For U.S. Healthcare Professionals Only.

AYVAKIT®
avapritinib | tablets

Suspecting and Diagnosing Advanced SM

SM=Systemic Mastocytosis.

Advanced SM is a clonal mast cell neoplasm caused by the KIT D816V mutation in ~95% of cases.[1-3]

INDICATION

AYVAKIT® (avapritinib) is indicated for the treatment of adult patients with 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 x 10^9/L.

Please see Important Safety Information on pages 6-7, and the full Prescribing Information for AYVAKIT.

Patient experience: Disease burden and diagnostic delay

Advanced SM is a clonal mast cell neoplasm **caused by the KIT D816V mutation in ~95% of cases.**[1-3] There are 3 different subtypes of Advanced SM: aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).[4,5]

People living with Advanced SM can experience significant symptom burden (including organ damage) and impact to their lives. [6,7]

Organ damage caused by mast cell infiltration is considered a "C" finding—part of the WHO diagnostic criteria for Advanced SM.[5]

DIAGNOSING ADVANCED SM CAN TAKE YEARS

3 YEARS

The median time from symptom onset to diagnosis for patients with Advanced SM is 3 years.[8]*

36%

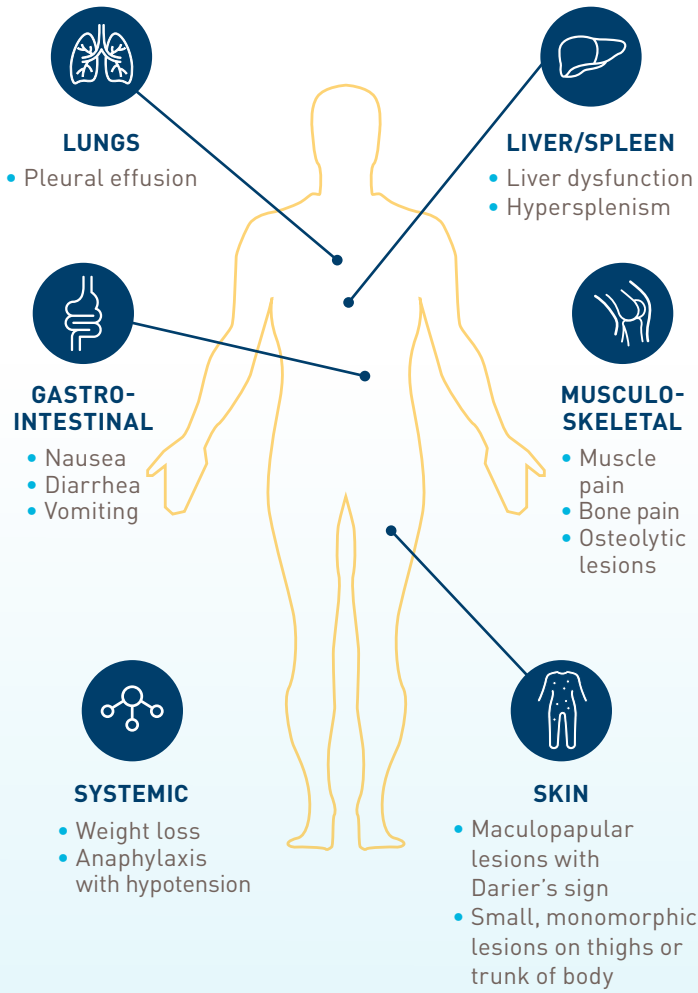
In a retrospective analysis of patients with Advanced SM, about 36% (51/140) were misdiagnosed.[9]

*Based on a survey in patients with Advanced SM (n=13).

Identifying Advanced SM in your practice

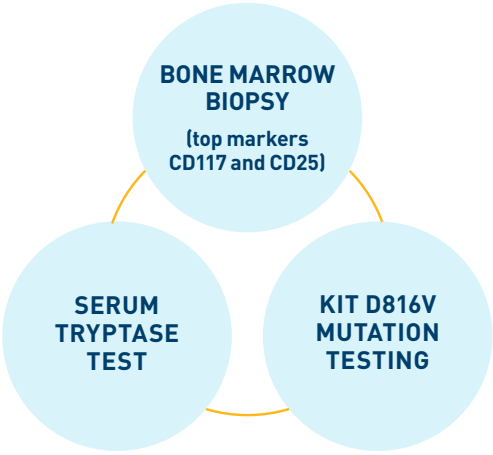
Knowing the symptoms of Advanced SM may help you shorten a patient's time to diagnosis.

Common mast cell mediator symptoms of Advanced SM include maculopapular rash and life-threatening anaphylaxis. Additionally, patients can experience organ damage and related symptoms depicted below[5,10-12]:



Testing for and diagnosing Advanced SM

Accurately evaluating a patient for Advanced SM is a multistep process. The diagnostic workup for suspected Advanced SM includes[7,13]:



Advanced SM may be missed in patients with suspected myeloid neoplasms. Incidental KIT mutation findings should prompt a full diagnostic workup for Advanced SM.[9,14]

Myeloid mutation panels alone may fail to detect KIT D816V, as NGS assays can exhibit low sensitivity. Higher-sensitivity assays can be used to detect KIT D816V in most patients with Advanced SM.[13,15]

Confirming a diagnosis of Advanced SM can help you determine the treatment course that may be best for your patient.

Performing a high-sensitivity (<1%) KIT D816V assay is recommended for patients where Advanced SM is suspected.[7,13]

NGS=next-generation sequencing.

WHO diagnostic criteria

DIAGNOSIS OF SM REQUIRES THE PRESENCE OF 1 MAJOR CRITERION AND ≥1 MINOR CRITERION, OR ≥3 MINOR CRITERIA[11]

MAJOR CRITERION

Multifocal aggregates of ≥15 mast cells in bone marrow sections and/or other extracutaneous organ(s)

MINOR CRITERIA

- In biopsy sections of bone marrow or other extracutaneous organs, >25% of mast cells in the infiltrate are spindle-shaped or have atypical morphology; or >25% of all mast cells in bone marrow aspirate smears are immature or atypical
- Detection of an activating point mutation at codon 816 in KIT in bone marrow, blood, or another extracutaneous organ
- Mast cells in bone marrow, blood, or other extracutaneous organs express CD25, with or without CD2, in addition to normal MC markers
- Serum total tryptase persistently >20 ng/mL (if the patient has an associated myeloid neoplasm, then this parameter is not valid)

FOR AN ADVANCED SM DIAGNOSIS, CRITERIA FOR ONE OF THE ADVANCED SM SUBTYPES MUST BE MET[11]

AGGRESSIVE SYSTEMIC MASTOCYTOSIS (ASM)

- ≥1 "C" findings[a] and no evidence of mast cell leukemia

SYSTEMIC MASTOCYTOSIS WITH AN ASSOCIATED HEMATOLOGICAL NEOPLASM (SM-AHN)

- Also meets criteria for AHN as a distinct entity per the WHO classification

MAST CELL LEUKEMIA (MCL)

- Bone marrow aspirate smears show ≥20% mast cells. In classic cases, mast cells account for ≥10% of peripheral blood white cells

Subtyping may be complex and require expert consultation[11]

[a]C-findings: Bone marrow dysfunction manifested by ≥1 cytopenia(s) (absolute neutrophil count <1.0 x 10^9/L, hemoglobin <10 g/dL, or platelets <100 x 10^9/L); palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension; palpable splenomegaly with hypersplenism; malabsorption with weight loss from gastrointestinal tract mast cell infiltrates; skeletal involvement with large osteolytic lesions and/or pathologic fractures.

IMPORTANT SAFETY INFORMATION

There are no contraindications for AYVAKIT.

Serious intracranial hemorrhage (ICH) may occur with AYVAKIT treatment; fatal events occurred in <1% of patients. Overall, ICH (eg, subdural hematoma, ICH, and cerebral hemorrhage) occurred in 2.9% of 749 patients who received AYVAKIT. In AdvSM patients who received AYVAKIT at 200 mg daily, ICH occurred in 2 of 75 patients (2.7%) who had platelet counts ≥50 x 10^9/L prior to initiation of therapy and in 3 of 80 patients (3.8%) regardless of platelet counts. Monitor patients closely for risk of ICH including those with thrombocytopenia, vascular aneurysm or a history of ICH or cerebrovascular accident within the prior year. Permanently discontinue AYVAKIT if ICH of any grade occurs. A platelet count must be performed prior to initiating therapy. AYVAKIT is not recommended in AdvSM patients with platelet counts <50 x 10^9/L. Following treatment initiation, platelet counts must be performed every 2 weeks for the first 8 weeks. After 8 weeks of treatment, monitor platelet counts every 2 weeks or as clinically indicated based on platelet counts. Manage platelet counts of <50 x 10^9/L by treatment interruption or dose reduction.

Cognitive adverse reactions can occur in patients receiving AYVAKIT. Cognitive adverse reactions occurred in 39% of 749 patients and in 28% of 148 SM patients (3% were Grade >3). Memory impairment occurred in 16% of patients; all events were Grade 1 or 2. Cognitive disorder occurred in 10% of patients; <1% of these events were Grade 3. Confusional state occurred in 6% of patients; <1% of these events were Grade 3. Other events occurred in <2% of patients. Depending on the severity, withhold AYVAKIT and then resume at same dose or at a reduced dose upon improvement, or permanently discontinue.

AYVAKIT can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females and males of reproductive potential to use an effective method of contraception during treatment with AYVAKIT and for 6 weeks after the final dose of AYVAKIT.

IMPORTANT SAFETY INFORMATION (CONT.)

Advise women not to breastfeed during treatment with AYVAKIT and for 2 weeks after the final dose.

The most common adverse reactions (≥20%) were edema, diarrhea, nausea, and fatigue/asthenia.

Avoid coadministration of AYVAKIT with strong and moderate CYP3A inhibitors. If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce dose of AYVAKIT. Avoid coadministration of AYVAKIT with strong and moderate CYP3A inducers.

To report suspected adverse reactions, contact Blueprint Medicines Corporation at 1-888-258-7768 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see the full Prescribing Information for AYVAKIT.

References: 1. Garcia-Montero AC et al. *Blood*. 2006;108(7):2366-2372. **2.** Evans EK et al. *Sci Transl Med*. 2017;9(414):eaao1690. **3.** Kristensen T et al. *J Mol Diagn*. 2011;13(2):180-188. **4.** Valent P et al. *Blood*. 2017;129(11):1420-1427. **5.** Gotlib J et al. *Blood*. 2013;121(13):2393-2401. **6.** Mesa RA et al. *Cancer*. Published online August 23, 2022. doi:10.1002/cncr.34420 **7.** Theoharides TC et al. *N Engl J Med*. 2015;373(2):163-172. **8.** Jennings SV et al. *Immunol Allergy Clin North Am*. 2018;38(3):505-525. **9.** Schwaab J et al. J *Allergy Clin Immunol Pract*. 2020;8(9):3121-3127. **10.** Hartmann K et al. *J Allergy Clin Immunol*. 2016;137(1):35-45. **11.** Pardanani A. *Am J Hematol*. 2021;96(4):508-525. **12.** Gilreath JA et al. *Clin Pharmacol*. 2019;11:77-92. **13.** Arock M et al. *Leukemia*. 2015;29(6):1223-1232. **14.** Craig JW et al. *Mod Pathol*. 2020;133(6):1135-1145. **15.** Shomali W, Gotlib J. *Hematology*. 2018;2018(1):127-136.

FOR MORE INFORMATION ON TREATING PATIENTS WITH ADVANCED SM WITH AYVAKIT, GO TO AYVAKIT.COM/HCP AND REVIEW THE PRESCRIBING INFORMATION

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