

For US Healthcare Professionals Only.



# IDENTIFYING INDOLENT AND ADVANCED SYSTEMIC MASTOCYTOSIS

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## 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  $<50 \times 10^9/L$ .

- Indolent systemic mastocytosis (ISM).

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**Please see Important Safety Information on pages 8-9 and the full Prescribing Information for AYVAKIT.**

# PATIENTS WITH ISM CAN EXPERIENCE A HIGH SYMPTOM BURDEN THAT MAY IMPACT WORK AND DAILY LIFE<sup>1,2</sup>

**SYMPTOMS, INCLUDING SKIN, NEUROCOGNITIVE, AND GASTROINTESTINAL (GI), CAN BE HETEROGENEOUS, CHRONIC, AND POTENTIALLY DEBILITATING<sup>1,2</sup>**



**76%** of patients reported experiencing skin and subcutaneous tissue disorders<sup>2\*</sup>



**65%** of patients reported experiencing nervous system disorders<sup>2\*</sup>



**80%** of patients reported experiencing GI disorders<sup>2\*</sup>

**PATIENTS REPORT IMPACT TO THEIR WORK AND PERSONAL LIFE DUE TO LIVING WITH ISM<sup>2†</sup>**

**Of 32 patients with moderate to severe ISM in the Blueprint Medicines–sponsored patient survey:**

**56%**

reported reducing work hours due to their ISM<sup>2†</sup>

**28%**

reported going on medical disability due to their ISM<sup>2†</sup>

**72%**

reported avoiding leaving home due to their ISM<sup>2†</sup>

\*Data based on ongoing medical history events in the PIONEER study (N=212). Events  $\geq 10\%$  in 1 or both trial arms from 3 of the organ classes include pruritus, urticaria pigmentosa, urticaria, rash maculo-papular for skin and subcutaneous tissue disorders; headache, dizziness, migraine, memory impairment, disturbance in attention for nervous system disorders; and diarrhea, abdominal pain, nausea, gastroesophageal reflux disease, abdominal distension, constipation for gastrointestinal disorders.<sup>2</sup>

<sup>†</sup>In the Blueprint Medicines–sponsored TouchStone SM Patient Survey, US adults with a self-reported SM diagnosis (N=56) completed an online survey of 100 items. An analysis was conducted in patients with ISM (n=37), including 32 patients with moderate to severe ISM (defined as ISM-SAF TSS  $\geq 28$ ), and results were analyzed using descriptive statistics. These analyses were made from the TouchStone SM Patient Survey but have not been published.<sup>2</sup>

# PATIENTS WITH ADVANCED SM CAN EXPERIENCE DISEASE BURDEN AND DIAGNOSTIC DELAY<sup>3-6</sup>

There are 3 subtypes of Advanced SM: aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).<sup>7-10</sup> Advanced SM is a more aggressive form of SM and is associated with organ damage and higher disease burden.<sup>1,4</sup>

**PEOPLE LIVING WITH ADVANCED SM CAN EXPERIENCE SIGNIFICANT SYMPTOM BURDEN (INCLUDING ORGAN DAMAGE) AND IMPACT TO THEIR LIVES<sup>3,4</sup>**

Organ damage caused by mast cell infiltration is considered a C-finding of the WHO diagnostic criteria for Advanced SM.<sup>8</sup>

## DIAGNOSING ADVANCED SM CAN TAKE YEARS

**3  
YEARS**

The median time from symptom onset to diagnosis for patients with Advanced SM is 3 years.<sup>5‡</sup>

**36%**

In a retrospective analysis of patients with Advanced SM, approximately 36% (51/140) were misdiagnosed.<sup>11</sup>

‡Based on a survey of patients with Advanced SM (n=13).<sup>5</sup>

WHO=World Health Organization.

# IDENTIFYING SM IN YOUR PRACTICE

Systemic mastocytosis (SM) is a clonal mast cell neoplasm associated with uncontrolled proliferation and activation of abnormal mast cells throughout the body.<sup>1</sup> SM is **driven by the KIT D816V mutation in ~95% of cases.**<sup>12-15</sup>

Indolent SM (ISM) and Advanced SM are 2 subtypes of SM, and **ISM is the largest subtype of the disease.**<sup>1,15-17</sup>

Knowing the symptoms of SM and its subtypes may help you shorten a patient's time to diagnosis.<sup>4,5</sup>

Common mast cell mediator symptoms of SM can include maculo-papular rash, GI symptoms, and life-threatening anaphylaxis.<sup>18-20</sup> Additionally, patients may experience organ damage and related symptoms, such as<sup>1</sup>:



## CARDIOVASCULAR

- Syncope
- Dizziness
- Palpitations



## NEUROLOGIC

- Memory/cognitive difficulties
- Depression
- Headache
- Sleep disturbances



## BONE

- Osteopenia
- Osteoporosis
- Back pain
- Bone pain



## SKIN

- Pruritus
- Flushing
- Hives



## SYSTEMIC

- Weight loss
- Anaphylaxis with hypotension and/or angioedema

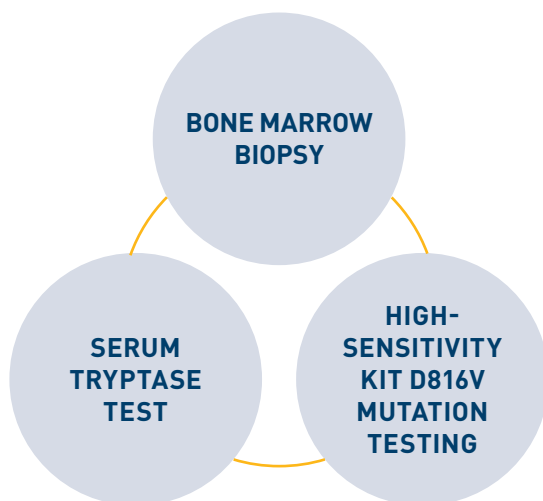


## GASTROINTESTINAL

- Nausea
- Diarrhea
- Vomiting
- Abdominal cramps
- Heartburn

# TESTING FOR AND DIAGNOSING SM

Accurately evaluating a patient for SM is a multistep process. The diagnostic workup for suspected SM includes<sup>4</sup>:



**Performing a high-sensitivity KIT D816V assay is recommended** for patients when SM is suspected.<sup>1,21</sup>

**SM may be missed in patients with suspected myeloid neoplasms. Incidental KIT mutation findings should prompt a full diagnostic workup for SM<sup>11,22,23</sup>**

Subtyping of SM depends on factors such as mast cell burden, organ damage, and signs of myeloproliferation or myelodysplasia.<sup>1,8</sup> ISM can be determined when there is no organ damage and no associated hematologic malignancy.<sup>1,8</sup>

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 SM.<sup>21,24,25</sup>

Confirming a diagnosis of SM can help you determine the treatment course that may be best for your patient.<sup>1</sup>

# WHO DIAGNOSTIC CRITERIA<sup>8§</sup>

**DIAGNOSIS OF SM REQUIRES THE PRESENCE OF 1 MAJOR CRITERION AND  $\geq 1$  MINOR CRITERION, OR  $\geq 3$  MINOR CRITERIA<sup>8</sup>**

## Major Criterion

Multifocal dense infiltrates of mast cells ( $\geq 15$  mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s)

## Minor Criteria

- Atypical mast cell morphology, including spindle shape or immature morphology, present in  $>25\%$  of all mast cells on bone marrow smears or in other extracutaneous organ(s)<sup>||</sup>
- Mast cells aberrantly express 1 or more of the following antigens: CD2, CD25, CD30
- KIT p.D816V mutation or other activating KIT mutation<sup>¶</sup> detected in peripheral blood, bone marrow, or other extracutaneous organ(s)
- Baseline serum tryptase concentration of  $>20$  ng/mL in the absence of an associated myeloid neoplasm; in the case of a known HaT, the tryptase level could be adjusted<sup>§</sup>

**Once a diagnosis of SM is confirmed, subtyping is a practical next step.<sup>1</sup>**

## INDOLENT SM<sup>1</sup>

- For ISM without skin lesions:  $\leq 1$  B-finding and/or basal serum tryptase  $\geq 125$  ng/mL and/or dense SM infiltrates in an extramedullary organ
- SM criteria fulfilled
- Typical skin lesions
- $\leq 1$  B-finding

## FOR AN ADVANCED SM DIAGNOSIS, CRITERIA FOR 1 OF THE ADVANCED SM SUBTYPES MUST BE MET<sup>1</sup>

### Aggressive systemic mastocytosis (ASM)

- SM criteria fulfilled
- $\geq 1$  C-finding

### Systemic mastocytosis with an associated hematological neoplasm (SM-AHN)

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

<sup>§</sup>According to the proposed changes for the 5th edition World Health Organization diagnostic criteria.  
<sup>||</sup>Well-differentiated round cell morphology may be seen in a small subset of cases; mast cells in such cases are usually positive for CD30 and negative for CD2 and CD25.

<sup>¶</sup>Any type of KIT mutation counts as a minor SM criterion when published solid evidence for its transforming behavior is available (an overview of potentially activating KIT mutations is provided in the supplementary material of Valent et al (2021).

HaT=hereditary alpha-tryptasemia.

# WHO DIAGNOSTIC CRITERIA (CONT'D)

## Mast cell leukemia (MCL)

- SM criteria fulfilled
- $\geq 20\%$  mast cells in bone marrow aspirate smears

## B-findings<sup>§</sup>

- **High mast cell burden:** Infiltration in bone marrow  $\geq 30\%$  and/or serum tryptase  $\geq 200$  ng/mL<sup>||</sup> and/or KIT p.D816V VAF  $\geq 10\%$  in bone marrow or peripheral blood leukocytes
- **Signs of myeloproliferation and/or myelodysplasia** not fulfilling criteria for AHN<sup>¶</sup>
- Hepatomegaly on palpation or imaging (ultrasound, CT, or MRI) without ascites or other signs of organ damage and/or splenomegaly on palpation or imaging without hypersplenism and/or lymphadenopathy on palpation or imaging ( $>20$  mm)

## C-findings<sup>§</sup>

- **Cytopenia(s) (1 or more found)**
  - Absolute neutrophil count  $< 1 \times 10^9/L$
  - Hemoglobin  $< 10$  g/dL
  - Platelet count  $< 1.0 \times 10^9/L$
- **Hepatopathy:** Ascites and elevated liver enzymes<sup>#</sup>  $\pm$  hepatomegaly or cirrhotic liver  $\pm$  portal hypertension
- **Spleen:** Palpable splenomegaly with hypersplenism  $\pm$  weight loss  $\pm$  hypoalbuminemia
- **GI tract:** Malabsorption with hypoalbuminemia  $\pm$  weight loss
- **Bone:** Large-sized osteolysis ( $\geq 20$  mm)  $\pm$  pathological fracture  $\pm$  bone pain

<sup>§</sup>A possible mode for adjustment has been proposed by Valent et al (2021): the basal tryptase level may be divided by 1 plus the number of extra copies of the  $\alpha$ -tryptase gene. For example, if the tryptase level is 30 ng/mL and 2 extra copies of the  $\alpha$ -tryptase gene are found in a patient with HaT, the HaT-corrected tryptase level is 10 ng/mL ( $30/3=10$ ), thereby not meeting the level of a minor SM criterion.

<sup>||</sup>In the case of a known HaT, the basal serum tryptase level can be adjusted. The optimal method of adjustment is not definitely defined. A common method is to divide the basal tryptase level by 1 plus the number of extra copies of the  $\alpha$ -tryptase gene. For example, with a tryptase level of 300 and 2 extra copies of the  $\alpha$ -tryptase gene in a patient with HaT, the HaT-corrected tryptase level is 100 ( $300/3=100$ ) and therefore does not qualify as a B-finding.

<sup>¶</sup>Signs of myeloproliferation and/or myelodysplasia must be discrete and stable and must not meet diagnostic criteria for an MPN, MDS, or MDS/MPN, excluding SM-AHN. The presence of a myeloid AHN excludes B-findings and smoldering systemic mastocytosis by definition.

<sup>#</sup>Alkaline phosphatase levels are typically elevated in patients with Advanced SM and SM-induced liver damage. In some of these patients, only elevated liver enzymes are found, without [clinically relevant] ascites.

## IMPORTANT SAFETY INFORMATION

**Intracranial Hemorrhage**—Serious intracranial hemorrhage (ICH) may occur with AYWAKIT 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 AYWAKIT in clinical trials. In AdvSM patients who received AYWAKIT at 200 mg daily, ICH occurred in 2 of 75 patients (2.7%) who had platelet counts  $\geq 50 \times 10^9/L$  prior to initiation of therapy and in 3 of 80 patients (3.8%) regardless of platelet counts. In ISM patients, no events of ICH occurred in the 246 patients who received any dose of AYWAKIT in the PIONEER study.

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 AYWAKIT if ICH of any grade occurs. In AdvSM patients, a platelet count must be performed prior to initiating therapy. AYWAKIT is not recommended in AdvSM patients with platelet counts  $< 50 \times 10^9/L$ . 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  $< 50 \times 10^9/L$  by treatment interruption or dose reduction.

**Cognitive Effects**—Cognitive adverse reactions can occur in patients receiving AYWAKIT and occurred in 33% of 995 patients overall in patients who received AYWAKIT in clinical trials including: 28% of 148 AdvSM patients (3% were Grade  $\geq 3$ ), and 7.8% of patients with ISM who received AYWAKIT + best supportive care (BSC) versus 7.0% of patients who received placebo + BSC (<1% were Grade 3). Depending on the severity and indication, withhold AYWAKIT and then resume at same dose or at a reduced dose upon improvement, or permanently discontinue.

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

**Embryo-Fetal Toxicity**—AYWAKIT 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 AYWAKIT and for 6 weeks after the final dose of AYWAKIT. Advise women not to breastfeed during treatment with AYWAKIT and for 2 weeks after the final dose.

**Please see additional Important Safety Information on page 9 and the full [Prescribing Information](#) for AYWAKIT.**



## IMPORTANT SAFETY INFORMATION (CONT'D)

**Adverse Reactions**—The most common adverse reactions ( $\geq 20\%$ ) in patients with AdvSM were edema, diarrhea, nausea, and fatigue/asthenia.

The most common adverse reactions ( $\geq 10\%$ ) in patients with ISM were eye edema, dizziness, peripheral edema, and flushing.

**Drug Interactions**—Avoid coadministration of AYWAKIT with strong or moderate CYP3A inhibitors. If coadministration with a moderate CYP3A inhibitor cannot be avoided in patients with AdvSM, reduce dose of AYWAKIT. Avoid coadministration of AYWAKIT 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](http://www.fda.gov/medwatch).

AYWAKIT is available in 25-mg, 50-mg, 100-mg, and 200-mg tablets.

**Please see additional Important Safety Information on previous page and the full [Prescribing Information](#) for AYWAKIT.**

**References:** 1. Pardanani A. *Am J Hematol*. 2023;98(7):1097-1116. 2. Data on file. Blueprint Medicines Corporation, Cambridge, MA. 2023. 3. Mesa RA et al. *Cancer*. 2022;128(20):3691-3699. 4. Theoharides TC et al. *N Engl J Med*. 2015;373(2):163-172. 5. Jennings SV et al. *Immunol Allergy Clin North Am*. 2018;38(3):505-525. 6. Russell N et al. *J Allergy Clin Immunol Pract*. 2019;7(4):1157-1165. 7. Valent P et al. *Blood*. 2017;129(11):1420-1427. 8. WHO Classification of Tumours Editorial Board. Haematolymphoid tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2024 [cited April 24, 2024]. (*WHO classification of tumours series*, 5th ed.; vol. 11). Available from: <https://tumourclassification.iarc.who.int/chapters/63> 9. Khoury JD et al. *Leukemia*. 2022;36(7):1703-1719. 10. Rossignol J et al. *F1000Research*. 2019;8:1961. 11. Schwaab J et al. *J Allergy Clin Immunol Pract*. 2020;8(9):3121-3127.e1. 12. Garcia-Montero AC et al. *Blood*. 2006;108(7):2366-2372. 13. Evans EK et al. *Sci Transl Med*. 2017;9(414):eaao1690. 14. Kristensen T et al. *Am J Hematol*. 2014;89(5):493-498. 15. Ungerstedt J et al. *Cancers*. 2022;14(16):3942. 16. Sperr WR et al. *Lancet Haematol*. 2019;6(12):e638-e649. 17. Cohen SS et al. *Br J Haematol*. 2014;166(4):521-528. 18. Gotlib J et al. *Blood*. 2013;121(13):2393-2401. 19. Gilreath JA et al. *Clin Pharmacol*. 2019;11:77-92. 20. Hartmann K et al. *J Allergy Clin Immunol*. 2016;137(1):35-45. 21. Arock M et al. *Leukemia*. 2015;29(6):1223-1232. 22. Craig JW et al. *Mod Pathol*. 2020;133(6):1135-1145. 23. Scherber RM, Borate U. *Br J Haematol*. 2018;180(1):11-23. 24. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) for Systemic Mastocytosis V.3.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed May 20, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 25. Shomali W, Gotlib J. *Hematology*. 2018;2018(1):127-136.



For more information on treating patients with ISM or Advanced SM with AYVAKIT, scan the QR code or go to [AYVAKITHCP.COM](https://www.ayvakithcp.com) and review the Prescribing Information

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