AYVAKIT®
avapritinib | tablets

The ONLY Targeted Therapy for Advanced Systemic Mastocytosis

Designed for **potent and selective inhibition of KIT D816V**[1]

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.

SELECT 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.

Please see Important Safety Information on pages 14-15 and the full Prescribing Information for AYVAKIT.

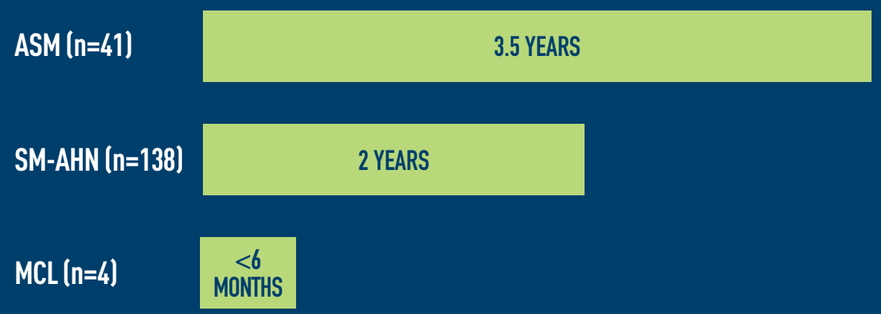
Advanced SM can lead to significant disease burden and shortened overall survival[2-4]

Advanced SM is a clonal mast cell neoplasm **causing significant symptom burden and impact to quality of life.[2,3]**

Patients may exhibit debilitating mast cell mediator symptoms, such as rash and life-threatening anaphylaxis.[3]

Additionally, patients with Advanced SM can experience organ damage, including ascites, osteolytic lesions, pleural effusion, liver dysfunction, weight loss, cytopenias, and hypersplenism.[3,5-7]

MEDIAN OVERALL SURVIVAL (OS) FOR PATIENTS WITH ADVANCED SM[4]



Overall survival was examined in a retrospective study at the Mayo Clinic between 1976 and 2007. Median follow-up was 20.7 months. A later study with 23 MCL patients demonstrated a median overall survival for patients with MCL of 1.9 years, with a 10-year survival of 29.9%.[4,8]

Advanced SM may be missed in patients with other myeloid neoplasms.[9]

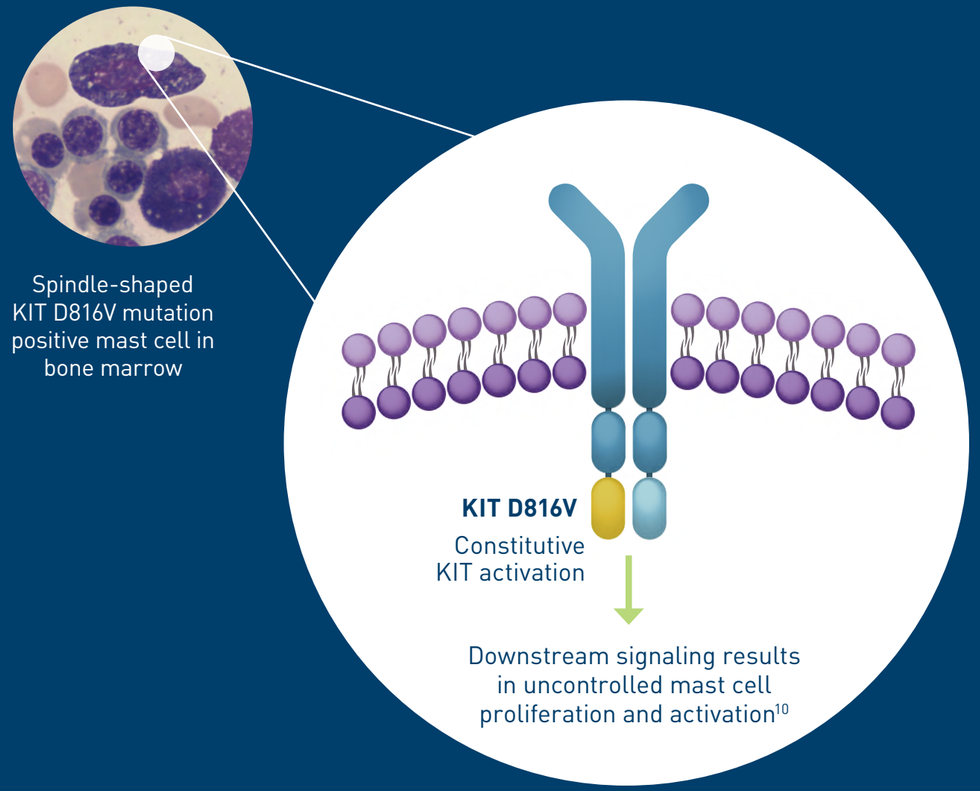
The median time from symptom onset to diagnosis for patients with Advanced SM is 3 years.[3]*

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

ASM=aggressive systemic mastocytosis; MCL=mast cell leukemia; SM=systemic mastocytosis; SM-AHN=systemic mastocytosis with an associated hematological neoplasm.

Advanced SM is driven by KIT D816V in ~95% of cases[6,10,11]

The KIT D816V mutation constitutively activates downstream pathways regulating cellular functions including proliferation and survival of abnormal mast cells.[12,13]



Historically, patients with Advanced SM had **no treatment options that selectively targeted the underlying mutation.[5,14]**

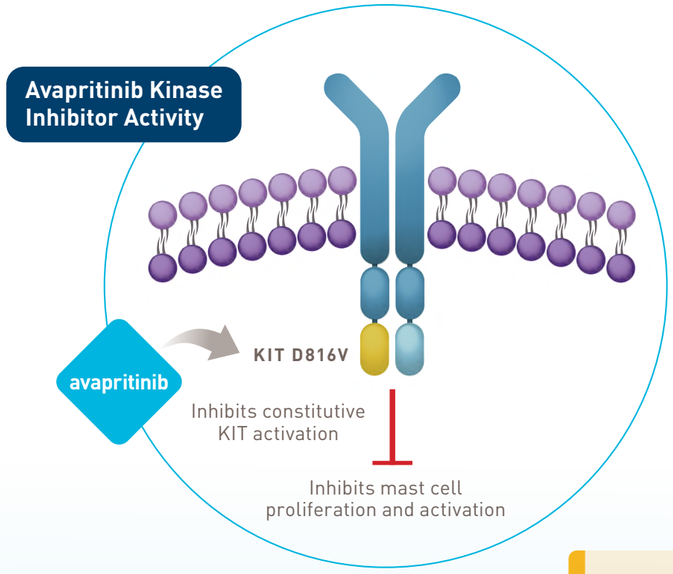
KIT=KIT proto-oncogene, receptor tyrosine kinase.

Target the underlying mutation ›

The ONLY treatment to selectively target the underlying mutation[1]

AVAPRITINIB IS A TYROSINE KINASE INHIBITOR DESIGNED FOR POTENT AND SELECTIVE INHIBITION OF KIT D816V

AYVAKIT potently and selectively inhibits autophosphorylation of the KIT receptor produced by the KIT D816V mutation, with an IC_{50} of 4 nanomoles in selective cellular assays.



KIT D816V testing is not required for AYVAKIT treatment

SELECT IMPORTANT SAFETY INFORMATION

Intracranial Hemorrhage (cont'd)—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.

Please see Important Safety Information on pages 14-15 and the full Prescribing Information for AYVAKIT.

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The efficacy and safety of AYVAKIT were evaluated in EXPLORER and PATHFINDER[1]

MULTICENTER, SINGLE-ARM, OPEN-LABEL CLINICAL TRIALS FOR PATIENTS WITH ADVANCED SM

53 patients were evaluable for a response across the 2 trials, with median follow-up of 11.6 months (95% CI: 9.9 to 16.3 months).*

EXPLORER[15]

- Phase 1 dose-finding study to determine maximum tolerated dose
- Patients received a starting, once-daily dose of 30-400 mg

PATHFINDER[16]

- Phase 2 study evaluating efficacy and safety
- Patients received a starting, once-daily dose of 200 mg

Efficacy was based on overall response rate (ORR) in 53 patients with Advanced SM dosed at up to 200 mg daily, per modified IWG-MRT-ECNM criteria as adjudicated by the central committee. In the subgroup of patients with MCL, the efficacy was based on CR.

Demographic Characteristics at Baseline (N=53)	
Median age	67 years (37-85)
Gender	58% male, 42% female
ECOG PS	0-1: 68%
	2-3: 32%
Ongoing corticosteroid use	40%
Presence of KIT D816V mutation	94% (as measured by ddPCR)
Prior antineoplastic therapy	66%
Prior midostaurin	47%
Advanced SM subtypes	ASM: 3.8% (n=2)
	SM-AHN: 75.5% (n=40)
	MCL: 20.7% (n=11)
Baseline platelet count ≥50 x 10^9/L	91%

*Response-evaluable patients: Confirmed diagnosis of Advanced SM per WHO criteria and deemed evaluable by modified IWG-MRT-ECNM criteria at baseline. Received at least 1 dose of AYVAKIT, had at least 2 post-baseline bone marrow assessments, and were on study for at least 24 weeks, or had an end-of-study visit.

CR=complete remission; ddPCR=droplet digital polymerase chain reaction; ECOG PS=Eastern Cooperative Oncology Group Performance Status; IWG-MRT-ECNM=International Working Group-Myeloproliferative Neoplasma Research and Treatment-European Competence Network on Mastocytosis; WHO=World Health Organization.

See how efficacy was evaluated ›

Efficacy tested by updated, clinically meaningful criteria[7,17]

AYVAKIT IS THE FIRST THERAPY APPROVED BY THE FDA USING THE MODIFIED IWG CRITERIA TO EVALUATE EFFICACY FOR ADVANCED SM PATIENTS

The modified IWG criteria evaluates overall response rate (CR + PR) by:

≥12 weeks
response duration

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

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

*Organ damage may include:

- Nonhematologic
  - Ascites or pleural effusions
  - Liver function abnormalities
  - Marked symptomatic splenomegaly
  - Hypoalbuminemia
  - Weight loss
- Hematologic
  - Neutropenia
  - Anemia
  - Thrombocytopenia

†Serum tryptase must be <20 ng/mL if baseline was ≥40 ng/mL for CR or CRh.

CRh=complete remission with partial hematologic recovery; FDA=Food and Drug Administration; PR=partial remission.

SELECT IMPORTANT SAFETY INFORMATION

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.

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SELECTIVE MODIFIED IWG-MRT-ECNM RESPONSE CRITERIA[18]

CR‡
Requires all 4 criteria and response duration must be ≥12 wk:
No presence of compact neoplastic mast cell aggregates in the bone marrow or other biopsied extracutaneous organ
Serum tryptase level <20 ng/mL§
Peripheral blood count remission defined as ANC ≥1x10⁹/L with normal differential, Hgb level ≥11 g/dL, and platelet count ≥100 × 10⁹/L
Complete resolution of palpable hepatosplenomegaly and all biopsy-proven or suspected SM-related organ damage (C-findings)‖
CRh‡
Requires all criteria for CR be met and response duration must be ≥12 weeks; however, patient may have residual cytopenias. The following minimum recovery of peripheral blood counts is required:
ANC >0.5 × 10⁹/L with normal differential (absence of neoplastic MCs and blasts <1%) *and*
Platelet count >50 × 10⁹/L *and*
Hgb level >8.0 g/dL
PR‡
Requires all 3 of the following criteria and response duration must be ≥12 weeks, in the absence of CR/CRh and progressive disease (PD):
Reduction by ≥50% in neoplastic mast cells in the marrow¶ and/or other extracutaneous organ at biopsy demonstrating eligible SM-related organ damage
Reduction of serum tryptase level by ≥50%§
Resolution of 1 or more biopsy-proven or suspected SM-related organ damage (C-finding[s])‖
Clinical improvement (CI)‡
Response duration must be ≥12 weeks
Requires 1 or more of the nonhematologic and/or hematologic response criteria to be fulfilled in the absence of CR, CRh, PR, or PD

‡Responses that are not maintained for a period of at least 12 weeks do not fulfill criteria for CR/CRh, PR, or CI; however, both maintained and unmaintained (<12 weeks duration) responses should be recorded in the electronic case report form each time they are observed to measure duration of response.
§Only valid as a response criterion if the pretreatment serum tryptase level is ≥40 ng/mL (ie, if pretreatment serum tryptase is <40 ng/mL, it will not be considered as a criterion in evaluation of response).
‖Biopsy of organ(s) in addition to the BM to evaluate for SM-related organ damage may be considered.
¶Only valid as a response criterion if the pretreatment BM MCs are ≥5% (ie, if pretreatment BM MCs are <5%, BM MCs will not be considered as a criterion in evaluation of response).

Explore clinical trial data

Proven efficacy and demonstrated duration of response[1]

ORR across all evaluable Advanced SM patients (N=53)[a] who were dosed up to 200 mg daily

(95% CI: 42%, 70%)*

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

72% ORR was achieved with the addition of patients who had a clinical improvement[b]

*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).

[a]Median duration of follow-up was 11.6 months (95% CI: 9.9, 16.3).
[b]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.[7]

Median DOR across all Advanced SM patients

38.3 MONTHS

[95% CI: 19, NE]
driven primarily by SM-AHN patients

PATIENT TIME TO TREATMENT RESPONSE:

2.1 MONTHS Median time to response (n=30)

9.2 MONTHS Median time to CR and CRh (n=15)[18]

DOR=duration of response; NE=not estimable.

SELECT IMPORTANT SAFETY INFORMATION

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.

Please see Important Safety Information on pages 14-15 and the full Prescribing Information for AYVAKIT.

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Proven efficacy across subtypes and regardless of prior antineoplastic therapy[1,18]

EFFICACY ACROSS ADVANCED SM SUBTYPES[1]

MCL (n=11)[1]

[95% CI: 17%, 77%]

SM-AHN (n=40)[1]

[95% CI: 41%, 73%]

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

ASM (n=2)[1]

[95% CI: 16%, 100%]

1/2 patients achieved CR/CRh

IN A PRE-PLANNED SUBGROUP ANALYSIS, AYVAKIT DEMONSTRATED EFFICACY REGARDLESS OF PRIOR ANTINEOPLASTIC THERAPY[18]

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

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

SELECT IMPORTANT SAFETY INFORMATION

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.

See adverse reactions from clinical trials ›

AYVAKIT was generally well tolerated[1]

THE MAJORITY OF ADVERSE REACTIONS WERE GRADE 1 OR 2

Adverse reactions (≥10%) for patients receiving 200 mg once-daily starting dose in EXPLORER and PATHFINDER (N=80)*

Adverse Reactions	All Grades %	Grade ≥3 %
General		
Edema[a]	79	5
Fatigue/asthenia	23	4
Gastrointestinal		
Diarrhea	28	1
Nausea	24	1
Vomiting	18	3
Abdominal pain[b]	14	1
Constipation	11	0
Nervous system		
Headache	15	0
Cognitive effects[c]	14	1
Taste effects[d]	13	0
Dizziness	13	0
Musculoskeletal and connective tissue		
Arthralgia	10	1
Respiratory, thoracic, and mediastinal		
Epistaxis	11	0

Among patients receiving AYVAKIT, 70% were treated for 6 months or longer and 37% were exposed for greater than 1 year.

For patients receiving the recommended starting dose of 200 mg in clinical trials (N=80):

- **Serious adverse reactions were seen in 34% of patients**
- **Fatal adverse reactions occurred in 2.5% [2/80] of patients**
- **No specific adverse reaction leading to death was reported in more than 1 patient**
- **10% of patients permanently discontinued due to any adverse reaction**

*Per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 and 5.0.
[a]Edema includes face swelling, eyelid edema, orbital edema, periorbital edema, face edema, peripheral edema, edema, generalized edema, and peripheral swelling.
[b]Abdominal pain includes abdominal pain, upper abdominal pain, and abdominal discomfort.
[c]Cognitive effects include memory impairment, cognitive disorder, confusional state, delirium, and disorientation.
[d]Taste effects include dysgeusia.

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 Important Safety Information on pages 14-15 and the full Prescribing Information for AYVAKIT.

Lab abnormalities (≥10%) for patients receiving 200 mg once-daily starting dose in EXPLORER and PATHFINDER (N=80)

Laboratory Abnormality	All Grades %	Grade ≥3 %
Hematology		
Decreased platelets	64	21
Decreased hemoglobin	55	23
Decreased neutrophils	54	25
Decreased lymphocytes	34	11
Increased activated partial thromboplastin time	14	1
Increased lymphocytes	10	0
Chemistry		
Decreased calcium	50	3
Increased bilirubin	41	3
Increased aspartate aminotransferase	38	1
Decreased potassium	26	4
Increased alkaline phosphatase	24	5
Increased creatinine	20	0
Increased alanine aminotransferase	18	1
Decreased sodium	18	1
Decreased albumin	15	1
Decreased magnesium	14	1
Increased potassium	11	0

Clinically relevant adverse reactions occurring in <10% of patients were:
Cardiac: cardiac failure (2.5%) and cardiac failure congestive (1.3%). Gastrointestinal: ascites (5%), gastrointestinal hemorrhage (1.3%), and large intestine perforation (1.3%). Hepatobiliary: cholelithiasis (1.3%). Infections and infestations: upper respiratory tract infection (6%), urinary tract infection (6%), and herpes zoster (2.5%). Vascular: flushing (3.8%), hypertension (3.8%), hypotension (3.8%), and hot flush (2.5%). Nervous: insomnia (6%). Musculoskeletal and connective tissue: pain in extremity (6%). Respiratory, thoracic, and mediastinal: dyspnea (9%) and cough (2.5%). Skin and subcutaneous tissue: rash (rash and rash maculo-papular) (8%), alopecia (9%), pruritus (8%), and hair color changes (6%). Metabolism and nutrition: decreased appetite (8%). Eye: lacrimation increased (9%). Laboratory abnormality: decreased phosphate (9%).

Learn about starting AYVAKIT ›

Starting AYVAKIT—dosing, cognitive effects, and platelet monitoring[1]

THE RECOMMENDED DOSAGE OF AYVAKIT FOR ADVANCED SM IS 200 MG ORALLY ONCE DAILY

AYVAKIT should be taken:

- One tablet orally
- One time each day
- On an empty stomach, at least 1 hour before or 2 hours after a meal

Treatment should continue until disease progression or unacceptable toxicity. Dose reductions as described in the AYVAKIT Prescribing Information may also be considered for adverse reactions as clinically appropriate. Do not initiate AYVAKIT in patients with platelet counts <50 x 10^9/L.

IT WAS COMMON TO MODIFY AYVAKIT DOSAGE

Many patients in the EXPLORER and PATHFINDER trials had their dose reduced or interrupted due to adverse reactions.

Dose modifications for patients in clinical trials who started at 200 mg (N=80):

- Dose interruption: **60%**
- Dose reduction: **68%** (median time to reduction: 6.9 weeks)[17]
- Permanent discontinuation due to adverse reaction: **10%**

Adverse reactions requiring dosage interruption or dose reduction in >2% of patients who received AYVAKIT at 200 mg once daily:

- Thrombocytopenia
- Neutropenia
- Anemia
- Elevated blood alkaline phosphatase
- Cognitive disorder
- Peripheral edema
- Periorbital edema
- Fatigue
- Arthralgia

Review the AYVAKIT **Prescribing Information** and download the **AYVAKIT Dosing and Patient Management Guide** at AYVAKITHCP.com/advsm for more detailed information on dose modifications.

SELECT IMPORTANT SAFETY INFORMATION

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

Please see Important Safety Information on pages 14-15 and the full Prescribing Information for AYVAKIT.

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PLATELET MONITORING FOR ICH IS ESSENTIAL FOR TREATMENT WITH AYVAKIT

Platelet monitoring schedule

Time on therapy	Monitoring and treatment plan
Prior to initiation	Perform a platelet count. AYVAKIT is not recommended in Advanced SM patients with platelet counts <50 x 10^9/L.
First 8 weeks	Perform platelet count every 2 weeks regardless of baseline platelet count.
After 8 weeks	Monitor platelet counts: • Every 2 weeks if values are <75 x 10^9/L (or more frequently as clinically indicated) • Every 4 weeks if values are 75-100 x 10^9/L • As clinically indicated if values are >100 x 10^9/L

Due to risk of ICH, dose interruption or reduction should be considered if platelet counts decrease below 50 x 10^9/L during treatment. If platelet count <50 x 10^9/L occurs, interrupt AYVAKIT until platelet count is ≥50 x 10^9/L, then resume at reduced dose. If platelet counts do not recover above 50 x 10^9/L, consider platelet support.

Platelet monitoring must be performed prior to initiating therapy and throughout treatment with AYVAKIT.

Serious ICH may occur with AYVAKIT treatment. ICH occurred in 2.7% (2/75) of the patients with Advanced SM who had platelet counts of ≥50 x 10^9/L at initiation of the recommended 200-mg dose and in 3.8% (3/80) of patients regardless of platelet counts. Fatal events of ICH have occurred in <1% of Advanced SM patients treated with any dose of AYVAKIT.

Thrombocytopenia was generally reversible by reducing or interrupting AYVAKIT. Dose interruptions and dose reductions for thrombocytopenia occurred in 20% and 22% of AYVAKIT-treated patients, respectively. Manage platelet counts of <50 x 10^9/L by treatment interruption or dose reduction of AYVAKIT.

Use with caution in patients with potential increased risk of ICH, including those with thrombocytopenia, vascular aneurysm, or a history of ICH or cerebrovascular accident within the prior year.

MONITOR PATIENTS FOR COGNITIVE EFFECTS DURING TREATMENT WITH AYVAKIT

Cognitive adverse reactions can occur in patients receiving AYVAKIT. For patients with Advanced SM started at the 200-mg recommended dose, cognitive effects occurred in 14% of 80 patients. Of the 148 patients with Advanced SM who received AYVAKIT at all doses, cognitive effects occurred in 28% of patients, with a median time to onset for the first cognitive adverse reaction of 13.3 weeks (range: 1 day to 1.8 years). Among patients who experienced a cognitive effect of Grade 2 or worse, the median time to improvement to Grade 1 or complete resolution was 8.1 weeks.

Cognitive effects include memory impairment, cognitive disorder, confusional state, delirium, and disorientation.

Advise patients and their caregivers of the potential cognitive effects, and the **importance of notifying their healthcare provider** of any new or worsening symptoms. Advise patients not to drive or operate hazardous machinery if they are experiencing cognitive adverse reactions.

SELECT IMPORTANT SAFETY INFORMATION

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.

Important Safety Information >

Important Safety Information

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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 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 the full Prescribing Information for AYVAKIT.

Summary

The ONLY targeted therapy for Advanced SM designed for potent and selective inhibition of KIT D816V[1]

~95%

Advanced SM is driven by the KIT D816V mutation in ~95% of cases.[6,10,11]

Proven efficacy across all Advanced SM subtypes and regardless of prior antineoplastic therapy.[1,17]

One tablet, once-daily dosing starting at 200 mg.[1]

Generally well tolerated with specific guidelines for patient monitoring and management; most common adverse reactions were Grade 1 or 2.[1]

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Please see Important Safety Information on pages 14-15 and the full Prescribing Information for AYVAKIT.

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YourBlueprint® provides dedicated, personalized support to help your patients from Day 1.

Blueprint Medicines offers a series of programs to support patient access, including:

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- Patient Assistance Program
- Quick Start
- Prior Authorization Support
- Coverage Interruption

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To see how we can help:

Call **1-888-BLUPRNT (1-888-258-7768)**
Monday-Friday, 8 AM-8 PM Eastern Time (ET)

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