 75 patients (2.7%), who had platelet counts of ≥50 x 10^9/L. AYVAKIT is not recommended in patients with AdvSM with baseline platelet counts <50 x 10^9/L. Dose reduction or interruption should be considered if platelet counts decrease below 50 x 10^9/L during treatment.[1]

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend avapritinib (AYVAKIT) as a preferred Category 2A treatment option (if platelets are ≥50 x 10^9/L) for ASM, SM-AHN when the SM component requires more immediate treatment, and MCL ± AHN). Avapritinib is not recommended for the treatment of patients with AdvSM with platelet counts of <50 x 10^9/L.[22]

Background on Gastrointestinal Stromal Tumor

Gastrointestinal stromal tumor (GIST) is the most common sarcoma of the GI tract.[23] The median age at diagnosis is 64 years. The highest incidence rates are among those aged 70 to 79 years, and it is 36% more common in men than women.[24] Common metastatic sites include liver and abdominal cavity.[25] Malignant GIST was once viewed as one of the most treatment-refractory tumors, with historically low response rates to conventional chemotherapy and/or radiation therapy. However, the identification of the spectrum of mutations in GIST (eg, *PDGFRA*) has resulted in improved outcomes in certain patient populations.[23]

PDGFRA exon 18 is a primary mutation in approximately 6% of all GIST cases.[26] The NCCN Guidelines® recommend testing for mutations in *KIT* and *PDGFRA* prior to initiation of treatment, given that the presence and type of these mutations are predictive of response to select first-line therapies.[27] The most common *PDGFRA* exon 18 mutation in GIST is the D842V mutation,[26] which is resistant to imatinib; in a retrospective study, out of 31 patients with the *PDGFRA* D842V mutation treated with imatinib, ORR was 0%, median progression-free survival was 2.8 months, and median OS was 14.7 months with 45.3 months of follow-up.[28]

The safety and efficacy of AYVAKIT in patients with unresectable or metastatic GIST were evaluated in NAVIGATOR (NCT02508532), a multicenter, open-label, single-arm trial. The major efficacy outcome measure was ORR per modified RECIST v1.1 criteria, at starting doses of avapritinib 300 mg/400 mg daily, and included CR and PR. An additional efficacy outcome measure was DOR. ORR for *PDGFRA* exon 18 (n=43) and *PDGFRA* D842V (n=38) mutations were 84% (CR 7%, PR 77%) [95% CI: 69, 93]

NCCN, National Comprehensive Cancer Network®(NCCN®); NE, not evaluable.

*Clinical improvement is defined as having a response duration of ≥12 weeks and fulfillment of 1 or more of the nonhematologic and/or hematologic response criteria.[29]

and 89% (CR 8%, PR 82%) [95% CI: 75, 97], respectively. Median DOR was not yet reached in either cohort.[1]

Serious adverse reactions occurred in 52% of patients receiving AYVAKIT. Serious adverse reactions occurring in ≥1% of patients who received AYVAKIT were 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%).[1]

Permanent discontinuation due to adverse reactions occurred in 16% of patients who received AYVAKIT. Adverse reactions requiring permanent discontinuation in more than one patient were fatigue, abdominal pain, vomiting, sepsis, anemia, acute kidney injury, and encephalopathy.[1]

The most common adverse reactions (≥20%) were edema, nausea, fatigue/asthenia, cognitive impairment, vomiting, decreased appetite, diarrhea, hair color changes, increased lacrimation, abdominal pain, constipation, rash, and dizziness.[1]

NCCN Guidelines recommend (2A) avapritinib as a first-line treatment option for unresectable, progressive or metastatic GIST with *PDGFRA* exon 18 mutations that are insensitive to imatinib, including *PDGFRA* D842V mutation. It also recommends avapritinib as a post-resection treatment option for GIST with significant morbidity and PDGFRA exon 18 mutations that are insensitive to imatinib (including PDFGRA D842V mutations) or persistent gross residual disease with *PDGFRA* exon 18 mutation (including D842V mutation).[27]

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***SAMPLE* Prior Authorization Criteria**

AYVAKIT® (avapritinib) tablet

Last Review Date: May 22, 2023

FDA-approved Indications:

Avapritinib is indicated for the treatment of adult (age 18 years or older) patients with:

- Unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (*PDGFRA)* exon 18 mutation, including *PDGFRA* D842V mutations
- Advanced systemic mastocytosis, including:
  - Aggressive systemic mastocytosis (ASM)
  - Systemic mastocytosis with associated hematological neoplasm (SM-AHN)
  - Mast cell leukemia (MCL)
  - Limitations of Use: AYVAKIT is not recommended for the treatment of patients with AdvSM with platelet counts of less than 50 x 10^9/L
- Indolent systemic mastocytosis
  - Limitations of Use: AYVAKIT is not recommended for patients with platelet counts of less than 50 X 10^9/L

Policy/Criteria:

I. Initial Approval Criteria

A. Gastrointestinal stromal tumor (GIST) – must meet all criteria:
   i. Age ≥18
   ii. Individual has a diagnosis of unresectable or metastatic gastrointestinal stromal tumor (GIST); AND
   iii. Individual has test results confirming a platelet-derived growth factor receptor alpha *(PDGFRA*) exon 18 mutation

B. Advanced systemic mastocytosis – must meet all criteria:
   i. Age ≥18
   ii. Individual has a confirmed diagnosis of one of the following:
      a) Aggressive systemic mastocytosis (ASM)
      b) Systemic mastocytosis with associated hematologic neoplasm (SM-AHN)
      c) Mast cell leukemia (MCL)

C. Indolent systemic mastocytosis – must meet all criteria:
   i. Age ≥18
   ii. Physician attestation of ISM diagnosis

D. NCCN-recommended regimens
   i. Other indications that are not listed but are cited in the National Comprehensive Cancer Network (NCCN) guidelines as a category 1, 2A, or 2B recommendation

Initial approval duration: 12 months

II. Contraindications:

1. There are no contraindications.

III. Continuation of Coverage (Renewal Request)

A. GIST
   i. Prescriber attests that the member has no evidence of disease progression
   ii. **Renewal approval duration:** 12 months

B. AdvSM
   i. Prescriber attests that the member has no evidence of disease progression
   ii. **Renewal approval duration:** 12 months

C. ISM
   i. Prescriber attests that the member has stable disease
   ii. **Renewal approval duration:** 12 months

Dosage and Administration:

I. GIST

A. Maximum dose does not exceed 300 mg (1 tablet) per day

II. AdvSM

A. Maximum dose does not exceed 200 mg (1 tablet) per day

III. ISM

A. Maximum dose does not exceed 25 mg (1 tablet) per day

Quantity Limit:

The quantity limit for all strengths of AYVAKIT® (avapritinib) is 30 tablets per 30 days.

Product Availability:

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

Warnings/Precautions:

I. Intracranial Hemorrhage
II. Cognitive Effects
III. Photosensitivity
IV. Embryo-fetal Toxicity

Please refer to current prescribing information for full safety information regarding adverse reactions and recommendations on dose administration and adjustments.