THE BURDEN OF **ADVANCED SYSTEMIC MASTOCYTOSIS**

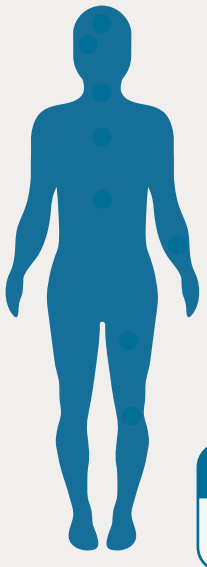
Advanced Systemic Mastocytosis (AdvSM), which is a subtype of SM, is a rare, clonal, mast cell neoplasm primarily driven by the *KIT* D816V mutation in ~95% of cases.[1-4] AdvSM patients may experience debilitating symptoms, organ damage, and shortened survival.[5-7]

~32,000
Total US SM prevalence[8,9]*

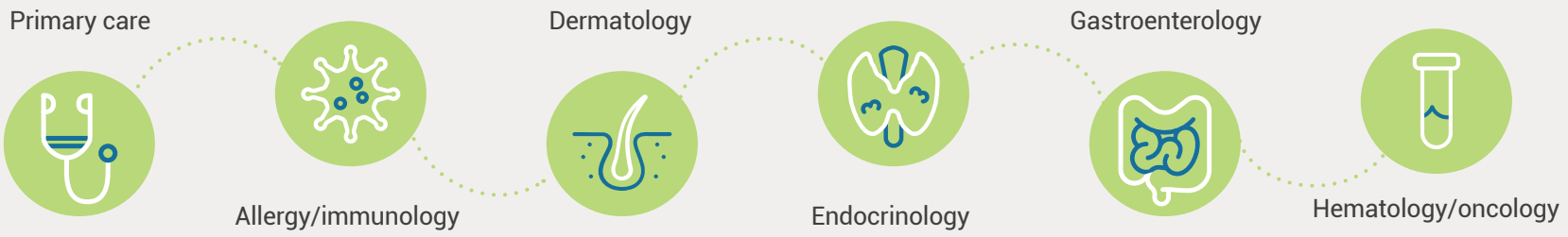
~21,300
Total SM
Total adults diagnosed with SM in the United States[10†]

~3,200
Total AdvSM
Total adults diagnosed with AdvSM[10†]

AdvSM is associated with nonspecific heterogenous symptoms, leading to challenges in diagnosis[5]



In a Blueprint Medicines patient-reported registry of participants with AdvSM (n=12), participants reported interacting with many different physicians before receiving a diagnosis[11‡]



Diagnostic odyssey for patients with AdvSM (n=12)[11]

Patients with AdvSM see an average of **3.6** specialists (range 1-6)

Median time to diagnosis from symptom onset[5]

AdvSM (n=13) **~3 years**

*As of January 24, 2022. †Based on US claims data between December 31, 2017, and July 31, 2023.[10] ‡Data are from Mast Cell Connect (NCT02620254), a patient-reported registry owned and managed by Blueprint Medicines Corporation. Enrollment occurred from 2015 to 2020 and the registry includes participants (n=280 at time of data cutoff) with self-reported diagnoses of systemic mastocytosis, including AdvSM (n=12).[5,11]

Advanced SM (AdvSM) is associated with decreased survival and increased rates of healthcare utilization[7,12]

Uncontrolled symptoms often result in ER visits and hospitalizations[11]

In a Blueprint Medicines patient-reported registry of **patients with AdvSM** (n=12):

of patients had been **admitted to the ER** due to their AdvSM

of patients had been **admitted to the hospital** due to their AdvSM

AdvSM is associated with shortened overall survival

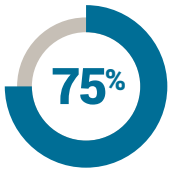
Median overall survival (OS) for patients with AdvSM[7]

OS was examined in a retrospective study at the Mayo Clinic between 1976 and 2007. Median follow-up was 20.7 months.[7] A later study with 23 MCL patients demonstrated a median OS for patients with MCL of 1.9 years, with a 10-year survival of 29.9%.[12]

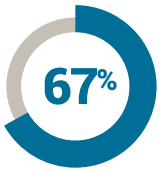
AdvSM is associated with high rates of polypharmacy[11]

In a Blueprint Medicines patient-reported registry of **patients with AdvSM** (n=12):

of patients reported taking **antihistamines**



of patients reported taking **oral steroids**



of patients reported taking **cromolyn sodium**

of patients reported using an **epinephrine injection**

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WHO Diagnostic Criteria[13]*

Diagnosis of SM requires the presence of 1 major criterion and ≥1 minor criterion, or ≥3 minor criteria

Major criterion

- **Multifocal dense infiltrates of mast cells (≥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)†
- Mast cells aberrantly express one or more of the following antigens: CD2, CD25, CD30
- *KIT* D816V mutation or other activating *KIT* mutation‡ 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 HαT, the tryptase level could be adjusted§

*According to the proposed changes for the WHO 5th edition diagnostic criteria. †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. ‡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]). §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 α-tryptase gene. For example, if the tryptase level is 30 ng/mL and 2 extra copies of the α-tryptase gene are found in a patient with HαT, the HαT-corrected tryptase level is 10 ng/mL (30/3=10), thereby not meeting the level of a minor SM criterion.

ER, emergency room; HαT, hereditary α-tryptasaemia; WHO, World Health Organization.

AYVAKIT®
avapritinib | tablets

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.

AYVAKIT: THE ONLY TARGETED THERAPY FOR ADVANCED SYSTEMIC MASTOCYTOSIS DESIGNED FOR POTENT AND SELECTIVE INHIBITION OF *KIT* D816V[14]

ONE TABLET | **ONCE-DAILY**

On an empty stomach, at least 1 hour before or 2 hours after a meal. Treatment should continue until disease progression or unacceptable toxicity.

Efficacy tested by updated, clinically meaningful criteria[15,16]

AYVAKIT is the first therapy approved by the FDA using the Modified International Working Group (IWG) criteria to evaluate efficacy for AdvSM patients

The modified IWG criteria evaluates overall response rate by:

≥12 weeks response duration

Full Resolution of ≥1 findings of nonhematologic and hematologic organ damage*

≥50% reduction in biomarker response (bone marrow mast cell aggregates and serum tryptase†)

***C-findings:**

- Bone marrow dysfunction manifested by 1 or more cytopenia (ANC <1 X 10^9/L, Hb <10 g/dL, or platelets <100 X 10^9/L)
- Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension
- Skeletal involvement with large osteolytic lesions and/or pathologic fractures
- Palpable splenomegaly with hypersplenism
- Malabsorption with weight loss from gastrointestinal tract mast cell infiltrates

†Serum tryptase must be <20 ng/mL if baseline was ≥40 ng/mL for complete remission or complete remission with partial hematologic recovery.
ANC, absolute neutrophil count; CR, complete response; PR, partial response.

Please see Important Safety Information on page 5 and full Prescribing Information for AYVAKIT.

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Proven efficacy and demonstrated duration of response[14]

57% ORR across all evaluable Advanced SM (AdvSM) patients who were dosed up to 200 mg daily (N=53)[14]*

AYVAKIT® avapritinib | tablets

(95% CI: 42%, 70%)‡

72% ORR was achieved with the addition of patients who had a clinical improvement§

- CR + CRh: 28%
- PR: 28%
- Clinical improvement: 15%

38.3 months (95% CI: 19, NE) driven primarily by SM-AHN patients

Median duration of response (DOR)

2.1 months Median time to response (n=30)

9.2 months Median time to CR and CRh (n=15)[11]

Proven efficacy across subtypes and regardless of prior antineoplastic therapy[11,14]

(95% CI: 16%, 100%)

ASM (n=2)[14]

50% of patients achieved CR/CRh

(95% CI: 41%, 73%)

SM-AHN (n=40)[14]

78% ORR was achieved with the addition of patients who had a clinical improvement

(95% CI: 17%, 77%)

MCL (n=11)[14]

In a pre-planned subgroup analysis, AYVAKIT demonstrated efficacy regardless of prior antineoplastic therapy:

In treatment-naive patients (n=18), **ORR was 72.2%** (95% CI: 46.5%, 90.3%)[11]

In patients with prior antineoplastic therapy (including midostaurin) (n=35), **ORR was 48.6%** (95% CI: 31.4%, 66%)[11]

Safety in patients treated with AYVAKIT in EXPLORER and PATHFINDER[14‖]

	AYVAKIT 200 mg once daily (recommended starting dose) (n=80)¶	All AYVAKIT doses (n=131)
Serious ARs, %	34	50
Permanent discontinuation due to an AR, %	10	15
Dosage interruptions, %	60	67
Dose reduction, %	68	70
Time to dose reduction		Median: 1.7 months

Most common ARs (≥20%)[14]

- Edema
- Diarrhea
- Nausea
- Fatigue/Asthenia

*Median duration of follow-up was 11.6 months (95% CI: 9.9, 16.3).[14] †ORR per modified IWG-MRT-ECNM is defined as patients who achieved a CR, CRh, or PR. ‡ORR per modified IWG-MRT-ECNM is defined as patients who achieved a CR, CRh, or PR. Modified IWG criteria evaluated overall response rate by ≥12 weeks response duration, resolution of ≥1 findings of nonhematologic and hematologic organ damage (C-findings), and ≥50% reduction in mast cell burden and serum tryptase (must be <20 ng/mL if baseline was ≥40 ng/mL for CR/CRh). §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.[15] ‖The safety of AYVAKIT was evaluated in 148 patients in EXPLORER and PATHFINDER. Patients received a starting dose of AYVAKIT ranging from 30 mg to 400 mg orally once daily and were centrally confirmed to have Advanced SM (N=131), including 80 patients who received the recommended starting dose of 200 mg once daily. Among patients receiving AYVAKIT, 70% were treated for ≥6 months and 37% were exposed for >1 year.[14] ¶A modified starting dosage of AYVAKIT 100 mg once daily is recommended for patients with severe hepatic impairment (Child-Pugh Class C).

AR, adverse reaction; ASM, aggressive systemic mastocytosis; CI, confidence interval; CR, complete remission; CRh, complete remission with partial hematologic recovery; MCL, mast cell leukemia; NE, not estimable; ORR, overall response rate; PR, partial remission; SM-AHN, systemic mastocytosis with an associated hematological neoplasm.

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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 x 10^9/L.

IMPORTANT SAFETY INFORMATION

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. 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. 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 www.fda.gov/medwatch.

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

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

References: 1. Vaes M, et al. *Front Med (Lausanne)*. 2017;4:110. **2.** Verstovsek S. *Eur J Haematol*. 2013;90(2):89-98. **3.** Gilreath JA, et al. *Clin Pharmacol*. 2019;11:77-92. **4.** Garcia-Montero AC, et al. *Blood*. 2006;108(7):2366-2372. **5.** Jennings SV, et al. *Immunol Allergy Clin North Am*. 2018;38(3):505-525. **6.** Gülen T, et al. *J Intern Med*. 2016;279(3):211-228. **7.** Lim K-H, et al. *Blood*. 2009;113(23):5727-5736. **8.** Cohen SS, et al. *Br J Haematol*. 2014;166(4):521-528. **9.** Data on file. Blueprint Medicines Corporation, Cambridge, MA. 2022. **10.** Data on file. Blueprint Medicines Corporation, Cambridge, MA. 2024. **11.** Data on file. Blueprint Medicines Corporation, Cambridge, MA. 2021. **12.** Sperr WR, et al. *Lancet Haematol*. 2019;6(12):e638-e649. **13.** 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 **14.** AYVAKIT [prescribing information]. Cambridge, MA: Blueprint Medicines Corporation; November 2024. **15.** Gotlib J, et al. *Blood*. 2013;121(13):2393-2401. **16.** Shomali W, et al. *Int J Mol Sci*. 2021;22(6):2983.