AYVAKIT®
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The **FIRST and ONLY** FDA-approved treatment for adults with Indolent Systemic Mastocytosis (ISM)

Limitations of Use: AYVAKIT is not recommended for the treatment of patients with ISM with platelet counts of <50 x 10^9/L.

Please see Important Safety Information on Page 7, and click here to see the full Prescribing Information for AYVAKIT.

blueprint MEDICINES

Systemic mastocytosis (SM) is a rare clonal mast cell neoplasm that can lead to proliferation and activation of abnormal mast cells[1-3]

SM IS DRIVEN BY THE *KIT* D816V MUTATION IN ~95% OF CASES[4,5]

~32K Total estimated prevalence of SM in the United States[3,6]*

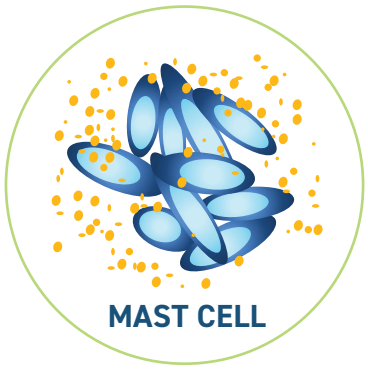
Patients with SM can suffer from a wide range of potentially severe and unpredictable symptoms[1,7,8]

There are more than 20 unpredictable symptoms that can occur across multiple organ systems in patients with SM[1,2,7-9]

Cardiovascular
- Anaphylaxis with hypotension and syncope
- Dizziness
- Palpitations

Gastrointestinal
- Abdominal pain and cramping
- Diarrhea
- Heartburn or reflux
- Nausea and/or vomiting

Musculoskeletal
- Bone pain
- Muscle pain
- Osteoporosis/osteopenia



Neurocognitive
- Anxiety
- Brain fog
- Depression
- Memory loss
- Lack of focus/ memory difficulties
- Migraines

Systemic
- Anaphylaxis
- Fatigue
- Malaise
- Weight loss

Skin
- Darier's sign (dermatographism)
- Extreme flushing
- Pruritus

Respiratory
- Dyspnea
- Nasal congestion
- Throat swelling
- Wheezing

This is not an exhaustive list of symptom categories. Symptoms may vary from person to person.

In the Blueprint Medicines–sponsored TouchStone survey, which included US adults with a self-reported SM diagnosis (N=56) who completed an online survey of 100 items†:

Patients with SM may face delays in receiving an accurate diagnosis[10]

~6 years
Mean time to diagnosis from symptom onset[10‡]

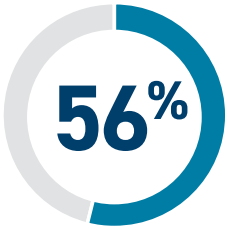
*As of January 24, 2022.
†Online survey included the 12-item Short-form Health Survey, the ISM Symptom-Assessment Form, and the Work Productivity and Activity Impairment Questionnaire.
‡Results were analyzed using descriptive statistics.

Indolent systemic mastocytosis (ISM) is a subtype of SM that represents ~75%-90% of cases of SM[3,11,12]

~7.5K
Estimated diagnosed adults in the United States with moderate to severe ISM[13]*

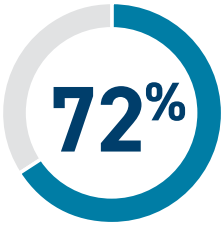
Patients report impact to their work and personal life due to living with ISM[13]

Of 32 patients with moderate to severe ISM in the Blueprint Medicines–sponsored TouchStone patient survey[13†]:



reported **reducing work hours** due to their ISM symptoms[13†]

reported **going on medical disability** due to their ISM symptoms[13†]



reported **avoiding leaving home** due to their ISM symptoms[13†]

The current ISM treatment paradigm manages the symptoms, not the underlying disease[1,14]

Some patients with ISM may experience an increase in symptom burden[13‡]

of patients with **lower-symptom-burden ISM progressed to higher-symptom-burden ISM over a 24-month interval** (n/N=493/3263)‡

ISM symptoms can result in high rates of healthcare utilization[15]

Healthcare resource utilization (HCRU) burden during 36-month period§
All ISM cohort (N=588)

All-cause hospitalizations **43%**	All-cause hospitalization length of stay, mean (SD) **6.2 days** (16.1)
ED visits resulting in inpatient admission **30.6%**	Prescription fills per patient, mean (SD)‖ **127.9** (114.4)

*As of May 2022. Based on US claims data analysis.[13]

†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 an ISM-SAF TSS ≥28) and results were analyzed using descriptive statistics. These analyses were made from the TouchStone Patient SM Survey but have not been published.[13]

‡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 ISM included remaining patient cohort excluding AdvSM.[13]

§A Blueprint Medicines–sponsored retrospective study based on Medicare claims data from 2017 to 2019 assessed all-cause medical and pharmacy HCRU in patients with ISM using a claims-based algorithm. Patients in the ISM cohort were required to have ≥2 ICD-10-CM diagnosis codes for SM (D47.02) or ≥1 ICD-10-CM diagnosis code for SM (D47.02), other mast cell neoplasms of uncertain behavior (D47.09), malignant mast cell neoplasm, unspecified (C96.20), mast cell sarcoma (C96.22), or diagnosis of other malignant mast cell neoplasm (C96.29) and SM (D47.02), with the date of the SM claim occurring after the date of the claim(s) containing other code(s).[15]

‖Pharmacy utilization was assessed for treatments used to manage ISM symptoms, including epinephrine, antihistamines, and corticosteroids.[15]

ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; SD, standard deviation.

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The FIRST and ONLY FDA-approved treatment for adults with ISM[16,17]

PIONEER: a phase 2, randomized, double-blind, placebo-controlled clinical trial[16,17]

PIONEER (N=212) was a phase 2, multipart, randomized, placebo-controlled, double-blind trial evaluating the safety and efficacy of AYVAKIT 25 mg QD + best supportive care (BSC) (n=141) vs placebo + BSC (n=71) over 24 weeks in adult (≥18 years) patients with ISM based on World Health Organization (WHO) classification. Enrolled patients had moderate to severe symptoms despite receiving at least 2 symptom-directed therapies. Patients were randomized 2:1 to receive AYVAKIT 25 mg QD + BSC or placebo + BSC. Patients who completed the 24-week double-blind portion of the trial had the option to enter an open-label extension treatment period for up to 5 years and receive AYVAKIT 25 mg QD + BSC. Double-blind treatment period data cut-off was June 23, 2022.

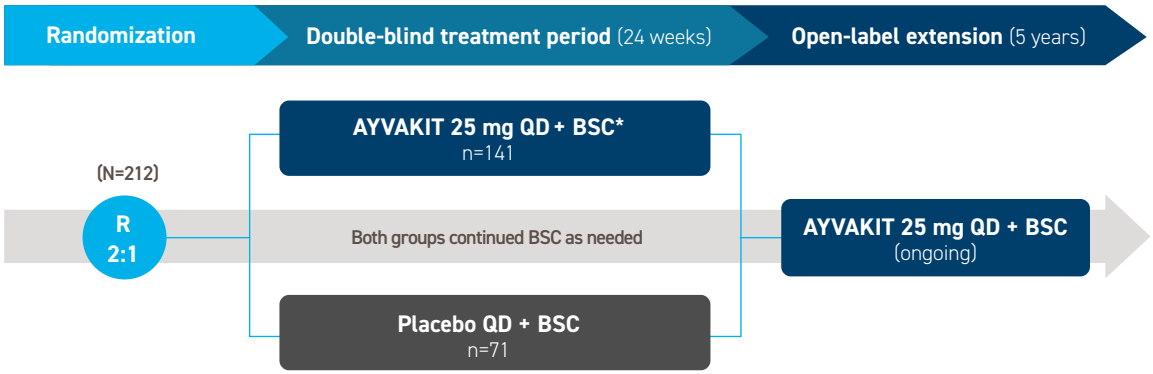
Screening period

Best supportive care (BSC) allowed in PIONEER included:

- Anti-immunoglobulin E antibody (omalizumab), glucocorticoids, cromolyn sodium, H1 antihistamines, H2 antihistamines, leukotriene inhibitors, and proton pump inhibitors

Key inclusion criteria

- Age ≥18 years
- Centrally confirmed ISM diagnosis per WHO criteria
- Moderate to severe ISM symptoms (ISM-SAF TSS ≥28) after ≥2 BSC



*The recommended dose of avapritinib for the double-blind period and open-label extension was identified in Part 1 of PIONEER.

IgE, immunoglobulin E; QD, once daily.

PRIMARY ENDPOINT

Absolute mean change in Indolent Systemic Mastocytosis Symptom Assessment Form (ISM-SAF) total symptom score **(TSS)** from baseline compared with placebo + BSC to Week 24

KEY SECONDARY ENDPOINTS

Proportion of patients achieving:

≥50% reduction

Objective measures of mast cell burden from baseline compared with placebo + BSC at Week 24

- **Serum tryptase** levels
- ***KIT* D816V VAF**
  - ≥50% reduction in peripheral blood *KIT* D816V VAF or undetectable
- Bone marrow (BM) **mast cell aggregates**
  - ≥50% reduction in bone marrow mast cells or no aggregates

VAF, variant allele fraction.

Select Safety Information

Cognitive Effects — Cognitive adverse reactions can occur in patients receiving AYVAKIT and occurred in 7.8% of patients with ISM who received AYVAKIT + best supportive care (BSC) versus 7.0% of patients who received placebo + BSC; <1% were Grade 3. Depending on the severity, withhold AYVAKIT and then resume at the same dose, or permanently discontinue AYVAKIT.

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AYVAKIT achieved the primary and key secondary endpoints[16]

AYVAKIT demonstrated significant reduction in symptoms versus placebo at Week 24[16]

Absolute mean change in ISM-SAF TSS at Week 24

2-sided *P*=0.012

ITT analysis: Markov chain Monte Carlo simulation was used to impute the missing values at Baseline or Week 24.

Significantly more patients treated with AYVAKIT vs placebo had reductions in objective measures of mast cell burden at Week 24[16]

	AYVAKIT 25 mg QD + BSC		Placebo + BSC
Proportion of patients with ≥50% reduction in serum tryptase at Week 24	53.9% (95% CI: 45.3–62.3) (N=141)	(2-sided *P*<0.0001)	0% (95% CI: 0.0–5.1) (N=71)
Proportion of patients with ≥50% reduction in peripheral blood *KIT* D816V VAF at Week 24*	67.8% (95% CI: 58.6–76.1) (N=118)	(2-sided *P*<0.0001)	6.3% (95% CI: 1.8–15.5) (N=63)
Proportion of patients with ≥50% reduction in BM mast cells or no aggregates at Week 24†	52.8% (95% CI: 42.9–62.6) (N=106)	(2-sided *P*<0.0001)	22.8% (95% CI: 12.7–35.8) (N=57)

ITT analysis: For patients with high-dose steroid use within 7 days before Week 24, or greater than 14 consecutive days at any point from baseline to Week 24, the Week 24 score was set to missing.

*Percentage of patients with a ≥50% reduction in peripheral blood *KIT* D816V VAF or undetectable.

†Percentage of patients with a ≥50% reduction in bone marrow mast cells or no aggregates.

CI, confidence interval.

Select Safety Information (cont'd)

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.

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AYVAKIT was generally well tolerated in PIONEER[16]

Adverse reactions occurring in ≥5% of AYVAKIT-treated patients and ≥2% more than placebo-treated patients with ISM during PIONEER trial

Adverse reactions*†	AYVAKIT 25 mg QD + BSC (n=141)	Placebo + BSC (n=71)
Eye edema‡	13%	7%
Dizziness§	13%	10%
Peripheral edema§	12%	6%
Flushing§	11%	4%
Respiratory tract infection‖	8%	1%
Face edema	7%	1%
Rash§	6%	4%
Liver transaminase increased§	6%	3%
Insomnia	6%	3%
Hematoma¶	6%	1%
Blood alkaline phosphatase increased	6%	1%
Hemorrhage#	5%	3%

- Serious adverse reactions occurred in 1 patient (0.7%) who received AYVAKIT due to pelvic hematoma[16]
- Permanent discontinuation of AYVAKIT due to an adverse reaction occurred in 1 patient (0.7%) due to dyspnea and dizziness[16]
- Dosage interruptions of AYVAKIT due to an adverse reaction occurred in 5% of patients[16]
- Of all adverse reactions, 55% were Grade 1, 38% were Grade 2, and 7% were Grade 3[16]
- 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[16]

*Adverse reactions that occurred in ≥5% of AYVAKIT-treated patients and ≥2% more than placebo-treated patients.
†Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
‡Eye edema includes periorbital edema, eye edema, swelling of eyelid, orbital edema, eye swelling, eyelid edema, and eyelid ptosis.
§Term includes several similar terms.
‖Respiratory tract infection includes pneumonia, upper respiratory tract infection, bronchitis, and respiratory tract infection.
¶Hematoma includes contusion, hematoma, and pelvic hematoma.
#Hemorrhage includes epistaxis, gingival bleeding, hematochezia, rectal hemorrhage, and retinal hemorrhage.

Select Safety Information (cont'd)

Embryo-Fetal Toxicity — 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 contraception during treatment with AYVAKIT and for 6 weeks after the final dose. Advise women not to breastfeed during treatment with AYVAKIT and for 2 weeks following the final dose.

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INDICATION

AYVAKIT® (avapritinib) is indicated for the treatment of adult patients with indolent systemic mastocytosis (ISM).

Limitations of Use: AYVAKIT is not recommended for the treatment of patients with ISM with platelet counts of <50 x 10^9/L.

IMPORTANT SAFETY INFORMATION

Cognitive Effects — Cognitive adverse reactions can occur in patients receiving AYVAKIT and occurred in 7.8% of patients with ISM who received AYVAKIT + best supportive care (BSC) versus 7.0% of patients who received placebo + BSC; <1% were Grade 3. Depending on the severity, withhold AYVAKIT and then resume at the same dose, or permanently discontinue AYVAKIT.

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Embryo-Fetal Toxicity — 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 contraception during treatment with AYVAKIT and for 6 weeks after the final dose. Advise women not to breastfeed during treatment with AYVAKIT and for 2 weeks following the final dose.

Adverse Reactions — The most common adverse reactions (≥10%) in patients with ISM were eye edema, dizziness, peripheral edema, and flushing.

Drug Interactions — Avoid coadministration of AYVAKIT with strong or moderate CYP3A inhibitors or inducers. If contraception requires estrogen, limit ethinyl estradiol to ≤20 mcg unless a higher dose is necessary.

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

Please click here to see the full Prescribing Information for AYVAKIT.

References: 1. Pardanani A. Systemic mastocytosis in adults: 2021 update on diagnosis, risk stratification and management. *Am J Hematol.* 2021;96(4):508-525. doi:10.1002/ajh.26118 **2.** Theoharides TC, Valent P, Akin C. Mast cells, mastocytosis, and related disorders. *N Engl J Med.* 2015;373(2):163-172. doi:10.1056/NEJMra1409760 **3.** Cohen SS, Skovbo S, Vestergaard H, et al. Epidemiology of systemic mastocytosis in Denmark. *Br J Haematol.* 2014;166(4):521-528. doi:10.1111/bjh.12916 **4.** Garcia-Montero AC, Jara-Acevedo M, Teodosio C, et al. KIT mutation in mast cells and other bone marrow hematopoietic cell lineages in systemic mast cell disorders: a prospective study of the Spanish Network on Mastocytosis (REMA) in a series of 113 patients. *Blood.* 2006;108(7):2366-2372. doi:10.1182/blood-2006-04-015545 **5.** Kristensen T, Vestergaard H, Bindslev-Jensen C, Møller MB, Broesby-Olsen S; Mastocytosis Centre, Odense University Hospital (MastOUH). Sensitive KITD816V mutation analysis of blood as a diagnostic test in mastocytosis. *Am J Hematol.* 2014;89(5):493-498. doi:10.1002/ajh.23672 **6.** Data on file. Blueprint Medicines Corporation, Cambridge, MA. 2022. **7.** Rossignol J, Polivka L, Maouche-Chrétien L, Frenzel L, Dubreuil P, Hermine O. Recent advances in the understanding and therapeutic management of mastocytosis. *F1000Res.* 2019;8:F1000 Faculty Rev-1961. doi:10.12688/f1000research.19463.1 **8.** Valent P, Akin C, Gleixner KV, et al. Multidisciplinary challenges in mastocytosis and how to address with personalized medicine approaches. *Int J Mol Sci.* 2019;20(12):2976. doi:10.3390/ijms20122976 **9.** Theoharides TC, Tsilioni I, Ren H. Recent advances in our understanding of mast cell activation - or should it be mast cell mediator disorders? *Expert Rev Clin Immunol.* 2019;15(6):639-656. doi:10.1080/1744666X.2019.1596800 **10.** Mesa RA, Sullivan EM, Dubinski D, et al. Patient-reported outcomes among patients with systemic mastocytosis in routine clinical practice: Results of the TouchStone SM Patient Survey. *Cancer.* 2022;128(20):3691-3699. doi:10.1002/cncr.34420 **11.** Sperr WR, Kundi M, Alvarez-Twose I, et al. International prognostic scoring system for mastocytosis (IPSM): a retrospective cohort study. *Lancet Haematol.* 2019;6(12):e638-e649. doi:10.1016/S2352-3026(19)30166-8 **12.** Ungerstedt J, Ljung C, Klimkowska M, Gulen T. Clinical outcomes of adults with systemic mastocytosis: a 15-year multidisciplinary experience. *Cancers (Basel).* 2022;14(16):3942. doi:10.3390/cancers14163942 **13.** Data on file. Blueprint Medicines Corporation, Cambridge, MA. 2023. **14.** Buonomo A, Nucera E, Criscuolo M. Treatment of indolent and advanced systemic mastocytosis. *Mediterr J Hematol Infect Dis.* 2022;14(1):e2022040. doi:10.4084/MJHID.2022.040 **15.** Data on file. Blueprint Medicines Corporation, Cambridge, MA. 2021. **16.** AYVAKIT [prescribing information]. Cambridge, MA: Blueprint Medicines Corporation; November 2024. **17.** Gotlib J, et al. *NEJM Evid.* 2023. Available online. doi:10.1056/EVIDoa2200339