Avapritinib (AYVAKIT) in Systemic Mastocytosis
National Drug Monograph
November 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION

Description / MOA	Tyrosine kinase inhibitor that targets KIT D816V, PDGFRA, KIT exon 11, 11/17 and 17 mutants, and PDGFRA D842 mutants. Avapritinib is the second targeted cytoreductive therapy for advanced systemic mastocytosis (**AdvSM**) and the first treatment specifically approved for indolent SM (**ISM**).
Indications Under Review[1]	**AdvSM**: Treatment of adults with AdvSM, which includes aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL). **ISM**: Treatment of adults with ISM. *Limitations of use for AdvSM and ISM*: Not recommended for treatment of patients with platelet count (PLT) < 50 × 10^9/L.
Dosage Regimen	**AdvSM**: 200 mg PO QD. Continue treatment until disease progression or unacceptable toxicity. **ISM**: 25 mg PO QD.
Dosage Modifications	Adverse reactions, strong or moderate CYP3A inhibitors, severe hepatic impairment
Dosage Forms Under Review	Tablets: 25 mg, 50 mg, 100 mg, 200 mg

EFFICACY CONSIDERATIONS – AdvSM

Trial	**EXPLORER**[2]	**PATHFINDER**[3,4,5]
Design	Phase 1 MN single-arm OL observational study (OBS) to evaluate safety, PK, efficacy, and patient-reported outcomes (PROs)	Phase 2 MN single-arm OL OBS, prespecified interim analysis
Population	69 adults with KIT- or PDGFR-mutant AdvSM, ECOG PS 0–3, PLT ≥ 50 × 10^9/L (safety population) 53 with evaluable C-findings response (primary efficacy population [PEP]) 41 (59%) of AdvSM patients had prior antineoplastic therapy including midostaurin (33%) and cladribine (14%)	62 adults with AdvSM; 32 patients with organ damage (C-findings; cohort 1); ECOG PS 0–3 72% of cohort-1 patients had received prior antineoplastic therapy, mainly midostaurin (53%)
Intervention	Avapritinib 30–400 mg QD ± Prednisone / equivalent up to 20 mg QD	Avapritinib 200 mg QD
Comparator	None	None. The authors tested the avapritinib ORR against a historical midostaurin ORR of 28%[†]
Results	Median follow-up: 23 mos	Median follow-up: 10.4 mos (interim results)

Outcome	Avapritinib
ORR, n/N (%)	40/53 (75)
95% CI	62, 86
DOR, median, mo (95% CI)	38 (22, NE)
PFS-24, n/N (%)	33/53 (63)
95% CI	48, 79
OS, median, mo (95% CI)	NR (47, NE)
OS-24, % (95% CI)	76 (64, 87)

DOR, Duration of response; NE, Not estimable; NR, Not reached; ORR, Overall response rate (complete remission + complete remission with partial recovery of peripheral blood counts + partial remission + clinical improvement); OS, Overall survival; OS-24, OS at 24 mos; PFS-24, Progression-free survival rate estimate at 24 mos

200 mg was selected as the optimal dose based on safety, rapid reduction in disease burden, and response rates.
Subgroup Analyses: ORR was numerically higher in midostaurin-naïve than midostaurin-exposed patients

Outcome	Avapritinib
ORR, n/N (%)	24/62 (75)[†]
95% CI	57, 89
PFS time, mo	NR
PFS-12, %	79
OS-12, %	86

See EXPLORER footnotes. OS-12, Overall survival rate estimated at 12 mos; PFS-12, Progression-free survival at 12 mos.
[†] P = 1.6 x 10^{-9}. Any time-related biases due to historical comparator would favor avapritinib.

In subgroup analyses, OS was similar in patients with vs without prior midostaurin exposure.

	(ORR 83% [67, 94] vs. 59% [33, 82], respectively, as well as in patients with no prior therapy vs any prior therapy (86% [64, 97] vs 69% [50, 84], respectively).	
Effect Size	OS effect is uncertain. For reference: OS was 31% at median 1.7 years in untreated AdvSM.[6] OS-24 with midostaurin in AdvSM was 53% (43, 62), intent-to-treat (ITT) analysis.[7]	OS effect is uncertain. For reference: OS-12 with midostaurin in AdvSM was 76% (67, 83), ITT.[7]
Evidence Gaps	Relative treatment effects, PFS time, quality of life	

EFFICACY CONSIDERATIONS – ISM

Trial	**PIONEER**[8]
Design	OL PC RCT (2:1) for 24 weeks then OL extension for up to 5 years. Randomization stratified by serum tryptase level (< 20 ng/mL for up to 20% of enrolled patients vs ≥ 20 ng/mL).
Population	212 adults with ISM (2016 WHO classification), ECOG PS 0–2 and, at screening, moderate or severe symptoms (defined as total symptom score [TSS] of ≥ 28 on the ISM Symptom Assessment Form (ISM-SAF; range, 0–110), ≥ 1 skin or GI symptom, and ≥ 1 symptom not controlled with at least 1 of the following symptomatic therapies at optimal (approved) dosages for ≥ 28 days: H1 antihistamines, H2 antihistamines, proton pump inhibitors, leukotriene inhibitors, cromolyn sodium, prednisone ≤ 20 mg daily or equivalent, or omalizumab. 10% of patients had TSS < 28 (mild disease) at baseline. 12.3% of patients had prior cytoreductive therapy, and 93% had ≥ 2 prior best supportive care (BSC) drugs at baseline.
Intervention	Avapritinib 25 mg QD for 4 weeks per cycle + BSC
Comparator	Placebo + BSC
Results	Week 24

Outcome	Avapritinib	Placebo	RR	Absolute Effect	NNT	Q
CFB in TSS	–15.6	–9.2	—	Diff –6.4	—	M[α]
95% CI	–18.6, –12.6	–13.1, –5.2		NS		
TSS-50	35/141 (25)	7/71 (10)	2.5	AAE 150	7	L[αγ]
95% CI	18, 33	4, 19	1.2, 5.4	50, 249	5, 20	
Tryptase-50	76/141 (54)	0/71 (0)	—	AAE 539	2	L[αβ]
95% CI	45, 62	NS		457, 621	2, 3	
MC-QoL, % CFB	–34	–18	—	Diff –16	—	M[α]
95% CI	–40, –29	–25, –11		NS		

AAE, Anticipated absolute effect per 1000; CFB, Change from baseline; MC-QoL, Mastocytosis Quality of Life (range 0 to 100; mean total scores of 29, 50, and 70 corresponded with 'mild,' 'moderate' and 'severe' QoL impairment, respectively); NE, Not estimable; NS, Not stated; Tryptase-50, At least 50% reduction from baseline in tryptase levels (a highly specific measure of mast cell burden and activation); TSS-30/-50, ≥ 30%/50% reduction in Total Symptom Score; Q, GRADE quality (L, Low; M, Moderate)

[α] Downgraded for risk of bias (open-label)
[β] Downgraded for indirectness
[γ] Downgraded for imprecision (wide CIs)

Achieved ≥ 50% reduction in bone marrow mast-cell burden from baseline to Week 24: 56/106 (53%; 43, 63) vs 13/57 (23%; 13, 36) with avapritinib vs placebo, respectively.
Subgroup Analyses (TSS difference in means, avapritinib – PBO).
Baseline ISM Status (post hoc): –4.2 (–9.1, 0.8) for moderate vs –7.8 (–14.3, –1.3) for severe.
Baseline Serum Tryptase (ng/mL) (planned): 1.6 (–10.1, 13.3) for < 20 vs –8.6 (–13.4, –3.9) for ≥ 20.

Effect Size	*CFB in TSS*: Small but clinically meaningful (equivalent to changing from a mean of 50 at baseline to 34 at Week 24, still in moderate to severe category, but associated with apparently small–moderate improvement in MC-QoL). For TSS, a clinically important response in an individual is a decrease of ≥ 30 percentage points, and a clinically important between-treatment difference is 10 percentage points.[9] *TSS-50*: Small. *MC-QoL*: Clinically important changes have not been determined.
Evidence Gaps	Efficacy in patients who failed prior cytoreductive therapy; long-term treatment effects

SAFETY CONSIDERATIONS	**Boxed Warnings**	None
	Contraindications	None
	Other Warnings	Intracranial hemorrhage, cognitive effects, photosensitivity, embryofetal toxicity
	Serious AEs	**AdvSM**: 34% (Top 5: anemia, subdural hematoma, pleural effusion, ascites, pneumonia) **ISM**: 0.7% (1 patient, pelvic hematoma)
	Discontinuations Due to AEs	**AdvSM**: 10%–15% (> 1 patient: subdural hematoma) **ISM**: 0.7% (1 patient, dyspnea and dizziness)
	Top 5 Grade 3/4 (G3/4) AEs	**AdvSM.** Top 5 G3/4 AEs: Edema, fatigue/asthenia, vomiting, diarrhea, nausea, abdominal pain, cognitive effects, arthralgia. Top 5 G3/4 Lab Abnormalities: Decreased neutrophils, decreased hemoglobin, decreased platelets, decreased lymphocytes, increased alkaline phosphatase **ISM.** G3/4: 7% of all AEs.
	Carcinogenesis and Mutagenesis	Non-mutagenic and non-genotoxic in nonclinical studies.
	Drug Interactions	Strong CYP3A inHIBitors: Avoid (increased avapritinib effects). Moderate CYP3A inHIBitors: Avoid or reduce dose of avapritinib. Strong or moderate CYP3A inDUCers: Avoid (decreased avapritinib effects)

INDIRECT COMPARISONS	**Avapritinib vs Midostaurin**	
	AdvSM	Unanchored matching-adjusted indirect comparison of avapritinib (K = 2) and midostaurin (K = 2). Avapritinib showed improvement in OS: aHR 0.44 (95% CI 0.25, 0.76); OS rates not reported.[10] All studies were single-arm OBSs. Prognostic factors and other treatment effect modifiers could not be fully accounted for. Avapritinib and midostaurin trials were done 6–12 years apart when standards of care would be different (any time-related biases would favor avapritinib).
	Avapritinib in EXPLORER + PATHFINDER vs Best Available Treatment (BAT) in real-world clinical practice	
	AdvSM.	Retrospective MC OBS supported by Blueprint Medicines Corporation (manufacturer of avapritinib). Median aOS: 49.0 (46.9, NE) vs 26.8 (18.2, 39.7) mos for avapritinib in single-arm clinical trials vs historical BAT, respectively; aHR 0.48 (0.29, 0.79). aOS at 36 mos: 68.0% vs 42.7%, respectively.[11] BAT consisted most frequently of TKIs (54.1%; midostaurin 50.5%) and other cytoreductive therapy (41.0%; cladribine 25.0%) while IFN alfa and pegIFN were used in 5.6% and 4.1% of cases, respectively. No indirect comparisons of safety could be made.
	SM-AHN.	Retrospective chart-review OBS (abstract) sponsored by Blueprint Medicines Corporation. Median OS 46.9 (44.9, NE) vs 18.0 (13.0, 26.8) mos for avapritinib in single-arm clinical trials vs historical BAT, respectively; aHR 0.42 (0.24, 0.74).[12] BAT mainly consisted of TKIs (60%) and other cytoreductive therapies (38%). No safety data were reported.

PLACE IN THERAPY

DRUG	VANF	CFU	FDA	NCCN SM GUIDELINES (v4.2023)[13]
AdvSM				
Avapritinib	TBD	TBD	1st line for **AdvSM** (**ASM**, **SM-AHN**, or **MCL**) Not recommended if PLT < 50 × 10^9/L.	1st-line option if PLT ≥ 50 × 10^9/L for **ASM**, **MCL** and **SM-AHN** with SM component requiring more immediate treatment than the AHN (e.g., ≥ 1 C-finding)
Midostaurin	PA-F	1st line	1st line for **ASM**, **SM-AHN**, and **MCL**	1st-line option for **ASM**, **MCL** and **SM-AHN** with SM component requiring more immediate treatment than the AHN (e.g., ≥ 1 C-finding)
Cladribine	F (inj) NF (tab)	—	Off-label	Other recommended option for **ASM** (useful for rapid debulking), **MCL** and **SM-AHN** with SM component requiring more immediate treatment (e.g., ≥ 1 C-finding)
Peginterferon alfa-2a ± prednisone	F	—	Off-label	Other recommended option for **ASM** (useful for slowly progressive disease without need for rapid cytoreduction) and **SM-AHN** with SM component requiring more immediate treatment (e.g., ≥ 1 C-finding)
Imatinib	F Heme / onc	—	1st line for **ASM** without D816V c-Kit mutation or with unknown c-Kit mutation status	Useful for **ASM** in certain circumstances (for negative or unknown KIT D816V mutation status; well-differentiated SM; and eosinophilia present with FIP1L1:PDGFRA gene fusion)
ISM				
Avapritinib	TBD	TBD	1st line for **ISM** Not recommended if PLT < 50 × 10^9/L.	Preferred regimen (2nd–3rd-line) for **ISM** if PLT ≥ 50 × 10^9/L with symptoms refractory to antimediators and possibly cladribine or pegIFN alfa-2a
Midostaurin†	PA-F	—	Off-label	Not mentioned.
Cladribine	F (inj) NF (tab)	—	Off-label	May be useful in selected patients with symptomatic **ISM** with severe, refractory symptoms or bone disease not responsive to antimediator therapy (at same level as antimediator drugs before trial of preferred regimen of clinical trial or **avapritinib**).
Peginterferon alfa-2a	F	—	Off-label	

† **Studies evaluating midostaurin in ISM**. A phase 2 single-arm OL OBS in 20 patients with ISM showed significant improvements in symptom severity and tryptase levels with midostaurin.[14] After 12 weeks of therapy, 75% of patients reported reduced symptoms, 80% had improved skin lesions, all had reductions in tryptase levels, and 50% showed reductions in bone marrow MC burden. Anaphylaxis and bone symptom scores on the Mastocytosis Quality of Life Questionnaire (MQLQ) showed minimal or no improvement. The initial dose was 100 mg twice daily but 5 patients successfully titrated dosages down to as low as 100 mg per day based on symptom severity and tryptase levels. The duration of an adequate trial appeared to be 24 weeks. A retrospective review by the Mayo Clinic in 13 patients with ISM (n = 11) or smoldering SM (n = 2) showed that midostaurin improved MC-related mediator symptoms and skin lesions in 62% and 44% of patients, respectively.[15] Associated decreases in tryptase levels and, in some patients, bone marrow MC burden were observed. The midostaurin dosage range was 50–200 mg daily for a median of 14 months, with a median dose at end of study of 100 mg daily.

VHA PLACE IN THERAPY

Potential Use in VHA

~~1.~~ **AdvSM** (ASM, SM-AHN, or MCL) with PLT ≥ 50 × 10^9/L

2. Symptomatic **ISM** with PLT ≥ 50 × 10^9/L in patients with an absolute contraindication or unmanageable intolerance to midostaurin.

Prepared: November 2023 by Francine Goodman, PharmD, BCPS, National PBM Clinical Pharmacy Program Manager, VA Pharmacy Benefits Management Services (12PBM)

Contact: Bernadette Heron, PharmD, BCOP, National PBM Clinical Pharmacy Program Manager, VA Pharmacy Benefits Management Services (12PBM)

References

1 AYVAKIT (avapritinib) tablets [prescribing information online]. Cambridge, MA: Blueprint Medicines Corporation. May 2023. Available at: AYVAKIT.pdf (blueprintmedicines.com). Accessed 18 August 2023.

2 DeAngelo DJ, Radia DH, George TI, Robinson WA, Quiery AT, Drummond MW, Bose P, Hexner EO, Winton EF, Horny HP, Tugnait M, Schmidt-Kittler O, Evans EK, Lin HM, Mar BG, Verstovsek S, Deininger MW, Gotlib J. Safety and efficacy of avapritinib in advanced systemic mastocytosis: the phase 1 EXPLORER trial. Nat Med. 2021 Dec;27(12):2183-2191. doi: 10.1038/s41591-021-01538-9. Epub 2021 Dec 6. PMID: 34873347; PMCID: PMC8674134.

3 Gotlib J, Reiter A, Radia DH, Deininger MW, George TI, Panse J, Vannucchi AM, Platzbecker U, Alvarez-Twose I, Mital A, Hermine O, Dybedal I, Hexner EO, Hicks LK, Span L, Mesa R, Bose P, Pettit KM, Heaney ML, Oh ST, Sen J, Lin HM, Mar BG, DeAngelo DJ. Efficacy and safety of avapritinib in advanced systemic mastocytosis: interim analysis of the phase 2 PATHFINDER trial. Nat Med. 2021 Dec;27(12):2192-2199. doi: 10.1038/s41591-021-01539-8. Epub 2021 Dec 6. PMID: 34873345; PMCID: PMC8674139.

4 Reiter A, Schwaab J, DeAngelo DJ, Gotlib J, Deininger MW, Pettit KM, Alvarez-Twose I, Vannucchi AM, Panse J, Platzbecker U, Hermine O, Dybedal I, Lin HM, Rylova SN, Ehlert K, Dimitrijević S, Radia DH. Efficacy and safety of avapritinib in previously treated patients with advanced systemic mastocytosis. Blood Adv. 2022 Nov 8;6(21):5750-5762. doi: 10.1182/bloodadvances.2022007539. PMID: 35640224; PMCID: PMC9647833.

5 Reiter A, Gotlib J, Álvarez-Twose I, Radia DH, Lübke J, Bobbili PJ, Wang A, Norregaard C, Dimitrijevic S, Sullivan E, Louie-Gao M, Schwaab J, Galinsky IA, Perkins C, Sperr WR, Sriskandarajah P, Chin A, Sendhil SR, Duh MS, Valent P, DeAngelo DJ. Efficacy of avapritinib versus best available therapy in the treatment of advanced systemic mastocytosis. Leukemia. 2022 Aug;36(8):2108-2120. doi: 10.1038/s41375-022-01615-z. Epub 2022 Jul 5. PMID: 35790816; PMCID: PMC9343245.

6 Lim KH, Tefferi A, Lasho TL, Finke C, Patnaik M, Butterfield JH, McClure RF, Li CY, Pardanani A. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. Blood. 2009 Jun 4;113(23):5727-36. doi: 10.1182/blood-2009-02-205237. Epub 2009 Apr 10. PMID: 19363219.

7 Gotlib J, Kluin-Nelemans HC, George TI, Akin C, Sotlar K, Hermine O, Awan FT, Hexner E, Mauro MJ, Sternberg DW, Villeneuve M, Huntsman Labed A, Stanek EJ, Hartmann K, Horny HP, Valent P, Reiter A. Efficacy and Safety of Midostaurin in Advanced Systemic Mastocytosis. N Engl J Med. 2016 Jun 30;374(26):2530-41. doi: 10.1056/NEJMoa1513098. PMID: 27355533.

8 Gotlib J, Castells M, Oude Elberink H, et al. Avapritinib versus Placebo in Indolent Systemic Mastocytosis. NEJM Evidence. 2023 May 23: 1–15. DOI: 10.1056/EVIDoa2200339.

9 Padilla, B., Shields, A.L., Taylor, F. *et al.* Psychometric evaluation of the Indolent Systemic Mastocytosis Symptom Assessment Form (ISM-SAF) in a phase 2 clinical study. *Orphanet J Rare Dis* **16**, 434 (2021). https://doi.org/10.1186/s13023-021-02037-3

10 Pilkington H, Smith S, Roskell N, Iannazzo S. Indirect treatment comparisons of avapritinib versus midostaurin for patients with advanced systemic mastocytosis. Future Oncol. 2022 Apr;18(13):1583-1594. doi: 10.2217/fon-2021-1509. Epub 2022 Feb 4. PMID: 35114819.

11 Reiter A, Gotlib J, Álvarez-Twose I, Radia DH, Lübke J, Bobbili PJ, Wang A, Norregaard C, Dimitrijevic S, Sullivan E, Louie-Gao M, Schwaab J, Galinsky IA, Perkins C, Sperr WR, Sriskandarajah P, Chin A, Sendhil SR, Duh MS, Valent P, DeAngelo DJ. Efficacy of avapritinib versus best available therapy in the treatment of advanced systemic mastocytosis. Leukemia. 2022 Aug;36(8):2108-2120. doi: 10.1038/s41375-022-01615-z. Epub 2022 Jul 5. PMID: 35790816; PMCID: PMC9343245.

12 Reiter A, Gotlib J, Álvarez-Twose I, Radia D, Lübke J, ScD PB, Wang A, Norregaard C, Dimitrijević S, Sullivan E, Louie-Gao M, Schwaab J, Galinsky I, Perkins C, Sperr W, Sriskandarajah P, Chin A, Sendhil S, ScD MSD, Valent P, DeAngelo D. MPN-435 Overall Survival in Patients With Systemic Mastocytosis With Associated Hematologic Neoplasm Treated With Avapritinib Versus Best Available Therapy. Clin Lymphoma Myeloma Leuk. 2022 Oct;22 Suppl 2:S337. doi: 10.1016/S2152-2650(22)01459-8. PMID: 36164009. Abstract.

13 National Comprehensive Cancer Network (NCCN) Guidelines [online], Systemic Mastocytosis Version 4.2023. Available at: mastocytosis.pdf (nccn.org) . Accessed 15 August 2023.

14 van Anrooij B, Oude Elberink JNG, Span LFR, de Monchy JGR, Rosati S, Mulder AB, Kluin-Nelemans JC. Midostaurin in patients with indolent systemic mastocytosis: An open-label phase 2 trial. J Allergy Clin Immunol. 2018 Sep;142(3):1006-1008.e7. doi: 10.1016/j.jaci.2018.06.003. Epub 2018 Jun 8. PMID: 29890238.

15 Farrukh F, Gangat N, Shah MV, Litzow MR, Elliott MA, Begna K, Hook CC, Tefferi A, Pardanani A. Midostaurin therapy for indolent and smoldering systemic mastocytosis: Retrospective review of Mayo Clinic experience. Am J Hematol. 2022 Apr;97(4):E138-E140. doi: 10.1002/ajh.26464. Epub 2022 Jan 19. PMID: 35015315.