Pacritinib (VONJO) in Myelofibrosis
National Drug Monograph
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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 / Mechanism of Action

- Pacritinib is a Janus kinase inhibitor (JAKI) with selectivity for the JAK2 receptor and activity against FMS-like tyrosine kinase 3 (FLT3), IRAK1 and CSF1R cellular kinases.[1] It lacks JAK1 activity at clinically relevant concentrations.
- Pacritinib is the third JAKI approved for myelofibrosis (after ruxolitinib and fedratinib), and the only one suitable to use in patients with platelet (PLT) counts < 50×10^9/L at baseline.

Indication Under Review in This Document

- Treatment of adults with intermediate- or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis with a PLT count below 50×10^9/L.
- This indication is approved under **accelerated approval** based on spleen volume reduction. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Pretreatment Evaluations and Tests

- Complete blood count (CBC)
- Coagulation tests
- Electrocardiogram (ECG)
- Consider potassium level especially in patients with a history of low blood potassium.
- Active serious infections: delay initiation of pacritinib until infection has resolved.
- Another kinase inhibitor: taper or discontinue.

Dosage Regimen and Dosage Form Under Review

- Recommended Dosage Regimen: 200 mg orally twice daily with or without food.
- Capsules: 100 mg

Dosage Modifications

Dosage modifications are required for the following conditions. Refer to the US Prescribing Information for details.

- **Planned Surgical or Other Invasive Procedures**: Hold doses for 7 days prior to procedure. Restart after hemostasis is regained.

- **Diarrhea, Grade 3 or 4**
- **Thrombocytopenia**, clinically worsening and lasting more than 7 days
- **Hemorrhage**, moderate, severe or life-threatening
- **QTc Prolongation** of > 500 msec or by > 60 msec from baseline

Efficacy Considerations

- Two phase 3 randomized clinical trials (RCTs), PERSIST-1 and PERSIST-2, compared pacritinib with best available therapy (BAT) in the treatment of patients with intermediate- or high-risk primary or secondary myelofibrosis with thrombocytopenia.[2,3] These active-controlled trials are the focus of this monograph review.
- A phase 2, dose-finding, ruxolitinib-controlled PAC203 RCT provided supportive evidence of efficacy in patients who had myelofibrosis and severe thrombocytopenia with inadequate response or intolerance to ruxolitinib.[4]
- Another phase 2 study showed that pacritinib was efficacious in the treatment of patients with MF who had an inadequate response to standard therapies or were newly diagnosed with intermediate- or high-risk MF.[5] Pacritinib caused minimal myelosuppression and was well tolerated in patients with anemia or thrombocytopenia at baseline.
- An ongoing trial (PACIFICA) is further evaluating the clinical benefits of pacritinib.

Phase 3 Randomized Clinical Trials

- Table 1 summarizes the methods of the phase 3 RCTs.

Table 1 Methods of Phase 3 RCTs

Topic	PERSIST-1	PERSIST-2
Study Design	MN OL AC RCT in US, EU, RU, AU, and NZ Patients with disease progression at W24 were allowed to cross over to pacritinib. Stratified randomization by risk category, PLT count, and region	OL AC RCT with ITT analyses in US, CA, EU, other Stratified randomization by geographic region, risk category, and rebound PLT count (defined as recovery of PLT count between informed consent and randomization, which suggests drug-induced thrombocytopenia).
	The FDA placed a full clinical hold on pacritinib because of bleeding, cardiovascular, and fatal events in interim results for PERSIST-1, resulting in incomplete data collection in both trials. The FDA removed the clinical hold after almost 1 year after reviewing final data from both trials and a planned dose comparison trial protocol.	
Major Entry Criteria	DIPSS-based INT-1, INT-2, or high-risk primary or secondary (PPV or PET) MF regardless of baseline cytopenias Palpable splenomegaly (≥ 5 cm below the left costal margin) *Exclusions*: Prior or planned HSCT; prior JAK2I; inflammatory or chronic functional bowel disorders; symptomatic and uncontrolled CV disease; significant cardiac conditions within prior 6 months; known HIV seropositivity; known active HAV, HBV, or HCV	DIPSS-based INT-1, INT-2, or high-risk primary or secondary (PPV or PET) MF with PLT ≤ 100×10^9/L Palpable splenomegaly (≥ 5 cm below the left costal margin) *Exclusions*: Active bleeding requiring hospitalization; significant cardiac abnormalities

Topic	PERSIST-1		PERSIST-2	
Interventions	• Pacritinib 400 mg PO once daily • BAT (excluding ruxolitinib and other JAK2Is; most common BAT was hydroxyurea 57%; watchful waiting 25%) BAT patients could cross over to pacritinib upon disease progression or without progression starting at W24. Of 106 BAT patients, 90 (85%) crossed over. Treatment was to be continued until disease progression (≥ 25% increase in spleen volume, splenic irradiation, splenectomy, or leukemic transformation) or unacceptable toxicity		• Pacritinib 400 mg PO once daily • Pacritinib 200 mg PO twice daily • BAT (including ruxolitinib 45%, hydroxyurea 19%, and prednisone or prednisolone 13%; only watchful waiting 19%) BAT patients with splenomegaly progression and those with or without progression at W24 were allowed to cross over to pacritinib. Treatment was to be continued for 48 weeks or until disease progression, unacceptable toxicity, or loss of benefit.	
Primary and Other Key Efficacy Measures	Primary: Week-24 SVR-35 TSS-50 (using MPN-SAF TSS and/or MPN-SAF TSS 2.0) Overall Survival and leukemia-free survival RBC transfusion independence PGIC (used to assess QOL)		Co-primary: Week-24 SVR-35 response and TSS–50 (using MPN-SAF TSS 2.0) Overall Survival (from randomization to clinical hold) RBC transfusion requirement Thrombocytopenia PGIC of very much improved or much improved	
Baseline Patient Characteristics	Median age: 66 y Male: 57% ECOG 0–1 / 2–3: 88% / 12% Primary MF: 60% Secondary MF: 40% JAK2V617 positive: 78%	PLT < 50 × 10^9/L: 16% Hg < 10 g/dL: 41% RBC transfusion dependent: 16%	Mean Age: 64 y Male: 55% ECOG 0–1 / 2–3: 80% / 18% Primary MF: 65% Secondary MF: 34% JAK2V617F positive: 77%	PLT < 50 × 10^9/L: 46% Hg < 10 g/dL: 59% RBC transfusion dependent: 20% No prior tx: 25% Prior ruxolitinib: 48%
Patient Disposition	Of 357 patients screened, 327 (92%) were eligible. For pacritinib and BAT, respectively: • Median duration of therapy: 15.6 and 5.9 months. Total patient-years of exposure were 280 and 60. • Median follow-up: 23 and 24 months • Discontinuations due to the clinical hold: 26% (84/327) overall		For pacritinib once daily, twice daily, and BAT, respectively: • Median duration of therapy: 23, 25, and 21 weeks. • Discontinuations due to the clinical hold: 60% (62/104), 71% (75/106), and 28% (27/98)	
Limitations	Final data to the end of treatment due to clinical hold included patients who crossed over from BAT to pacritinib.		The premature discontinuation of the trial because of the FDA clinical hold reduced the effective sample size and reduced follow-up time for time-to-event measures such as overall survival and for safety. Crossovers from BAT to pacritinib confounded time-to-event analyses.	

DIPSS, Dynamic International Prognostic Scoring System; **INT**, Intermediate; **PET**, Post-essential thrombocythemia; **PPV**, Post-polycythemia vera; **SVR-3**5, Spleen volume reduction of ≥ 35%; **TSS-50**, ≥ 50% reduction / improvement in total symptom score as measured on the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score [MPN-SAF TSS 2.0]

Results

- Efficacy data are summarized in Table 2 to Table 4.

Table 2 Selected ITT efficacy results from PERSIST-1

Outcome	PAC400QD	BAT	Relative Risk (95% CI)	Difference (95% CI)
SVR-35 at W24, n/N (%)	**42/220 (19)**	5/107 (5)	4.1 (1.66, 10.03)	14 (6.5, 20.3)
TSS-50 at W24, n/N (%)	19/100 (19)	5/48 (10)	1.8 (0.72, 4.59)	9 (–4.3, 19.5)
TSS-50 at W48, n/N (%)	**15/100 (15)**	0/48 (0)	15.0 (0.92, 246.20)	15 (5.6, 23.3)
Overall Survival† at W24, n/N (%)	189/199 (95)	98/101 (97)	1.0 (0.34, 1.03)	2 (–3.9, 6.4)

Sources: 2
Bold blue text indicates statistically significant difference vs BAT ($p < 0.05$).
SVR-35, ≥ 35% improvement in spleen volume reduction; **TSS-50**, ≥ 50% improvement in total symptom score
† Overall survival from randomization to clinical hold. Overall survival was an exploratory end point in PERSIST-1.

Table 3 Selected ITT efficacy results in PERSIST-2 patients with Week-24 data (≥ 22 weeks before clinical hold)

Outcome	PAC400QD	PAC200BID	Pooled PAC	BAT
SVR-35 at W24, n/N (%)	**11/75 (15)**	**16/74 (22)**	**27/149 (18)**	2/72 (3)
RR (95% CI)	5.3 (1.21, 23.00)	7.8 (1.86, 32.65)	6.5 (1.60, 26.68)	Ref
Diff (95% CI)	12 (2.6, 22.0)	19 (8.5, 29.9)	15 (6.3, 22.3)	Ref
TSS-50 at W24, n/N (%)	13/75 (17)	**24/74 (32)**	37/149 (25)	10/72 (14)
RR (95% CI)	1.2 (0.58, 2.66)	2.3 (1.20, 4.53)	1.8 (0.94, 3.39)	Ref
Diff (95% CI)	3 (–9.0, 14.8)	18 (4.3, 30.9)	11 (–0.7, 20.7)	Ref
Overall Survival,† n/N (%)	15/104 (14)	10/107 (9)	25/211 (12)	14/100 (14)
RR (95% CI)	1.0 (0.52, 2.02)	0.7 (0.31, 1.43)	0.8 (0.46, 1.56)	Ref
Diff (95% CI)	0 (–9.7, 9.8)	5 (–3.8, 14.1)	2 (–5.5, 11.0)	Ref

Sources: 3
See footnotes for Table 2.

Table 4 Absolute Effects for Achieving Outcomes SVR-35 Response

Outcome Measure	Treatment Comparison			Q
PERSIST-1	**PAC400QD vs BAT**			
AAE, per 1000 pts (95% CI)	145 (31 to 422) more			VL[αβ]
NNT (95% CI)	7 (5, 16)			
PERSIST-2	**PAC400QD vs BAT**	**PAC200BID vs BAT**	**Pooled PAC vs BAT**	
AAE, per 1000 pts (95% CI)	119 (6, 610) more	189 (24, 879) more	153 (17 to 713) more	VL[αβ]
NNT (95% CI)	9 (5, 35)	6 (4, 12)	7 (5, 17)	

AAE, Anticipated absolute effect for achieving the outcome; **NNT**, Number needed to treat for one additional patient to benefit; **Q**, GRADE quality of evidence (H = High, M = Moderate, L = Low, VL = Very low)
[α] Downgraded for risk of bias (no blinding or allocation concealment; reduction in sample size and follow-up time because of FDA-imposed clinical hold).
[β] Downgraded for imprecision (wide CIs)

PERSIST-1 Results

- **SVR-35**. Pacritinib once daily (400 mg QD) was significantly better than BAT in achieving SVR-35 (Table 2). The superiority of pacritinib 400 mg QD was maintained irrespective of baseline spleen volume, type of MF (primary or secondary), or baseline platelet count stratum (< 100×10^9/L or < 50×10^9/L). The median duration of SVR-35 was 34.3 weeks with pacritinib 400 mg QD and was not estimable with BAT. SVR-35 rates remained stable from Week 24 to Week 108.

  - Of 90 patients who crossed over from BAT to pacritinib 400 mg QD, 11 patients (12%) achieved SVR-35 after Week 24.

- **TSS-50 using MPN-SAF TSS 2.0**. The original protocol required the use of the MPN-SAF TSS to assess TSS-50. An FDA-requested modification resulted in switching to the MPN-SAF TSS 2.0 midway through the study. Based on the data from the subgroup of patients assessed using the MPN-SAF TSS 2.0 version, there was no significant treatment difference in rates of achieving TSS-50 from baseline to Week 24, whereas a significant difference was observed from baseline to Week 48: 15% (15/100) vs 0% (0/48) with pacritinib 400 mg QD vs BAT, respectively.
  - No significant treatment differences were seen by PLT count subgroups, but the numbers of patients and events were small. Results were consistent between the two versions of the MPN-SAF TSS.
  - Using six symptoms common to both MPN-SAF TSS versions (TSS-6-50 response; fatigue / tiredness, early satiety, abdominal discomfort, night sweats, pruritus, and bone pain), a post hoc combined analysis including all patients showed that pacritinib 400 mg QD was significantly better than BAT in achieving TSS-6-50 at Week 24: 25% (54/220) vs 7% (7/107), respectively.
- **Overall Survival**. No significant treatment difference in the probability of survival to Week 24 was observed. After Week 24, BAT showed a nonsignificant greater improvement in survival relative to pacritinib 400 mg QD. These results were confounded by the crossover of 90 BAT patients (84%) to pacritinib 400 mg QD, mostly at Week 24. Overall, 35% (76/220) vs 27% (29/107) of patients had died in the pacritinib 400 mg QD and BAT groups, respectively.
- **Transfusion Requirements**. Among the subgroup of RBC-transfusion-dependent patients at baseline, a significantly higher percentage of patients became transfusion independent with pacritinib 400 mg QD than with BAT: 25% (9/36) vs 0% (0/16), respectively.
- **Patient Global Assessment of Change** (PGIC; range, 1/very much improved to 7/very much worse). The PGIC was used as a measure of quality of life in PERSIST-1. Pacritinib 400 mg QD was significantly better than BAT in achieving PGIC of *very much improved* or *much improved* (51% [73/144] vs 9% [6/68], respectively) at Week 24 (RR 5.7 [95% CI 2.6, 12.5]; NNT 3 [2, 4]). The majority of BAT patients (59%) vs 12% of pacritinib 400 mg QD patients reported *no change*.
- **Allele Burden**. Pacritinib 400 mg QD showed a nonsignificantly greater reduction in median JAK2V617F allele burden than BAT at Week 24: –15.8% vs –7.9%. The median greatest reduction from baseline to any time point was –31.6% on pacritinib 400 mg QD vs –10.4 with BAT.

PERSIST-2

- **SVR-35 and TSS-50**. Only pacritinib 200 mg BID met both co-primary outcome measures (Table 2). In subgroup analyses by patients with prior ruxolitinib, similar percentages of patients achieved SVR-35 and TSS-50 among the three treatment groups. In the subgroup analyses by baseline PLT count < 50×10^9/L, similar percentages of patients achieved SVR-35 and TSS-50 among the treatment groups.
- **Overall Survival**. Kaplan-Meier estimates of overall survival showed no significant differences between each pacritinib group and the BAT group, although a nonsignificant greater improvement in the probability of overall survival was seen with pacritinib 200 mg twice daily (BID) from Week 24 to Week 84. Hazard ratios (95% CI) were 1.18 (0.57, 2.44) and 0.68 (0.30, 1.53) for pacritinib 400 mg QD and pacritinib 200 mg BID, respectively, relative to BAT.
- **Transfusion Requirements.** Transfusion independence occurred in 2 pacritinib patients (1 on 400 mg QD and 1 on 200 mg BID). Among patients who received ≥ 1 unit of RBCs during the trial, pacritinib 200 mg BID and 400 mg QD each had a lower median number of RBC transfusion units per month than BAT at Week 12 (0.74 and 1.64 vs 2.25, respectively) and Week 24 (0.67 and 1.00 vs 1.33, respectively). Among patients with baseline hemoglobin (Hg) < 10 g/dL, pacritinib 200 mg BID had the highest percentage of

patients with clinical improvement in Hg relative to pacritinib 400 mg QD and BAT: 25% (11/44), 13% (6/45), and 12% (5/41), respectively. Clinical improvement in Hg was defined as ≥ 2.0 g/dL or RBC transfusion independence for ≥ 8 weeks prior.

- **Worsening Thrombocytopenia**. Although pacritinib 200 mg BID was associated with a transient decrease in the median percent change in platelets at Week 24, no trends for increasing thrombocytopenia were noted with pacritinib or BAT.
- **Patient Global Impression Assessment**. Pacritinib 400 mg QD and 200 mg BID were numerically better than BAT in the percentage of patients achieving *very much improved* or *much improved*: 36% (16/45) and 57% (26/46 (pooled pacritinib 47% [42/91]) vs 28% (11/40), respectively (RR for pooled pacritinib vs BAT, 1.7 [0.97, 2.91]; NNT 6 [3, 146]). Only the pacritinib groups (400 mg QD and 200 mg BID) achieved *very much improved*, and only BAT patients endorsed *much worse*.

Onset of Treatment Benefit and Duration of an Adequate Therapeutic Trial

- The onset of treatment benefit and duration of an adequate therapeutic trial could be estimated only from PERSIST-1 results and they depended on the outcome measure.
    - Based on the mean percentage change in spleen volume, the onset of improved benefit with pacritinib vs BAT seemed to occur at 12 weeks and duration of an adequate therapeutic trial seemed to be 12 weeks.
    - Based on TSS-50 response rates, the onset of improved benefit occurred at about 4 weeks and the duration of an adequate therapeutic trial seemed to be 32 weeks.
- Statistical analyses were not reported in the graphs for spleen volume and TSS-50 response rates over time in PERSIST-1, therefore, the onset of benefit is based only on the apparent separation in results between treatments.

Durability of Response

- SVR-35 response was maintained through Week 108.

Safety Considerations

Mortality and Other Safety Signals Leading to Clinical Hold

- The FDA's review of PERSIST-1 safety data was notable for increased mortality with pacritinib 400 mg QD vs BAT: 26% (58/220) vs 6% (6/106), respectively).[6] The group that crossed over from BAT to pacritinib also showed a higher mortality rate (19% [17/90]) than in the BAT group.[6]
    - In time-to-event analyses of overall survival, increased mortality with pacritinib was observed with a hazard ratio (HR) of 1.29 (95% CI 0.81, 2.13).[6]
    - Excess risks of serious bleeding events (7% vs 1%) and heart failure (7% vs 2%) were also seen with pacritinib vs BAT, respectively. In patients who had crossed over from BAT to pacritinib, similar results (higher rates in the BAT-to-pacritinib group than in the BAT group) were seen for serious bleeding (15%) and cardiac failure (5%).[6]
- A mortality signal was also observed in PERSIST-2: pacritinib 12% vs BAT 7%.[6] In Kaplan-Meier analyses of overall survival, death rates were 12.0% (25/209) vs 10.2% (10/98) for pacritinib vs BAT, respectively (HR 1.29; 0.63, 2.81).[6]
    - Serious and fatal adverse events of intracranial bleeding, cardiac failure, and cardiac arrest were also reported in PERSIST-2.
- Based on an Independent Data Safety Monitoring Committee's recommendations, both trials were placed on clinical hold and permanently closed in February 2016, recognizing the difficulties in interpreting the mortality rates with statistically nonsignificant differences by 95% confidence intervals for overall survival

hazard ratios. The safety issues were subsequently resolved based on safety data from PERSIST-2, which showed numerically lower mortality rates with the eventually approved dose (200 mg BID) than the 400 mg QD dose and BAT: 4.7% vs 10.6% and 12.2%, respectively.[6] A similar pattern was seen in subgroup analyses by platelet counts ($< 50 \times 10^9$/L and $\geq 50 \times 10^9$/L). The small number of events driving the difference in mortality rates (fewer than 4 events) limited conclusions.

- No study comparing the pharmacokinetics of the two dosages (200 mg BID vs 400 mg QD) was found.

Safety Profile from US Prescribing Information

- **Boxed Warnings**: None.
- **Contraindications**: Co-use of strong CYP3A4 inhibitors or inducers.
- **Other Warnings / Precautions**:
  - Hemorrhage (avoid if there is active bleeding and hold pacritinib for 7 days prior to any planned surgical or invasive procedures)
  - Diarrhea
  - Thrombocytopenia
  - Prolonged QT interval (avoid if baseline QTc of > 480 msec; avoid drugs with significant QTc-prolonging effects; correct hypokalemia)
  - Major adverse cardiac events (MACE)
  - Thrombosis
  - Secondary malignancies
  - Risk of infection
  - Moderate CYP3A4 inhibitors or inducers (avoid co-use)

  PBM Note: A mortality signal has not been observed in patients treated with ruxolitinib and fedratinib for myeloproliferative disorders. Therefore, pacritinib carries no warning about the increased mortality that has been associated with JAKIs in rheumatoid arthritis and ulcerative colitis populations.[6]

- **Avoid Use**:
  - Active bleeding
  - Baseline QTc > 480 msec
  - Moderate CYP3A4 inhibitors or inducers
  - Sensitive P-gp, BCRP, or OCT1 substrates
  - Moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment.
  - Renal impairment with eGFR < 30 mL/min.
  - Lactation: Avoid breastfeeding during therapy and for 2 weeks after discontinuation.
- **Most Common Adverse Events (≥ 20%):** Diarrhea, thrombocytopenia, nausea, anemia, and peripheral edema.

- The gastrointestinal adverse events were typically low grade, tolerated, and less common with the pacritinib divided-dose regimen (200 mg BID) than the single daily dose regimen (400 mg QD).
- Diarrhea usually resolved in 1 to 2 weeks and was manageable with standard antidiarrheal agents.

Safety Results from Clinical Trials

- In PERSIST-1, pacritinib and BAT were not significantly different in terms of PLT count changes from baseline to Week 24.[2]
- In the subgroups of patients with baseline PLT < 50 × 10^9/L in the pacritinib 400 mg QD group, the PLT count increased over time to Week 24 in PERSIST-1 and to Week 36 in PERSIST-2.[2,3] PLT counts in the pacritinib 200 mg BID group in PERSIST-2 remained relatively stable and similar to those seen in the BAT group.[3]
- Table 5 and Table 6 summarize safety data from the phase 3 clinical trials.

Table 5 Selected Adverse Events in PERSIST-1

Outcome	PAC400QD N = 220	BAT N = 106
Death, n (%)	76 (34.5)	29 (27.4)
SAEs, n/N (%)	65 (29.5)	23 (21.7)
Grade 3 / 4 AEs, n (%)	107 (48.6)	42 (39.6)
DAEs, n (%)	22 (10.0)	3 (2.8)
Deaths due to AEs, n (%)	27 (12.3)	14 (13.0)

Source: 2
AE, Adverse event; **BAT**, Best available therapy; **DAE**, Discontinuation due to adverse event; **PAC**, Pacritinib; **SAE**, Serious adverse event

Table 6 Selected Adverse Events in PERSIST-2

Outcome	PAC400QD N = 104	PAC200BID N = 106	BAT N = 98
Death, n (%)	14 (14)	6 (6)	9 (9)
SAEs in ≥ 5%, n (%)	48 (46)	50 (47)	30 (31)
Anemia, n (%)	5 (5)	8 (8)	3 (3)
Thrombocytopenia, n (%)	2 (2)	6 (6)	2 (2)
Pneumonia, n (%)	5 (5)	6 (6)	4 (4)
Renal failure, acute, n (%)	5 (5)	2 (2)	2 (2)
Congestive heart failure, n (%)	1 (1)	4 (4)	2 (2)
Cardiac arrest, n (%)	2 (2)	0 (0)	0 (0)
Subdural hematoma, n (%)	2 (2)	0 (0)	0 (0)
Grade 3 / 4 AEs, n (%)	79 (76)	74 (70)	48 (49)
DAEs, n (%)	20 (19)	16 (15)	12 (12)

Source: 3
Adverse events leading to death were not mentioned.
Abbreviations: See footnote for Table 5.

- **Deaths and Serious Adverse Events**: In PERSIST-1 and PERSIST-2, rates of death and rates of serious adverse events were numerically higher on pacritinib 400 mg QD than BAT. The approved dose of pacritinib (200 mg BID) showed numerically lower rates of death but numerically higher rates of serious

adverse events relative to BAT. The most common serious adverse events were anemia, cardiac failure, pyrexia, and pneumonia with pacritinib 400 mg QD vs anemia, sepsis, and dyspnea with BAT in PERSIST-1, and anemia, thrombocytopenia, pneumonia, and acute renal failure with pacritinib 400 mg QD or 200 mg BID vs pneumonia, anemia, and thrombocytopenia, acute renal failure, and congestive heart failure with BAT in PERSIST-2.

- **Discontinuations Due to Adverse Events**: In PERSIST-1, 23.2% (51/220) on pacritinib 400 mg QD and 2.8% (3/106) on BAT discontinued therapy because of adverse events. More patients on pacritinib 400 mg QD than those on BAT had discontinued therapy by Week 24: 12.0% vs 2.8%, respectively. In PERSIST-2, rates of discontinuations due to adverse events were numerically higher in each pacritinib group than in the BAT group. The most common reason for discontinuations due to adverse events was thrombocytopenia in the pacritinib 400 mg QD group and anemia with pacritinib 200 mg BID.
- **Deaths Due to Adverse Events**. The rates of adverse events leading to death were reported in PERSIST-1 and not in PERSIST-2. In PERSIST-1 the overall rates of deaths due to adverse events were 12% and 13% in the pacritinib 400 mg QD and BAT groups (Table 5). Deaths due to adverse events occurred in 4% of patients on pacritinib 400 mg QD and 3% on BAT in the first 24 weeks. After Week 24, the rates were 8% on pacritinib 400 mg QD and 10% in the BAT group after crossover to pacritinib 400 mg QD. The most common adverse events leading to death in the pacritinib group were disease progression and pneumonia.
- **Cardiac Events**: In PERSIST-1 and PERSIST-2, the rates of cardiac events were similar between / among the treatment groups.
- **Bleeding Events**: In PERSIST-1, pacritinib 400 mg QD and BAT were similar in the rates of bleeding events, with severe (grade 3–4) bleeding events occurring in small numbers of patients and at similar rates in the two treatment groups. In PERSIST-2, the rates of bleeding events, most commonly epistaxis, were similar among the three treatment groups. Grade 3 or 4 bleeding events were reported in 7% (7/104), 14% (15/106), vs 7% (7/98) of patients in the pacritinib 400 mg QD, pacritinib 200 mg BID, vs BAT groups, respectively.
- **Leukemic Transformation**. There was no significant difference between pacritinib 400 mg QD and BAT in the rate of leukemia transformation in PERSIST-1. Data on leukemic transformation were not reported in PERSIST-2.
- **Safety Subgroup Analyses**:
    - In PERSIST-1 subgroup analyses by baseline PLT count, the selected adverse events that occurred numerically more frequently in the subgroup with PLT $< 50 \times 10^9$/L (n = 35) than subgroups with PLT $< 100 \times 10^9$/L (n = 72) and/or PLT $\geq 100 \times 10^9$/L (n = 148), respectively, were grade 3 or 4 AEs (82.9%, 84.7%, and 64.9%); AEs leading to discontinuation (40.0%, 34.7%, and 16.9%), and AEs leading to death (25.7%, 19.4% and 8.8%).
    - In PERSIST-2, subgroup analyses by baseline PLT $< 50 \times 10^9$/L vs $\geq 50 \times 10^9$/L showed that the rates of hematologic adverse events were similar between these two subgroups in the pacritinib 400 mg QD and pacritinib 200 mg BID groups, while they were higher in the subgroup with PLT $< 50 \times 10^9$/L vs PLT $\geq 50 \times 10^9$/L with BAT. Rates of grade 3 or 4 bleeding events were more common in the subgroup with baseline PLT $< 50 \times 10^9$/L vs PLT $\geq 50 \times 10^9$/L with pacritinib 400 mg QD (12% vs 2%, respectively) and BAT (12% vs 4%, respectively), whereas the rates were similar between the two subgroups by PLT count with pacritinib 200 mg BID.

Drug Interactions

Affect Pacritinib

- **Strong and moderate CYP3A4 inhibitors**. Co-use with strong CYP3A4 inhibitors (e.g., clarithromycin) is contraindicated. Use with moderate CYP3A4 inhibitors should be avoided.

- **Strong and moderate CYP3A4 inducers**. Co-use with strong CYP3Ar inducers (e.g., rifampin) is contraindicated. Use with moderate CYP3A4 inducers should be avoided.

Affect Other Drugs

- **CYP1A2 or CYP3A4 substrates**. Co-use of pacritinib with sensitive substrates of CYP1A2 or CYP3A4 should be avoided because of a risk of increased plasma concentrations of the substrates.
- **P-gp, BCRP, or OCT1 Substrates**. Co-use of pacritinib with sensitive P-gp, BCRP, or OCT1 substrates should be avoided because of a risk of increased plasma concentrations of the substrates.

Evidence Gaps

- Hospitalization or readmission
- Health-related Quality of Life
- Functional ability / Disability
- Patient Satisfaction

Network Meta-analyses

- A single network meta-analysis included the two phase 3 (PERSIST-1 and PERSIST-2) pacritinib trials. The analysis included a total of 7 BAT- or placebo-controlled studies (N = 1953) evaluating ruxolitinib, momelotinib (not available in the US and excluded from this monograph review), fedratinib (K = 1, N = 289), or pacritinib (K = 2; N = 638 randomized, 548 analyzed). Although there was high risk of bias related to allocation concealment, the overall risk of bias of the included studies was assessed as low.
- Comparisons between ruxolitinib and the other active treatments (JAKI or BAT) are shown in Table 7. The authors reported findings of between-treatment comparisons from Bayesian network analyses but data were not presented.

Table 7 Summary of Meta-analysis Comparing JAKIs with Ruxolitinib

Comparator	Indirect Estimate, OR (95% CrI) vs Ruxolitinib
SVR-35 at Week 24	
Pacritinib	**0.11 (0, 0.79)**
Fedratinib	NR (NSD)
BAT	**0.6 (0.39, 0.88)**
Grade 3 / 4 Anemia, Week 24	
Pacritinib	0.82 (0.48, 1.41)
Fedratinib	0.85 (0.51, 1.47)
BAT	**0.6 (0.39, 0.88)**
Grade 3 / 4 Thrombocytopenia, Week 24	
Pacritinib	1.31 (0.51, 3.29)
Fedratinib	**0.21 (0.03, 0.92)**
BAT	0.9 (0.36, 2.01)

Bold blue text indicates statistically significant difference

- Analyses of the 7 studies of JAKIs as first- or second-line therapy for SVR-35 response resulted in moderate heterogeneity across trials (I^2 = 67.9%; 95% 0.0, 90.7).
- In a Bayesian network meta-analysis of studies evaluating only first-line JAKI therapy, fedratinib and ruxolitinib were shown to be significantly better than placebo in achieving SVR-35 response.
- In terms of SVR-35 response, the following comparative results were shown:

  - No significant differences between fedratinib and either ruxolitinib or pacritinib.
  - Ruxolitinib was significantly better than pacritinib.
- Unexpectedly, pacritinib did not differ significantly from ruxolitinib in risk of grade 3 or 4 thrombocytopenia at Week 24, whereas fedratinib showed a lower risk than ruxolitinib (OR 0.21; 95% CrI 0.03, 0.92).

Other Considerations

- **Pregnancy**. No human data. Animal data suggest risk of maternal toxicity, post-implantation loss, reduced fetal body weights, and external malformations.[1] Advise pregnant women of potential risk to the fetus; weigh risks and benefits.
- **Lactation**. No human or animal data. There is potential for serious adverse events in the breastfed child.[1] Advise breastfeeding patients that breastfeeding is not recommended during pacritinib therapy and for 2 weeks after the last dose.
- **Infertility**. Based on animal data, pacritinib may impair human male fertility.[1]

Benefit-Risk Assessment for Pacritinib vs BAT

Table 8 Benefit-Risk Assessment for Outcomes in Clinically Significant Areas

Parameter	Overall Survival	PGIC†
Effect size	NSD	Inconsistent; NSD to moderate
Potential harms	Include diarrhea, thrombocytopenia, bleeding, JAKI-class AEs (malignancy, MACE, thrombosis)	
Net clinical benefit	Pacritinib showed a consistent benefit in terms of spleen volume reduction but has not shown a significant benefit in overall survival over best available treatment. Improvements in patient-reported global assessment were inconsistent, as were measures of patient symptoms. Adverse events may be potentially serious but manageable in most cases. Data quantity and quality were compromised by the FDA-imposed clinical hold on the trials. Considering that there are no other drugs approved for use in myelofibrosis patients with severe thrombocytopenia (PLT < 50 × 10^9/L) and few therapeutic options for myelofibrosis, the net potential benefits to risks of pacritinib may be favorable but clinical benefits require confirmation, as required under its accelerated approval status.	

AE, Adverse event; **MACE**, Major adverse cardiovascular event; PGIC, Patient global impression of change

† Surrogate for quality of life

Other Therapeutic Options

- Alternative JAKI treatments for MF according to the NCCN Guidelines for Myeloproliferative Neoplasms (version 3.2022)[7] are summarized in Table 9.
- Pacritinib is the only JAKI with approved dosage regimens for MF patients with PLT counts < 50 × 10^9/L.

Table 9 JAKIs Used for Myelofibrosis (NCCN 2022)

Consideration	Ruxolitinib	Fedratinib	Pacritinib
General Considerations			
Kinase Activity	JAK1, JAK2	JAK2 and FLT3 JAK2 > JAK1, JAK3, and TYK2	JAK2, FLT3, IRAK1 JAK2 > JAK3 and TYK2. Negligible JAK1 inhibition
FDA Indication	Intermediate or high-risk primary or secondary (PPV or PET) MF	Intermediate-2 or high-risk primary or secondary (PPV or PET) MF	Intermediate or high-risk primary or secondary (PPV or PET) MF with PLT < 50 × 10^9/L. **Accelerated approval** based on spleen volume reduction.
Prognostic Scoring System Used in Major RCTs	IPSS	IPSS	DIPSS
On VANF	Yes w/CFU	No w/CFU	TBD
CFU Place in Therapy	1st-line	2nd-line after ruxolitinib	TBD
FDA Place in Therapy	1st-line Recommended dosage pertains to patients with PLT ≥ 50 × 10^9/L	1st-line Recommended dosage pertains to patients with PLT ≥ 50 × 10^9/L	1st-line
NCCN Guideline Place in Therapy	Higher risk MF with PLT ≥ 50 × 10^9/L and not HSCT candidate (*category 1 recommendation*) Higher-risk MF with PLT ≥ 50 × 10^9/L and not HSCT candidate, after no response or loss of response to initial non-ruxolitinib JAKI (*category 2A recommendation*) Symptomatic higher-risk MF with PLT < 50 × 10^9/L and not HSCT candidate (*can be considered*; off-label) Symptomatic lower-risk MF as a first-line option or a second-line option after no response or loss of response to initial non-ruxolitinib (i.e., pegIFN alfa-2a or HU) tx (*category 2A recommendation*)	Higher risk MF with PLT ≥ 50 × 10^9/L and not HSCT candidates (*category 1 recommendation*)	Higher risk MF with PLT < 50 × 10^9/L and not HSCT candidate (*category 2A recommendation*) Higher-risk MF with PLT ≥ 50 × 10^9/L and not HSCT candidate, after no response or loss of response to one initial JAKI (*category 2A recommendation*) Symptomatic lower-risk MF after no response or loss of response to initial non-pacritinib therapy and PLT < 50 × 10^9/L (*category 2A recommendation*)
Safety Considerations			
Avoid Use of JAK2I	Moderate (CrCl 30–59 mL/min) or severe (CrCl 15–29 mL/min) renal impairment with PLT < 50 × 10^9/L	Thiamine deficiency until repleted Severe (Child-Pugh C) hepatic impairment Lactation / Breastfeeding is	Active serious infection until resolved Active bleeding and for 7 d prior to planned surgeries or other invasive procedures

Consideration	Ruxolitinib	Fedratinib	Pacritinib
	ESRD (CrCl < 15 mL/min) not requiring dialysis Hepatic impairment, any degree, and PLT < 50 × 10^9/L Lactation / Breastfeeding during tx and for 2 wks after last dose See Drug Interactions	not recommended during tx and for ≥ 1 month after last dose See Drug Interactions	Pre-existing diarrhea until controlled Baseline QTc > 480 msec Moderate renal impairment (eGFR < 30 mL/min) Moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment Lactation / Breastfeeding is not recommended during tx and for 2 wks after last dose See Drug Interactions
Reasons to Modify Dosage of JAK2I	Interrupt dosing for PLT < 50 × 10^9/L or ANC < 0.5 × 10^9/L. Reduce dose for PLT 50 × 10^9/L to < 200 × 10^9/L. Moderate (CrCl 30–59 mL/min) or severe (CrCl 15–29 mL/min) renal impairment with PLT 50 × 10^9/L to 150 × 10^9/L. Hepatic impairment, any degree, and PLT 50 × 10^9/L to 150 × 10^9/L	Grade 4 thrombocytopenia or grade 3 thrombocytopenia (PLT 25 × 10^9/L to 50 × 10^9/L)[6] with active bleeding Grade 4 neutropenia Grade ≥ 3 AEs as follows: elevations in ALT, AST, or bilirubin; nausea, vomiting, or diarrhea; amylase and/or lipase elevations; other nonhematologic toxicities Severe renal impairment (CrCl 15–29 mL/min)	Worsening thrombocytopenia that lasts > 7 d. Grade ≥ 3 diarrhea Moderate or severe bleeding
Notable AEs	Infections, OI, viral reactivation (HBV, HSV, HZV), TB (pre-tx TB screening in high-risk pts), PML, NMSC, lymphomas, hyperlipidemia	Encephalopathy including Wernicke's (replete low thiamine levels), ↑ liver enzymes, ↑SCr, ↑ amylase and lipase, infections Warnings of MACE, thrombosis and secondary malignancies are based on experiences with another JAKI	Infections, hemorrhage, prolonged QTc, MACE, thrombosis, secondary malignancies Warnings of *serious* infections, MACE, and thrombosis are based on experiences with another JAKI
Drug Interactions With Contraindication or Recommendation to Avoid Concomitant Drug Use	Strong CYP3A4 inhibitors and fluconazole doses > 200 mg (avoid)	Strong and moderate CYP3A4 inducers (avoid) Co-use with dual CYP3A4 and CYP2C19 inhibitors (avoid)	Strong CYP3A4 inhibitors or inducers (contraindicated) Moderate CYP3A4 inhibitors or inducers (avoid co-use) P-gp, BCRP, or OCTI substrates (avoid co-use with sensitive substrates) Drugs that significantly prolong QTc (avoid)
Other Considerations	Initial dosage depends on baseline PLT count Dose-related	Lacks Warning / Precaution for infections	Fatal intracerebral hemorrhage and CV events led to temporary FDA clinical hold.

Consideration	Ruxolitinib	Fedratinib	Pacritinib
	myelosuppression limits ability to increase doses Rapid return of disease symptoms can occur over about a 1-wk period after ruxolitinib interruption or discontinuation (consider gradual dosage taper for reasons other than thrombocytopenia or neutropenia).		Longer elimination half-life of about 40 h may reduce drug exposure gradually; however, abrupt discontinuation of pacritinib resulted in withdrawal syndrome with increase in spleen size and rapid, difficult-to-control symptom recurrence.

Source: NCCN Guidelines Version 3.2022

NCCN Categories of Evidence and Consensus: Category 1 recommendations were based on high-level evidence and there was uniform NCCN consensus that the intervention is appropriate. Category 2A recommendations were based on lower-level evidence and there was uniform NCCN consensus that the intervention is appropriate.

FLT3, FMS-like tyrosine kinase 3; **HSCT**, Hematopoietic stem cell transplant; **HBV**, Hepatitis B virus; **HSV**, Herpes simplex virua; **HZV**, Herpes zoster virus; **OI**, Opportunistic infection; **PET**, Post-essential thrombocythemia; **PPV**, Post-polycythemia vera

Projected Place in Therapy

- **Epidemiology and Prevalence of Myelofibrosis in Veterans**. Myelofibrosis is a rare, progressive, potentially fatal, hematologic disorder involving abnormal maturation of blood cells. Complications include anemia, thrombocytopenia, splenomegaly, and debilitating symptoms such as pain, fatigue, bleeding, pruritus, night sweats, early satiety, and bone pain. Thrombocytopenia, which has been reported in 18% to 28% of patients with myelofibrosis,[8] seems to be associated with a lower likelihood of survival.[9]
- **Potential Place in Therapy Based on the Evidence**. Very low quality evidence from two BAT-controlled trials supports using pacritinib to reduce spleen volume in patients with intermediate- or high-risk, primary or secondary myelofibrosis regardless of baseline cytopenias (PERSIST-1) or in the presence of thrombocytopenia (PLT ≤ 100 × 10^9/L; PERSIST-2). PERSIST-2 subgroup analyses of patients with severe thrombocytopenia (PLT < 50 × 10^9/L) at baseline showed no worsening of PLT counts and supported the FDA-approved indication limiting use of divided-dose pacritinib (200 mg BID) to MF patients with PLT < 50 × 10^9/L. The PERSIST-1 and PERSIST-2 results apply mainly to treatment-naïve patients but 48% of PERSIST-2 patients had prior ruxolitinib exposure. Although spleen volume reduction is expected to be clinically meaningful, the clinical benefits of pacritinib are uncertain, and pacritinib did not improve overall survival compared with BAT. No head-to-head trials comparing JAKIs were performed. Limited indirect comparisons in a meta-analysis showed an unexpected similarity between ruxolitinib and pacritinib in the odds of grade 3 or 4 thrombocytopenia. The recommended dose of pacritinib is 200 mg twice daily. A dosage of 400 mg once daily is not recommended because of a potentially higher risk of mortality.
- **Potential Place in Therapy in VHA**. Pacritinib is the first JAKI approved for use in patients who have myelofibrosis with platelet counts < 50 × 10^9/L. In accordance with the 2022 National Comprehensive Cancer Network (NCCN) guidelines,[7] pacritinib may be used as a first-line therapy in patients who have higher-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis with a platelet count < 50 × 10^9/L and who are not candidates for hematopoietic stem cell transplant. Pacritinib may be used as second-line therapy after no response or loss of response to one prior JAKI (i.e., ruxolitinib or fedratinib) in patients who have higher-risk myelofibrosis with platelet count ≥ 50 × 10^9/L and are not HSCT candidates. Pacritinib may also be used as second-line therapy after no response or loss of response to initial therapy (i.e., clinical trial or, in certain cases, ruxolitinib,

peginterferon alfa-2a, or hydroxyurea) in patients who have symptomatic lower-risk myelofibrosis with platelet count < 50 × 10^9/L. Issues for consideration include weighing the potential spleen volume benefits of pacritinib against the uncertain effects on clinical outcomes and the potential safety signals of mortality, serious bleeding, and heart failure. Other considerations include the incomplete data and shortened follow-up due to the clinical hold placed on the studies and the lack of a comparative pharmacokinetic study to further evaluate the apparently better safety of giving the same 400-mg daily dose of pacritinib in two divided doses over a single dose.

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