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%

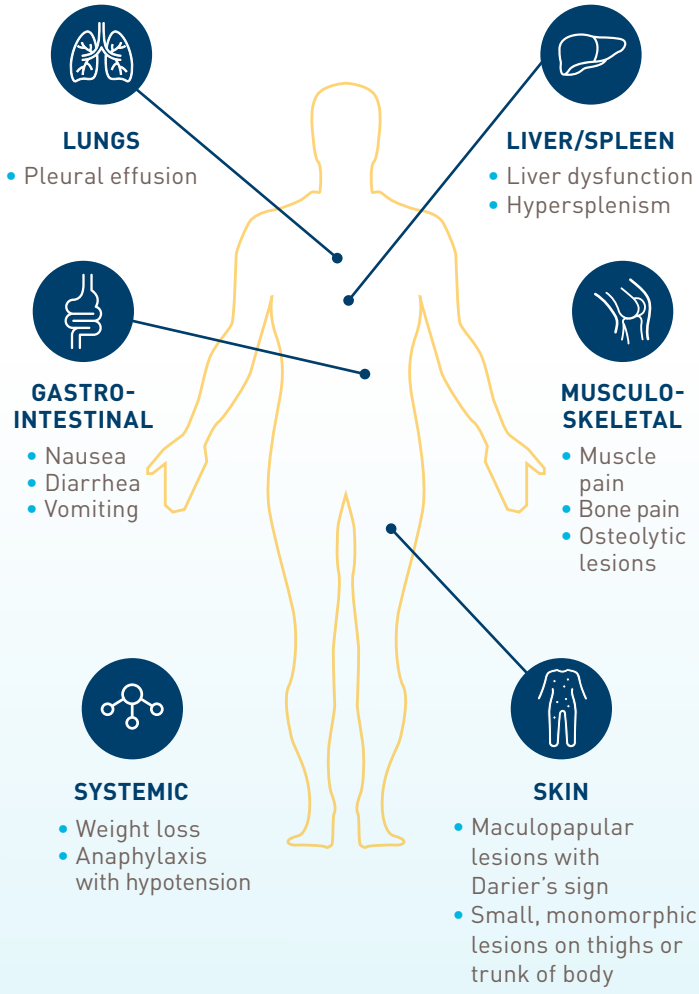
In a retrospective analysis of patients with Advanced SM, about 36% (51/140) were misdiagnosed.[9]

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

Identifying Advanced SM in your practice

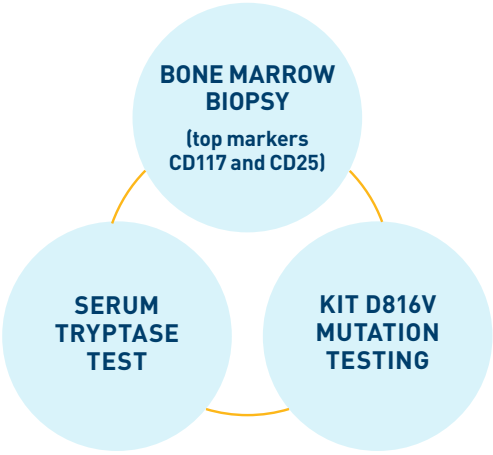
Knowing the symptoms of Advanced SM may help you shorten a patient's time to diagnosis.

Common mast cell mediator symptoms of Advanced SM can 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 and no evidence of mast cell leukemia
- 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

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]

IMPORTANT SAFETY INFORMATION

There are no contraindications for AYVAKIT.

Intracranial Hemorrhage—Serious intracranial hemorrhage (ICH) may occur with AYVAKIT treatment; fatal events occurred in <1% of patients. Overall, ICH (e.g., subdural hematoma, ICH, and cerebral hemorrhage) occurred in 2.9% of 749 patients who received AYVAKIT in clinical trials. 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 factors of ICH which may include history of vascular aneurysm, ICH or cerebrovascular accident within the prior year, concomitant use of anticoagulant drugs, or thrombocytopenia. Symptoms of ICH may include headache, nausea, vomiting, vision changes, or altered mental status. Advise patients to seek immediate medical attention for signs or symptoms of ICH. 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 Effects—Cognitive adverse reactions can occur in patients receiving AYVAKIT and occurred in 33% of 995 patients overall in patients who received AYVAKIT in clinical trials including 28% of 148 AdvSM patients (3% were Grade ≥3). Depending on the severity and indication, withhold AYVAKIT and then resume at same dose or at a reduced dose upon improvement, or permanently discontinue.

Photosensitivity—AYVAKIT may cause photosensitivity reactions. In all patients treated with AYVAKIT in clinical trials (n=1049), photosensitivity reactions occurred in 2.5% of patients. Advise patients to limit direct ultraviolet exposure during treatment with AYVAKIT and for one week after discontinuation of treatment.

Embryo-Fetal Toxicity—AYVAKIT can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus.

IMPORTANT SAFETY INFORMATION (CONT.)

Embryo-Fetal Toxicity (cont.)—Advise females and males of reproductive potential to use an effective contraception during treatment with AYVAKIT and for 6 weeks after the final dose of AYVAKIT. Advise women not to breastfeed during treatment with AYVAKIT and for 2 weeks following the final dose.

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

Drug Interactions—Avoid coadministration of AYVAKIT with strong or moderate CYP3A inhibitors. If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce dose of AYVAKIT. Avoid coadministration of AYVAKIT with strong or 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 click here to 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 AYVAKITHCP.COM/ADVSM AND REVIEW THE PRESCRIBING INFORMATION

07/2023 USBP-PRAVAASM-21.075.4