Momelotinib (OJJAARA) in Myelofibrosis

National Drug Monograph
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VA National Formulary Committee

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.

Abbreviations: AAE, anticipated absolute effect per 1000 cases; ACT, active controlled trial; AE, adverse event; ACVR1, activin A receptor type I; ALK2, activin receptor-like kinase 2; AlloHCT, allogeneic hematopoietic stem cell transplant; BAT, best available therapy; BCRP, breast cancer resistance protein; DB, double-blind; DD, double dummy; Diff, difference; ECOG, Eastern Cooperative Oncology Group; EPO, erythropoietin; HR, hazard ratio; INT, intermediate; IPSS, International Prognostic Scoring System; JAKI, Janus kinase inhibitor; MF, myelofibrosis; MFSAF TSS-50, ≥ 50% reduction from baseline in the Myelofibrosis Symptom Assessment Form; MMB, momelotinib; MN, multinational; MOA, mechanism of action; NE, not estimable; NI, noninferiority; OATP, organic anion transporting polypeptide; OL, open-label; OS, overall survival; PLT, platelet or platelet count; PMF, primary myelofibrosis; PMN, polymorphonuclear leukocytes; PN, peripheral neuropathy; PS, performance status; Q, Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) quality rating; RBC, red blood cell; RCT, randomized clinical trial; RUX, ruxolitinib; SMF, secondary myelofibrosis; SUP, superiority; SVR, spleen volume response; SVR-35, ≥ 35% reduction from baseline in SVR; TI, transfusion independence; TSS, total symptom score; ULN, upper limit of normal

FDA APPROVAL INFORMATION	
Description / MOA	Selective inhibitor of JAK1, JAK2, and activin A receptor type I (**ACVR1**, aka activin receptor-like kinase 2 [ALK2]). Inhibition of ACVR1 results in decreased hepatic hepcidin production and hepcidin-related inflammation and increased serum iron availability and erythropoiesis.[1] The FDA granted Fast Track designation to momelotinib (**MMB**). It is the fourth JAK inhibitor (**JAKI**) approved for myelofibrosis (**MF**) and the first JAKI approved for MF with anemia.
Indication Under Review[2]	Treatment of intermediate or high-risk MF, including primary MF (**PMF**) or secondary MF (**SMF**; post polycythemia vera and post-essential thrombocythemia), in adults with anemia.
Dosage Regimen	200 mg PO once daily with or without food. *Severe hepatic impairment (Child-Pugh Class C):* Reduce starting dose to 150 mg PO once daily.
Dosage Forms Under Review	Tablets: 100, 150, and 200 mg

EFFICACY CONSIDERATIONS	
Trial	**MOMENTUM**[3,4]
Design	24-wk phase 3 MN DB DD ACT, randomized 2:1, stratified by total symptom score (**TSS**; < 22 vs ≥ 22), spleen size (< 12 cm vs ≥ 12 cm), RBC or whole blood units transfused in previous 8 wks (0 units vs 1–4 units vs ≥ 5 units), and study site. Primary efficacy measure: ≥ 50% reduction from baseline to Wk 24 in the Myelofibrosis Symptom Assessment Form (**MFSAF TSS-50**) TI response was defined as no RBC transfusion and no Hg < 8 g/dL in the last 12 wks of the 24-wk randomized period.
Population	*Included:* Adults with symptomatic Dynamic International Prognostic Scoring System (DIPSS) high-, INT-2, or INT-1 risk PMF or SMF previously exposed to ruxolitinib (**RUX**) for ≥ 90 days or ≥ 28 days if therapy was complicated by RBC transfusion of ≥ 4 units in 8 weeks, or grade 3 or 4 adverse events (**AEs**) of thrombocytopenia (PLT < 50×10^9/L), anemia (Hg < 8 g/dL), or hematoma; anemia (Hg < 10 g/dL) and platelet (**PLT**) count > 25×10^9/L without requirement for PLT transfusion; splenomegaly (palpable ≥ 5 cm below left costal margin or volume of ≥ 450 cm^3 on imaging); Eastern Cooperative Oncology Group (**ECOG**) Performance Status (**PS**) of 0–2. Any previous JAKI was tapered off with at least a 2-week washout before baseline assessments. *Characteristics (N = 195):* 63% male, median age 71 y; mainly intermediate (**INT**)-2–risk (58%) or high-risk (33%) PMF (64%); 76% JAK2 mutation positive; mean Hg 8.0 g/dL; mean PLT count 145 × 10^9/L; 50% transfusion dependent; prior JAKI: ruxolitinib 100% (50% immediately before enrollment); 5% fedratinib
Intervention	MMB 200 mg QD + danazol placebo with dose adjusted for toxicity to lowest allowed dose of 50 mg.

Comparator

Danazol 300 mg BID + MMB placebo with dose adjusted for toxicity to lowest allowed dose of 200 mg.

Results

Week 24 Results of MOMENTUM

Outcome	Momelotinib	Danazol	Relative Effect (95% CI)	Absolute Effect (95% CI)	Q
TI response, n/N (%)	39/130 (30)	13/65 (20)	RR 1.50 (0.86, 2.61)	NI Diff 14 (2, 25)† SUP Diff 10 (–2, 22)	M[α]
Zero transfusions, n/N (%)	46/130 (35)	11/65 (17)	RR 2.09 (1.16, 3.76)	AAE 185 (62, 307)	M[α]
Deaths, n/N (%)	25/130 (19)	16/65 (25)	HR 0.73 (0.38, 1.41)	AAE 54 (–71, 179)	M[α]
MFSAF TSS-50, n/N (%)	32/130 (25)	6/65 (9)	RR 2.67 (1.18, 6.0)	AAE 154 (60, 256)	L[αβ]
SVR-35, n/N (%)	29/130 (22)	2/65 (3)	RR 7.25 (1.78, 29.45)	AAE 192 (109, 275)	L[αβ]

AAE, Anticipated absolute effect per 1000; NI, Noninferiority; Q, GRADE quality (L=low; M=moderate); SUP, Superiority
† Noninferiority margin for TI was 0.8 in response ratio scale
α Downgraded for imprecision (optimal information size not met; wide CIs)
β Downgraded for indirectness (not a clinical outcome)

Subgroup Analyses

- By Hg ≥ 8 g/dL vs < 8 g/dL, respectively: TI response rate at Wk 24 was higher in the group with Hg ≥ 8 g/dL in both the MMB (26 [39%] of 67 vs 12 [19%] of 62) and danazol groups (9 [27%] of 33 vs 4 [13%] of 32).

Secondary Outcomes

- Median overall survival (**OS**): Not estimable (**NE**; 95% CI NE, NE) vs NE (55.7, NE) for MMB vs danazol, respectively.
- 24-week survival rate: 88% vs 80%, respectively; HR 0.51 (0.24, 1.08).
- Leukemia-free survival: HR 0.65 (0.35, 1.21).
- Leukemic transformation: 2% vs 6% for MMB vs danazol, respectively.

Comments

MF-associated anemia, which can be worsened by previously approved JAKIs for MF particularly RUX and fedratinib, is a common and debilitating problem that often results in dependence on red blood cell (**RBC**) transfusions.

The MOMENTUM results suggested that, in patients with MF and anemia with or without thrombocytopenia and previous exposure, inadequate response, or hematotoxicity to RUX, MMB was noninferior to danazol in obtaining TI and was better than danazol in the percentages of patients requiring no RBC transfusion, achieving ≥ 50% symptom improvement, and obtaining ≥ 35% reduction in spleen size.

Limitations: Unfair comparison between a MF-directed therapy (MMB) and an anemia-directed therapy (danazol). (Danazol is a National Comprehensive Cancer Network [NCCN]-recommended treatment for MF-associated anemia.[5])

Trials	**SIMPLIFY-1**[6,7,8]	**SIMPLIFY-2**[7,8,9]
Design	24-wk phase 3 MC DB DD noninferiority (NI) RCT with randomization stratified by transfusion dependence and PLT count and NI determined by the lower limit of 95% CI of the NI difference > 0, stratum adjusted. Crossover to MMB in OL extension phase Primary outcome measure: Wk-24 SVR-35 response TI was defined as no RBC transfusions and no Hg < 8 g/dL in previous 12 wks.	24-wk phase 3 MN OL RCT (2:1) without washout of prior RUX; randomization stratified by transfusion dependence and baseline TSS. Crossover to MMB in OL extension phase. Primary outcome measure: Wk-24 SVR-35 response TI was defined as no RBC transfusions and no Hg < 8 g/dL in previous 12 wks.
Population	*Included*: JAKI-naïve adults with PMF or SMF; International Prognostic Scoring System (IPSS) high, INT-2, or INT-1 risk with symptomatic splenomegaly or hepatomegaly or anemia (Hg < 10.0 g/dL) and/or unresponsive to non-JAKI therapy; PMN ≥ 0.75 × 10^9/L; PLT ≥ 50 × 10^9/L (or ≥ 100 × 10^9/L if AST or ALT ≥ 2 x ULN; ECOG PS ≤ 2; life expectancy > 24 wks. *Excluded*: Prior JAKI, spleen irradiation (< 3 mos prior), certain cancers; eligible for alloHCT.	*Included*: Had ≥ 28 days of RUX therapy; either required RBC transfusions on RUX or required dosage reduction to < 20 mg BID and had anemia, grade ≥ 3 thrombocytopenia (PLT < 50 × 10^9/L) or grade ≥ 3 bleeding on RUX; adults with PMF or SMF; DIPSS high, INT-2, or INT-1 risk with splenomegaly or hepatomegaly; ECOG PS ≤ 2; life expectancy > 24 wks. No minimum PLT count cutoff

	Characteristics: Mean age 65 y; 56% male; 83% white; 57% PMF; 33% INT-2 risk; 46% high risk; Hg 10.6 g/dL; 69% TI; PLT count 301 × 10^9/L	was required. Patients did not necessarily fail RUX therapy (i.e., did not have MF progression). *Excluded*: Spleen irradiation (< 3 mos prior); unresolved nonhematologic toxicity; grade ≥ 2 peripheral neuropathy (**PN**) *Characteristics*: Mean age 68 y; 56% male; 83% white; 60% PMF; 57% INT-2 risk; 16% high risk; Hg 9.4 g/dL; 34% TI; PLT count 149 × 10^9/L
Intervention	MMB 200 mg QD	MMB 200 mg QD
Comparator	RUX 20 mg BID (or dosage modified as per label)	BAT: could include no therapy; most commonly RUX 89%, RUX + additional therapies 27%, hydroxyurea 23%, corticosteroids 12%
Results	MMB vs RUX, respectively: • Median follow-up: 3.43 y vs 3.47 y. • Discontinued: 40/215 (18.6%) vs 16/217 (7.4%), mainly because of AEs (19/215 [8.8%] vs 9/217 [4.1%]). • MMB was noninferior to RUX in Wk-24 SVR-35 response: 57/215 (26.5%) vs 63/217 (29.0%). NI proportion difference 0.09 (95% CI, 0.02, 0.16), meeting NI criteria with lower bound of the 95% CI > 0. • MMB was worse than RUX in Wk-24 TSS-50 response: 60/211 (28.4%) vs 89/211 (42.2%); RR 0.67 [0.52, 0.88]; AAE 137 [47, 228]. Noninferiority was not met. • MMB was nominally* significantly better than RUX in Wk-24 TI response rates: 143/215 (66.5%) vs 107/217 (49.3%); RR 1.35 (1.14, 1.59); AAE 172 (80, 264). • MMB was nominally* significantly better than RUX in Wk-24 median RBC transfusion rate: 0 vs 0.4 units/mo • Deaths: 66 (30.8%) vs 73 (33.8%); HR 1.02 (0.73, 1.43).[7] • OS rates at 2 | 4 | 6 y: 81.6% vs 80.6% | 62.9% vs 64.4% | 56.5% vs 52.7% with MMB vs RUX → MMB, respectively.[7] • TI response at Wk 24 was significantly associated with improved OS in MMB patients and was not significantly associated with improved OS with RUX.[7] • Leukemic transformation: 12 (5.6%) vs 9 (4.2%) of MMB vs RUX → MMB, respectively.[7] HR 1.08 (0.78, 1.50).[7] Subset of Patients with Anemia (Hg < 10 g/dL) at Baseline • SVR-35: 27/86 (31.4%) vs 31/95 (32.6%)[2] – *Analysis did not adjust for multiplicity	MMB vs BAT, respectively: • Imbalance in baseline patient requirement for RUX dose reduction for grade 3 AEs, as per inclusion criterion: 60/104 (58%) vs 20/52 (39%). The authors did not discuss the potential impact of this imbalance on treatment effects. • Median follow-up: 3.07 y vs 3.22 y. • Primary Endpoint: MMB did not provide additional Wk-24 SVR-35 responses: 7/104 (7%) vs 3/52 (6%), respectively (diff 0.01; –0.09, 0.10). • MMB was nominally* significantly better than BAT in Wk-24 TSS-50 response: 27/103 (26%) vs 3/51 (6%); RR 4.5 (1.4, 14.0); AAE 203 (97, 310) • MMB was nominally* significantly better than BAT in Wk-24 TI response (45/104 [43%] vs 11/52 [21%]; RR 2.0 [1.16, 3.61]; AAE 221 [75, 367]) and rate of requiring no transfusion (42/104 [40%] vs 14/52 [27%]); RR 1.5 (0.9, 2.5); ARR 13.5 (–1.8, 28.8). • Deaths: 47 (45.2%) vs 23 (44.2%) with MMB vs BAT → MMB, respectively.[7] • Median OS: 2.9 vs 3.1 y, respectively. HR 0.98 (0.59, 1.62).[7] • OS rate at 2 y: 65.8% vs 61.2%, respectively.[7] • TI response at Wk 24 was nonsignificantly associated with improved OS in MMB and BAT. • Leukemic transformation: 7 (6.7%) vs 1 (1.9%); HR 0.97 (0.59, 1.60).[7]
Comments	MMB missed the endpoint of noninferiority vs RUX in symptom improvement. The SIMPLIFY-1 results suggested that relative to RUX, MMB therapy was noninferior in SVR-35 and similar in overall survival rates but may involve a trade-off between a potentially greater likelihood of TI (statistically	MMB missed the primary endpoint of superiority vs BAT in spleen response. The SIMPLIFY-2 results suggested that relative to BAT including RUX, MMB was noninferior in SVR-35 response, similar in overall survival rates and, with some statistical uncertainty, better in obtaining symptomatic

		uncertain but potentially clinically important improvement) and lower likelihood of symptomatic response in JAKI-naïve patients with high, INT-2, or INT-1 risk MF with or without anemia. *Limitations.* Use of Wk-24 TI response as a surrogate for predicting OS requires further studies to validate. Survival data are mostly descriptive because most patients crossed over to MMB early in the extension phase. Quality of life was not assessed.	response and TI in patients who have high, INT-2, or INT-1 risk MF with or without anemia and an inadequate response or toxicity on RUX. *Limitations.* Lack of washout of prior JAKI may have influenced the lack of treatment difference in OS. Quality of life was not assessed.
	Other Studies of Interest	*12-Year Survival Data*: Single-arm observational study (OBS) by Mayo Clinic involving 79 JAKI-naïve patients with intermediate or high-risk MF treated with MMB in initial phase 1/2 study and followed for long-term survival data. Median overall survival (OS) was 3.5 y; 5-y OS rate 32%; 10-y OS rate 20%.[10] Median on-treatment survival was 25 mos. The 3-y and 5-y treatment discontinuation rates were 68% and 84%, respectively.	

SAFETY CONSIDERATIONS	**Boxed Warnings**	None
	Contraindications	None
	Other Warnings	*Risk of Infections* including reactivation of hepatitis B *Thrombocytopenia and Neutropenia* *Hepatotoxicity.* Check liver enzymes at baseline, every month for the first 6 months, then as needed during therapy. *Major Adverse Cardiovascular Events (MACE), Thrombosis, and Malignancies (excluding nonmelanoma skin cancer).* Another JAKI increased the risk of MACE relative to tumor necrosis factor (TNF) blockers in patients with rheumatoid arthritis.
	Top Grade ≥ 3 AEs	Thrombocytopenia (22%), bacterial infection, viral infection, neutropenia
	Top AEs (≥ 20%)	MOMENTUM: Thrombocytopenia, diarrhea, hemorrhage, fatigue
	Drug Interactions	*Organic Anion Transporting Polypeptide (OATP)1B1/B3 Inhibitors*: Increased MMB effects. Monitor, adjust dose. *Breast Cancer Resistance Protein (BCRP) Substrates*: Increased BCRP substrate effects. Initiate rosuvastatin (BCRP substrate) at 5 mg and do not exceed 10 mg once daily. Other BCRP substrates may need dose adjustment.
	Pregnancy	Only use during pregnancy if expected benefits to the mother outweigh the potential risks to the fetus.
	Lactation	Patients should not breastfeed during treatment and for at least 1 week after the last dose.
	Contraception	Advise nonpregnant patients of reproductive potential to use highly effective contraception during therapy and for at least 1 week after the last dose of MMB.
	Comparative Safety	MOMENTUM,[3] MMB (N = 130) vs Danazol (N = 65), respectively: • Fatal AEs: 12% vs 17% (most commonly infections and infestations with MMB and anemia with danazol). • Serious AEs: 35% vs 40%. Most commonly infections: 15% vs 17%. • Discontinuation due to AE: 18% vs 23%. • Drug interruption or dose reduction due to AE: 34% vs 29%. • Grade ≥ 3 AE (%): Anemia 61% vs 75%; thrombocytopenia 28% vs 26%; neutropenia 12% vs 9%; acute kidney injury 3% vs 9%; pneumonia 2% vs 9%. • Mean PLT counts remained stable over time on MMB and increased on danazol during the RCT and were similar on both treatments during the OL extension. Of 18 MMB patients and 13 danazol patients with baseline PLT count < 50×10^9/L, 9 (50%) and 6 (46%), respectively, received PLT transfusions in the RCT. • PN (all grade 1–2) was reported in 5 (4%) of 130 MMB patients vs 1 (2%) of 65 danazol patients.

		SIMPLIFY-1, MMB (N = 214) vs RUX (N = 216), respectively: • Fatal AEs: 3.3% vs 3.2% • Serious AEs: 22.9% vs 18.1% • Discontinuations due to AEs: 13.1% vs 5.6% (none due to PN) • Grade 3–4 Anemia: 6.1% vs 22.7% • Leukemic transformation: 0.5% vs 0.9% • PN: 10.3% (grade 1–3) vs 4.6%
		SIMPLIFY-2, MMB (N = 104) vs BAT (N = 52), respectively: • Fatal AEs: 6% vs 8%. • Serious AEs: 35% vs 23% • Discontinuations due to AEs: 21% vs 2%, including 3% due to PN with MMB • Grade 3–4 Anemia: 13.5% vs 17.3% • Leukemic transformation: 3% vs 2% • PN: 11% (grade 1–3) vs 0%
	AEs of Interest	*PN*: Phase 1 or 2 studies showed grade 1–2 (no grade 3–4) PN in 50 (30.1%) of 166 MF patients[11] and grade 1–3 mostly sensory PN in 27 (44.3%) of 61 MF patients.[12] PN may be potentially irreversible. *First-dose Effect*: Dizziness, nausea, hypotension, headache, flushing.**Error! Bookmark not defined.**

INDIRECT COMPARISONS

Network Meta-analysis

Results at Week 24, RCTs Evaluating JAKIs in Patients With PMF or SMF[13]

OUTCOME	POPULATION	K	N	I^2	MMB BETTER / SAFER THAN	MMB SIMILAR TO	MMB WORSE THAN
SVR-35 Response	1st-line JAKI	5	1576	NS	Pacritinib	Fedratinib Ruxolitinib	—
Anemia Grade 3–4 (Hg < 8 g/dL)	Mixed 1st- or 2nd-line JAKI	7	1953	54%	Ruxolitinib Fedratinib Pacritinib	—	—
Thrombocytopenia Grade 3–4 (PLT < 50 × 10^9/L)	Mixed 1st- or 2nd-line JAKI	7	1953	33%	—	Ruxolitinib Pacritinib	Fedratinib

	DRUG	VANF	CFU	FDA	NCCN MPN GUIDELINES[5]
PLACE IN THERAPY	**Momelotinib**	TBD	TBD	Treatment for INT or high-risk PMF or SMF with anemia	1st line option (category 2A) or 2nd line (after another JAKI; category 2A) for higher risk MF with PLT ≥ 50 × 10^9/L, not alloHCT candidate. Other recommended regimen (category 2B) for higher risk MF with PLT < 50 × 10^9/L, not alloHCT candidate. 1st line treatment useful in certain circumstances (category 2B) or 2nd line alternative after initial treatment† (category 2B) for symptomatic lower risk MF. One of preferred regimens‡ (category 2A) for MF-associated anemia with serum EPO ≥ 500 mU/mL.
	Ruxolitinib	PA-F	1st line for INT or high-risk PMF or SMF	Treatment for INT or high-risk PMF or SMF	1st line (category 1) or 2nd line (after another JAKI; category 2A) for higher risk MF with PLT ≥ 50 × 10^9/L, not alloHCT candidate. 1st line for symptomatic lower risk MF, useful in certain circumstances.
	Fedratinib	NonF	2nd line after ruxolitinib for INT-2 or high-risk PMF or SMF	Treatment for INT-2 or high-risk PMF or SMF	1st line (category 1) or 2nd line (after another JAKI; category 2A) for higher risk MF with PLT ≥ 50 × 10^9/L, not alloHCT candidate.
	Pacritinib*	PA-F	1st line for higher risk PMF or SMF with PLT < 50 × 10^9/L, not alloHCT candidate 2nd line after one JAKI for higher risk PMF or SMF with PLT ≥ 50 × 10^9/L, currently not alloHCT candidate. 2nd line after initial therapy for symptomatic lower risk PMF or SMF with PLT < 50 × 10^9/L.	Treatment for INT or high-risk PMF or SMF with PLT below 50 × 10^9/L. *Approved under accelerated approval* based on spleen volume reduction. Continued approval may be contingent upon verification of clinical benefit in a confirmatory trial.	1st line (preferred, category 1) for higher risk MF with PLT < 50 × 10^9/L, not alloHCT candidate. 1st line (category 2B) or 2nd line (after another JAKI; category 2B) for higher risk MF with PLT ≥ 50 × 10^9/L, not alloHCT candidate. Consider for 2nd-line therapy after initial treatment† for symptomatic lower risk MF with PLT < 50 × 10^9/L.

* Pacritinib has been shown to be more potent than momelotinib in ACVR1 inhibition and to improve transfusion independence (**TI**) relative to best available therapy (**BAT**)[14]; however, it is not FDA approved for MF with anemia.

† Initial therapy may be ruxolitinib, peginterferon alfa-2a, hydroxyurea (if cytoreduction is indicated) or momelotinib (category 2B).

‡ The other preferred regimen for MF-associated anemia with EPO ≥ 500 mU/mL is a clinical trial. Useful in certain circumstances: danazol or lenalidomide ± prednisone or thalidomide ± prednisone or luspatercept (category 3).

VHA PLACE IN THERAPY		
	Potential Use in VHA[5,15]	1. Treatment of alloHCT-ineligible adults with INT- or high-risk primary or secondary MF and one of the following: a. MF-related anemia (Hg < 10 g/dL), symptomatic splenomegaly or constitutional symptoms, and the primary reason for treatment is anemia. b. Myelofibrosis-related anemia (hemoglobin < 10 g/dL)[2] with neither symptomatic splenomegaly nor constitutional symptoms, and had a prior trial of ONE **non-Janus kinase inhibitor (non-JAKI) treatment for myelofibrosis-related anemia.**[3] c. Splenomegaly or symptoms, primary reason for treatment is platelet count < 50 × 10^9/L, and had a prior trial of **pacritinib** unless medically inadvisable. d. Splenomegaly or symptoms, platelet count ≥ 50 × 10^9/L, and had a prior trial of **ruxolitinib** unless medically inadvisable (e.g., because of pre-existing severe anemia [hemoglobin < 8 g/dL] or thrombocytopenia with platelets < 50 × 10^9/L). e. Persistent grade 3 anemia (hemoglobin < 8.0 g/dL) despite ruxolitinib dosage reductions.

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