Ropeginterferon alfa-2b-njft (BESREMi)
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

- Ropeginterferon (ropegIFN) alfa-2b-njft is an originator biologic product (as opposed to a biosimilar). It is an N-terminal monopegylated covalent conjugate of proline interferon (IFN) alfa-2b produced in *Escherichia coli* cells by recombinant DNA technology.[1,2] It is a site-specific, long-acting IFN with only one major isoform rather than 8–14 isoforms of other pegylated IFN drugs.[1]
- RopegIFN alfa-2b-njft differs from pegylated IFN (pegIFN) alfa-2a in that it is approved for every 2- to 4-week dosing in the treatment of polycythemia vera (PV). The pegIFN alfa-2a product is dosed on a weekly basis and has been used off-label for PV.

Indication Under Review in This Document

- Treatment of adults with polycythemia vera (PV).

Pretreatment Evaluations and Tests

- Pregnancy testing
- Estimated GFR (eGFR)
- Liver enzyme / function tests

Dosage Regimen Under Review

- **Patients Not on Hydroxyurea**. Initiate at 100 mcg SC every 2 weeks. Increase dose by 50 mcg every 2 weeks up to a maximum of 500 mcg until hematologic parameters are stabilized (hematocrit less than 45%, platelets less than 400 x 10^9/L, and leukocytes less than 10 x 10^9/L).
- **Patients Transitioning from Hydroxyurea**. Initiate at 50 mcg SC every 2 weeks in combination with hydroxyurea. Increase ropegIFN alfa-2b-njft by 50 mcg every 2 weeks up to a maximum of 500 mcg until hematologic parameters are stabilized as described above. During Weeks 3–12, gradually taper off hydroxyurea by reducing the total biweekly dose by 20%–40% every 2 weeks. Discontinue hydroxyurea by Week 13.
- **Maintenance Dosage**. For at least 1 year, maintain the 2-week dosing interval of ropegIFN alfa-2b-njft that achieved hematologic stability. Thereafter, the dosing interval may be extended to every 4 weeks.
- **Dose Modifications Because of Adverse Reactions**. Refer to prescribing information.[1]

Dosage Form Under Review

- 500 mcg/mL injection in a single-dose prefilled syringe

Clinical Evidence Summary

Efficacy Considerations

Randomized Clinical Trials (RCTs)

- This review focuses on the PROUD-PV trial and its open-label extension study CONTINUATION-PV (aka CONTI-PV). The phase 3 PROUD-PV study compared ropegIFN alfa-2b with standard therapy and evaluated long-term outcomes in its phase 3b CONTI-PV extension study.[3,4]
- An open-label, multicenter, single-arm, phase I/II dose escalation trial conducted in Austria (N = 51), the PEGINVERA Study, supported the effectiveness of ropegIFN. The PEN-PV Study, an open-label, single-arm, phase 3 trial evaluated the ease of patient self-administration of subcutaneous injections[6] (although a pen product has not been approved as of the date of this review).
- The multicenter, open-label, phase 2 Low-PV trial compared the efficacy and safety of ropegIFN alfa-2b plus a standard phlebotomy regimen with the standard phlebotomy regimen (including low-dose aspirin) in 127 Italian patients with low-risk PV.[5] At the second pre-planned interim analysis, ropegIFN + phlebotomy produced a higher response rate than phlebotomy (42/50, 84% vs 30/50, 60%), respectively (difference 24 percentage points, 95% CI 7, 41). Patient accrual was stopped early because of overwhelming efficacy. No significant differences in the rates of grade 3 or higher adverse events were observed.

Active Comparator Clinical Trials

Methods

Table 1 Methods of the Phase 3 RCTs

Topic	PROUD-PV and CONTI-PV
Study Design (Country)	Phase 3 multicenter open-label, noninferiority RCT (EU) and extension study Randomization stratified by prior HU tx, age, and h/o thromboembolic event. Noninferiority margin 10.5%. Per-protocol efficacy analysis. For CONTI-PV, ropegIFN alfa-2b pts in PROUD-PV continued tx. HU pts received investigator-selected BAT (HU, conventional IFN alfa, pegIFN alfa, anagrelide, JAK2I, phosphorus-32, or busulfan).
Major Entry Criteria	**Inclusion**: Age ≥ 18 years, diagnosis of PV including JAK2 V617F mutation, need for cytoreductive therapy in cytoreductive-naïve patients, inadequate response or intolerance to hydroxyurea if previously treated with hydroxyurea, stable HCT of < 45%. **Exclusion**: Non-hydroxyurea cytoreductive therapy. **CONTI-PV Inclusion**: Normalization of ≥ 2 of 3 blood parameters (HCT, PLT, WBC), or a reduction of > 35% in at least 2 of 3 blood parameters from baseline, or normalization of spleen size, or clinically confirmed benefit from ropegIFN alfa-2b.

<table>
<tr><th>Topic</th><th>PROUD-PV and CONTI-PV</th></tr>
<tr><td>Interventions</td><td>All pts: Low-dose ASA

First Year

• RopegIFN alfa-2b initiated at 100 mcg SC Q2W (50 mcg if transitioning from HU)
• Hydroxyurea initiated at 500 mg PO QD
• Doses of study drug were increased until HCT <45% without phlebotomy, PLT WNL (< 400 × 10^9/L, and WBC WNL (< 10 × 10^9/L). Median stable dose at M36 was 425 mcg ropegIFN alfa-2b and 1000 mg HU.

Subsequent Years

• RopegIFN alfa-2b
• Best Available Treatment</td></tr>
<tr><td>Maintenance Phase or Long-term Extension</td><td>CONTINUATION-PV (CONTI-PV), a 5-year phase 3b extension trial with published data for up to 3 years

RopegIFN alfa-2b dosing continued at individualized intervals of every 2, 3, or 4 weeks

Hydroxyurea patients from PROUD-PV received investigator-selected BAT (hydroxyurea [97% of 66 pts] or another standard 1st-line tx [3% conventional IFN alfa] with individualized dosing)</td></tr>
<tr><td>Primary Efficacy Measure(s)</td><td>PROUD-PV: Complete hematologic response (defined as HCT < 45% without phlebotomy x 3 mos, PLT < 400 x 10^9/L, WBC < 10 x 10^9/L) with normal spleen size.

CONTI-PV: Coprimary endpoints were complete hematologic response + normal spleen size and CHR with improved disease burden (splenomegaly, microvascular disturbances, pruritus, and/or headache).

Other outcomes:

Complete Hematologic Response (CHR): HCT < 45% without phlebotomy, PLT ≤ 400 x 10^9/L, WBC ≤ 10 × 10^9/L, and no disease-related symptoms.

Molecular Response (MR): complete [undetectable JAK2 V617F allele burden] or partial [≥ 50% reduction if < 50% allele burden at baseline or ≥ 25% if ≥ 50% allele burden at baseline.</td></tr>
<tr><td>Baseline Patient Characteristics</td><td><table><tr><th>Characteristic</th><th>PROUD-PV (N = 154)</th><th>CONTI-PV (N = 171)</th></tr><tr><td>Male</td><td>47%</td><td>48%</td></tr><tr><td>Age, median (range)</td><td>60 (21–85)</td><td>58 (30–85)</td></tr><tr><td>HU experienced</td><td>32%</td><td>29%</td></tr><tr><td>Duration of PV, median, mos</td><td>2.3</td><td>1.7</td></tr><tr><td>Prior Thromboembolic event</td><td>19%</td><td>20%</td></tr><tr><td>Splenomegaly</td><td>11%</td><td>9%</td></tr></table></td></tr>
</table>

HU, Hydroxyurea

Key Results

- Efficacy data from PROUD-PV and CONTI-PV are summarized in Table 2.

Table 2 Efficacy results from PROUD-PV and CONTI-PV

Outcome	Time Point	Study	RopegIFN alfa-2b	HU / BAT	Relative Risk (95% CI)	Difference (95% CI)
CHR + Normal spleen size, n/N (%)	M12	PROUD-PV	26/122 (21.3)	34/123 (27.6)	0.77 (0.49, 1.20)	7 (–17.23, 4.09)
CHR + Improvement in disease burden, n/N (%)	M60	CONTI-PV	50/94 (53.2)	28/74 (37.8)	1.41 (0.99, 1.99)	15.4 (0.23, 29.51)
CHR, n/N (%)	M60	CONTI-PV	53/95 (55.8)	33/75 (44.0)	1.30 (0.95, 1.77)	11.8 (−3.27, 26.13)
Molecular Response, n/N (%)	M60	CONTI-PV	**65/94 (69.1)**	**16/74 (21.6)**	**3.04 (1.96, 4.71)**	**47.5 (32.93, 59.02)**
JAK2 V617F Allele Burden < 10%, n/N (%)	M60	CONTI-PV	**50/92 (54.3)**	**10/72 (13.9)**	**3.91 (2.14, 7.16)**	**40.4 (26.28, 51.98)**

Sources: 6
Bolded results show significant treatment differences by confidence intervals.
CFB, Change from baseline; **CHR**, Complete hematologic response (see Table 1 for definitions); **Q**, GRADE quality of evidence (H = High, M = Moderate, L = Low, VL = Very low)

- In PROUD-PV, noninferiority was not shown for ropegIFN alfa-2b relative to hydroxyurea / Best Available Treatment in terms of the composite primary end point of complete hematologic response with normal spleen size at Month 12.[4] This result may have been affected by the relatively small number of patients with splenomegaly at baseline. The FDA criticized the study protocol for not having a prospectively planned end point for noninferiority and not adequately justifying the margin.[6]
- The FDA considered the results of CONTI-PV exploratory because of the risks of selection bias and confounding.[6]
- The anticipated absolute effects for achieving molecular response and JAK2 V617F allele burden < 10% in 60 months are presented in Table 3.

Table 3 Absolute Effects for Achieving Molecular Responses With RopegIFN alfa-2b vs Best Available Treatment at Month 60 in CONTI-PV

Outcome Measure	AAE, per 1000 pts (95% CI)	NNT (95% CI)	Q
Molecular Response	441 (208, 802) more	2.1 (1.6, 2.9)	VL[α]
JAK2 V617F Allele Burden < 10%	404 (158, 856) more	2.5 (1.9, 3.7)	VL[α]

AAE, Anticipated absolute effect for achieving the outcome; **NNT**, Number needed to treat for one additional patient to benefit
[α] Downgraded for risk of bias (open-label interventions; no re-randomization at start of extension study) and imprecision (wide CIs).

Secondary efficacy results:

- **Median Time to CHR**. In the patients who achieved CHR, the median time to CHR was 7.8 months. The time for 50% of patients to achieve CHR was 1.2 years in the hydroxyurea-naïve subgroup and 1.4 years in the hydroxyurea-exposed subgroup.
- **Hematologic Response**. Of 51 patients, 41 (80%; 95% CI 67, 90) achieved hematocrit, platelet, and leukocyte responses, with a median duration of response of 20.8 months (95% CI 13.0, 43.8).
- **JAK2 V617F Allelic Burden / Molecular Response**. There was no significant difference in achievement of complete or partial molecular response at Month 12 in PROUD-PV and Month 12 in CONTINUATION-PV. Subsequently, ropegIFN alfa-2b was significantly better than Best Available Treatment in achieving complete or partial molecular response at Month 24 (64/94 [68%] vs 25/75 [33%], respectively) and Month 36 (62/94 [66%] vs 20/74 [27%], respectively).
- **Spleen Size**. In CONTI-PV, spleen size analyses were limited by the small number of patients with splenomegaly at baseline (9% of 127 patients vs 12% of 127 patients in the ropegIFN alfa-2b and Best Available Treatment groups, respectively).

- **Quality of Life**. In CONTI-PV, there was no significant difference between ropegIFN alfa-2b and Best Available Treatment in change from baseline to Month 36 in the European Quality of Life-5 dimensions-3 levels (EQ-5D-3L) total scores.

Long-term Efficacy: CONTI-PV

- Based on efficacy data up to Month 36 of the extension study (N = 171), ropegIFN alfa-2b (n = 95) was significantly better than Best Available Treatment (mainly hydroxyurea) (n = 76) in achievement of the following end points[4,]
    - Maintenance of complete hematologic response (37 [39%] of 95 patients vs 11 [15%] of 76 patients, respectively);
    - Maintenance of complete hematologic response and improvement in disease burden (28 [30%] of 95 patients vs 11 [15%] of 76 patients, respectively);
- At Month 60, ropegIFN alfa-2b was significantly better than Best Available Treatment in terms of the following[3]:
    - Complete hematologic response and improvement in disease burden (50 [53%] of 95 patients vs 28 [38%] of 74 patients, respectively); and
    - Complete or partial molecular response (65 [69.1%] of 94 patients vs 16 [21.6%] of 74 patients, respectively; RR 3.04 [1.96, 4.71]).
- A nonsignificantly higher Month-60 complete hematologic response occurred with ropegIFN alfa-2b than Best Available Treatment (53 [55.8%] of 95 patients vs 33 [44.0%] of 75 patients, respectively; RR 1.30 [95% CI 0.95, 1.77]).
- RopegIFN alfa-2b was better than hydroxyurea in reducing the JAK2 V617F allele burden.
    - Allele burden from baseline of CONTI-PV to Months 24 and 36 progressively decreased from 42.8% to 20.9% and 19.7%, respectively, for ropegIFN alfa-2b, whereas allele burden only transiently decreased from 42.9% to 32.1% then increased to 39.3%, respectively, for hydroxyurea.[4]
    - At Month 60, allele burden was 8.5% on ropegIFN alfa-2b therapy and 44.4% (higher than baseline) on hydroxyurea.[3]
    - A total of 18 (19.6%) of 92 patients achieved allele burden of < 1% on ropegIFN alfa-2b in comparison to 1 patient (1.4%) on Best Available Treatment.[3]
    - JAK2 V617F allele burden < 10% correlated with younger age, lower baseline allele burden, and higher complete hematologic response at Month 60.[3]

Subgroup Analyses

Age group (< 60 years and ≥ 60 years; post hoc analyses, CONTI-PV)[7]

- Significantly higher rates occurred on ropegIFN alfa-2b than Best Available Treatment at Month 24 in patients aged < 60 years and nonsignificantly higher rates in patients aged ≥ 60 years in the following outcomes:
    - Maintenance of complete hematologic response (from first occurrence to Month 24): 49.0% vs 17.9%, respectively; RR: 2.82 (95% CI: 1.37 to 5.79) in patients < 60 years and 37.0% vs 18.9%, respectively; RR: 1.96 (0.91 to 4.22) in patients ≥ 60 years.
    - Molecular response: 77.1% vs 33.3%, respectively; RR: 2.17 (1.38, 3.42) in patients aged < 60 years and 58.7% vs 36.1%; RR: 1.53 (0.95 to 2.48) in patients ≥60 years.
    - Change from baseline in JAK2 V617F allele burden: −54.8% vs −4.5%, respectively; RR: −51.15 (−78.92 to −23.37) in patients < 60 years and −35.1% vs −18.4%; RR: −15.85 (−32.16 to 0.46) in patients ≥ 60 years.
- Nonsignificantly higher rates occurred on ropegIFN alfa-2b than Best Available Treatment at Month 24 in both age categories in the following outcomes:

  - Complete hematologic response
  - CHR with improved disease burden
  - Maintenance of CHR with improved disease burden
- Significantly higher molecular response rates

Exploratory Analyses

- Operational cure (defined as allele burden < 10%, maintenance of complete hematologic response for ≥ 2 years, and no disease progression, thromboembolic events, or symptom worsening during 5 years of follow-up) was achieved in 27 (28.4%) of 95 patients receiving ropegIFN alfa-2b in CONTI-PV.[8] This data was reported only in a conference abstract.

Onset of Treatment Benefit and Duration of an Adequate Therapeutic Trial

- Onset of effects (earliest significant treatment difference) and duration of an adequate therapeutic trial (time at which peak response occurs and is sustained) are summarized by outcome measure in Table 4.

Table 4 Onset of Benefit and Adequate Therapeutic Trial

Trial	Outcome Measure	Onset of Significant Treatment Benefit (mos)	Duration of an Adequate Therapeutic Trial (mos)
PROUD-PV	Complete hematologic response	6	—
CONTI-PV	Complete hematologic response	6	21
	Molecular response, complete or partial	6	24

Durability of Response

- The median duration of CHR was 14.3 months (95% CI 5.5, 30.1). This is a clinically relevant result because it is a significant improvement from the natural course of PV, which has no spontaneous remissions or random improvements in HCT, WBC, or PLTs.[6]

Evidence Gaps

- Survival / Mortality without thromboembolism or major adverse cardiovascular event (The correlation between molecular response and mortality in PV is not fully known.[6])
- Hospitalization or readmission
- Functional ability / Disability
- Patient Satisfaction

Safety Considerations

Labelled Safety Information

- **Boxed Warnings**: Risk of serious disorders; may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Monitor closely and discontinue therapy if these disorders are persistently severe or worsen.
- **Contraindications**: Existence of, or history of severe psychiatric disorders, particularly severe depression, suicidal ideation, or suicide attempt; hypersensitivity to IFNs including IFN alfa-2b or any of the inactive ingredients; moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment; history or presence of active serious or untreated autoimmune disease; immunosuppressed transplant recipients.
- **Other Warnings / Precautions**: Depression and suicide; endocrine toxicity; cardiovascular toxicity; decreased peripheral blood counts; hypersensitivity reactions, pancreatitis, colitis, pulmonary toxicity, ophthalmologic toxicity, hyperlipidemia, hepatotoxicity, renal toxicity, dental and periodontal toxicity, dermatologic toxicity, avoid driving and operating machinery.

- **Common Adverse Events (> 40%)**: Influenza-like illness, arthralgia, fatigue, pruritus, nasopharyngitis, musculoskeletal pain.

Long-term (Month 60) Comparative Safety Results from CONTI-PV

- Table 5 summarizes safety data up to Month 60 from CONTI-PV.

Table 5 Adverse Events in PROUD-PV and CONTI-PV to Month 60

Adverse Event / Disorder	RopegIFN alfa-2b (N = 127)	HU / BAT (N = 127)
Serious Adverse event, n (%)	30 (23.6)	32 (25.2)
Serious Adverse Event, treatment-related, n (%)	4 (3.1)	5 (3.9)
Death, treatment-related, n (%)	0 (0)	1 (1)
Death, not related to treatment, n (%)	2 (2)	1 (1)
Discontinuation due to treatment-related adverse event, n (%)	13 (10.2)	4 (3.1)
Grade ≥ 3 adverse event, n (%)	21 (16.5)	21 (16.5)
Adverse Events of Special Interest		
Major Adverse Thromboembolic Event, n (%)	4 (3.1)	5 (3.9)
Any neoplasm, n (%)	12 (9.4)	15 (11.8)
Disease progression (myelofibrosis or leukemia), n (%)	1 (0.8)	4 (3.1)
Skin cancer, treatment-related, n (%)	0 (0)	3 (2.4)

Source: 3

- Disease progression to secondary myelofibrosis or leukemia occurred in 1 case (myelofibrosis) per 499 patient years on ropegIFN alfa-2b (0.2% per patient-year [PPY]) vs 4 cases (2 myelofibrosis, 2 acute leukemia) per 401 PY (1.0% PPY) on Best Available Treatment.[3]
- Major thromboembolic events occurred 5 times in 4 patients (1.0% PPY) vs 5 times in 5 patients (1.2% PPY) on ropegIFN alfa-2b and Best Available Treatment, respectively.[3]
- Rates of adverse events, serious adverse events and treatment-related adverse events were similar between the treatment groups.[3]
- Influenza and influenza-like illness were reported in various ways (Table 6). "Influenza-like illness" per se was more common on ropegIFN alfa-2b than hydroxyurea.

Table 6 Influenza Events

	PROUD-PV		All Studies Combined
Adverse Event	RopegIFN alfa-2b n (%), N = 127	Hydroxyurea n (%), N = 127	RopegIFN alfa-2b n (%), N = 178
URI, cold, rhinitis, flu-like illness	39 (30.7)	30 (23.6)	73 (41)
Influenza	6 (4.7)	13 (10.2)	8 (4.5)
Influenza-like illness	10 (7.9)	0 (0)	—

Source: 6

PBM Note: For reference on the tolerability and influenza events of pegIFN alfa-2, the rates of treatment discontinuation due to adverse events were 30% vs 5% at 36 months in pegIFN alfa-2a or -2b vs hydroxyurea groups, respectively, in the DALIAH study (newly diagnosed or previously phlebotomized patients with PV)[9] and 15% vs 11%, at a median of 22 months with pegIFN alfa-2a vs hydroxyurea, respectively, in the MPD-RC-112 study (treatment-naïve, high-risk patients with PV or essential thrombocythemia).[10] Flu-like symptoms occurred in 24.4% vs 5% of pegIFN alfa-2a vs hydroxyurea, respectively, in the MPD-RC-112 study.

Subgroup Safety Analyses

Age categories (< 60 years and ≥ 60 years)[7]

- Rates were comparable in the treatment groups in patients < 60 years and numerically lower on ropegIFN alfa-2b vs Best Available Treatment in patients ≥ 60 years in the following safety outcomes:
    - Treatment-related adverse events: 77.6% vs 74.4%, respectively, in patients < 60 years and 63.0% vs 89.2%, respectively in patients aged ≥ 60 years.
    - Treatment-related serious adverse events: 0% vs 0%, respectively, in patients < 60 years and 0% vs 10.8% for ropegIFN alfa-2b vs Best Available Treatment, respectively, in patients ≥ 60 years.
- Rates were comparable on ropegIFN alfa-2b and Best Available Treatment in the two age categories in the following safety outcomes:
    - Adverse events
    - Serious adverse events

Comparative Effectiveness and Safety of Interferons: Systematic Review / Meta-analyses

- No *network* meta-analyses compared ropegIFN alfa-2b with pegIFN alfa.
- A single-arm meta-analysis of 37 studies (N = 1794) evaluated the efficacy of interferon therapy in patients with essential thrombocythemia (ET) or PV.[11] Three studies were RCTs, 25 were prospective cohort studies, and 9 were retrospective studies.
    - Subgroup analyses included evaluations by type of interferon for overall hematologic response and overall molecular response for myeloproliferative neoplasms, where the definitions for responses were based on the European LeukemiaNet (ELN) criteria, ELN-equivalent criteria, or revised ELN criteria.
    - Based on the 95% confidence intervals, ropegIFN alfa-2b was comparable to pegIFN alfa products in overall hematologic response and overall molecular response for myeloproliferative neoplasms; however, there was substantial to considerable heterogeneity among studies (Table 7 and Table 8).

Table 7 Subgroup Analyses by Type of Interferon for Overall Hematologic Response for Myeloproliferative Neoplasms

Subgroup	K	Incidence Rate (95% CI)	I^2
RopegIFN alfa-2b	2	0.87 (0.80, 0.93)	0.00%
PegIFN alfa-2a	8	0.85 (0.76, 0.92)	86.90%
PegIFN alfa-2b	3	0.87 (0.63, 0.99)	79.60%
PegIFN alfa	2	0.97 (0.79, 1.00)	89.20%

I^2 is used to measure the percentage of variability in effect estimates due to heterogeneity in meta-analyses and can be roughly interpreted as follows: 0%–40%, Might not be important; 30%–60%, May represent moderate heterogeneity; 50%–90%, May represent substantial heterogeneity; and 75%–100%, Considerable heterogeneity.[12]

Table 8 Subgroup Analyses by Type of Interferon for Overall Molecular Response for Myeloproliferative Neoplasms

Subgroup	K	Incidence Rate (95% CI)	I^2
RopegIFN alfa-2b	3	0.41 (0.18, 0.67)	91.80%
PegIFN alfa	3	0.56 (0.40, 0.72)	64.60%

For I^2 description, see footnote for Table 7.

- Adverse events were not analyzed by type of interferon.
- The results are only indirectly applicable to a comparison of ropegIFN alfa-2b and pegIFN alfa-2a in patients with PV because of the lack of directly comparative trials, lack of network meta-analyses, and lack of subgroup data analyzed by type of myeloproliferative neoplasm (ET or PV).

Drug Interactions

- **CYP450 Substrates with Narrow Therapeutic Index**. Monitor for adverse reactions; adjust dose of concomitant drug if needed.
- **Myelosuppressive Agents**. Avoid concomitant use. Monitor patients receiving concomitant myelosuppressives.
- **Narcotics, Hypnotics, or Sedatives**. Monitor patients for excessive central nervous system toxicity.

Other Considerations

Specific Populations

- **Pregnancy.** Can cause fetal harm based on its mechanism of action and role of interferon in pregnancy and fetal development.[2,13] Advise patients of childbearing potential of possible risks to a fetus and to use effective contraception. Can cause disruption of menstrual cycles. No animal fertility studies have been conducted. Pregnant women and women of childbearing potential not on contraception were excluded from clinical trials.

  PBM Note: The pregnancy risk description for pegIFN alfa-2a/-2b agents state that fetal risk cannot be ruled out (i.e., available evidence is inconclusive or inadequate).[14,15] The National Comprehensive Cancer Network (NCCN) guideline on myeloproliferative disorders states that pegIFN alfa-2a can be considered for pregnant patients with PV who require cytoreductive therapy.[16]

- **Lactation.** Advise women not to breastfeed during treatment and for 8 weeks after the final dose.
- **Renal Impairment.** Avoid use in patients with eGFR < 30 mL/min. No dosage adjustment is necessary for eGFR ≥ 30 mL/min.
- **Hepatic Impairment.** Contraindicated in patients with Child-Pugh B or C hepatic impairment. Reduce dosage if increased liver enzymes are progressive and persistent.
- **Geriatric Use.** There was insufficient data to determine whether elderly patients differ in response from younger patients. Use cautious dosing in elderly patients.

Risk-Benefit Assessment

RopegIFN alfa-2b-njft relative to pegIFN alfa

- Unable to fully assess.
- RopegIFN alfa-2b-njft therapy carries an unacceptable risk-benefit in pregnant women with PV, whereas pegIFN alfa-2a can be considered in pregnant women, as described under Specific Populations above.

RopegIFN alfa-2b-njft relative to hydroxyurea

- Rates of major thromboembolic events recorded as adverse events rather than efficacy outcomes were similar. Relative to hydroxyurea, ropegIFN alfa-2b-njft may produce large molecular improvements with increased risks of neuropsychiatric, autoimmune, and infectious complications (Table 9).

Table 9 Summary of risk-benefit assessment of ropegIFN alfa-2b-njft vs hydroxyurea

Parameter	Description		
Outcome in Clinically Significant Area	Complete hematologic response + Normal spleen size at M12	Complete hematologic response + Improvement in disease burden at M60	Major adverse thromboembolic events
Effect Size	–6.3 %p (NSD)	15.4 %p (NSD)	–0.8 %p
Potential Harms	Compared with hydroxyurea, ropegIFN alfa-2b carries additional boxed warning risks of neuropsychiatric, autoimmune, and infectious events, and lacks malignancies as a boxed warning. Discontinuations due to adverse events and reports of "influenza-like illness" were more frequent with ropegIFN alfa-2b than hydroxyurea. Flu-like symptoms can be managed with simple analgesics / antipyretics or by taking doses at bedtime.		
Net Clinical Benefit	Whether ropegIFN alfa-2b adds benefit over hydroxyurea in reducing thromboembolic and hemorrhagic events is unclear. The studies may have been too short or small to detect meaningful differences in these uncommon events. Relative to hydroxyurea, ropegIFN alfa-2b confers nonsignificantly higher hematologic responses and a large benefit in terms of molecular response with longer treatment. Like with other interferons, cytogenetic remission may be possible; however, the clinical benefits associated with differences in molecular response are as yet unclear.		

Other Therapeutic Options

- The main alternative to ropegIFN alfa-2b-njft is pegIFN alfa-2a, which has been used off-label for the treatment of PV for decades. PegIFNs improved upon the previously used standard IFN alfa by reducing the flu-like adverse effects and requiring once weekly rather than three-times-a-week dosing. The development of ropegIFN alfa-2b was a further attempt to improve the tolerability and dosing frequency of pegIFNs.
- RopegIFN alfa-2b-njft has become the only cytoreductive therapy recommended by the NCCN for the treatment of patients with low-risk PV who have indications for cytoreduction (Table 10).

Table 10 NCCN Guidelines for Cytoreductive Therapies for Polycythemia Vera

Step in Therapy	Treatment Alternatives	Category†	Comments
Low-risk PV			
Other recommended therapy for initial therapy (when cytoreductive therapy is indicated)	RopegIFN alfa-2b-njft	2B	Low-dose aspirin, phlebotomy, and management of cardiovascular risk factors are the preferred initial therapies for low-risk PV. RopegIFN alfa-2a may be considered for symptomatic patients with potential indications for cytoreductive therapy.‡ Of note, neither pegIFN alfa-2a nor hydroxyurea is mentioned as cytoreductive therapy for low-risk PV.
High-risk PV or Refractory Low-risk PV			
Preferred regimen	Hydroxyurea	2A	
	PegIFN alfa-2a	2A	
Other recommended regimen	RopegIFN-alfa-2b-njft	2A	
Preferred regimens for inadequate response or loss of response to initial preferred regimen	Clinical trial	2A	Considered by NCCN to be the best management for any patient with cancer.
	Ruxolitinib	1 for high-risk PV	FDA-approved for patients with PV who have had an inadequate response or intolerance to hydroxyurea. Increases risks of infection, hematocytopenias, tuberculosis, hepatitis B, herpes zoster, PML, NMSC.

Step in Therapy	Treatment Alternatives	Category†	Comments
Other recommended regimens for inadequate response or loss of response to initial preferred regimen	RopegIFN alfa-2b-njft	2A	If not previously used
	Hydroxyurea	2A	If not previously used
	PegIFN alfa-2a	2A	Can be considered for patients who are younger, pregnant, or defer hydroxyurea or ropegIFN alfa-2b-njft, if not previously used.

Source: 16
NCCN, National Comprehensive Cancer Network; NMSC, Nonmelanoma skin cancer; PML, Progressive multifocal leukoencephalopathy
† NCCN Categories of Evidence and Consensus. **Category 1** is based on high level evidence with uniform NCCN consensus that the intervention is appropriate. **Category 2A** is based on lower level evidence with uniform NCCN consensus that the intervention is appropriate. **Category 2B** is based on lower level evidence with NCCN consensus that the intervention is appropriate.
‡ Potential indications for cytoreductive therapy: New thrombosis or disease-related major bleeding; frequent phlebotomy or intolerant of phlebotomy; splenomegaly; progressive thrombocytosis and/or leukocytosis; disease-related symptoms such as pruritus, night sweats, fatigue.

- The European LeukemiaNet (ELN) recommendations state that cytoreductive therapies should be considered only in specific clinical subgroups (strength of recommendation: weak negative).[17] The ELN recommends starting cytoreductive therapy in patients with low-risk PV if ≥ 1 of the following criteria are met: leukocytosis, poor hematocrit control (hematocrit ≥ 45%) with phlebotomy only, or high cardiovascular risk. In patients with low-risk PV, cytoreductive therapy is recommended, should be considered, or can be considered depending on the clinical subgroup.
    - Cytoreductive therapy is **recommended** in patients with low-risk PV who report (1) a poor tolerance to phlebotomy (strictly defined as recurrent episodes of post-phlebotomy syncope despite appropriate preventive interventions or blood phobia leading to avoidance behavior despite counseling, or severe difficulties in venous access); (2) symptomatic progressive splenomegaly (> 5-cm increase in past year) without transformation to myelofibrosis; (3) *persistent leukocytosis* (leukocyte count > 20 x 10^9 cells/L confirmed at 3 months).[17]
    - Cytoreductive therapy **should be considered** in patients with (1) *progressive leukocytosis* (at least 100% increase if baseline count is < 10 x 10^9 cells/L or at least 50% increase if baseline count is > 10 x 10^9 cells/L confirmed at 3 months); (2) *extreme thrombocytosis* (> 1500 x 109 platelets/L), disease-related bleeding regardless of platelet count, or both; or (3) inadequate hematocrit control with phlebotomies (i.e., the need for ≥ 6 phlebotomies per year for ≥ 2 years during the maintenance phase after achieving hematocrit < 45% during the induction phase).[17]
    - Cytoreductive therapy **can be considered** (1) in patients reporting a high symptom burden (total symptom score ≥ 20) or severe itching (score ≥ 5) not relieved by phlebotomy, antiplatelets, or antihistamines; or (2) on a case-by-case basis in patients with relevant cardiovascular risk despite primary prevention strategies.[17]
- If there is an inadequate response or intolerance to hydroxyurea, switching to IFN alfa or ruxolitinib can improve disease transformation (quality of evidence: moderate or low, respectively), vascular events (low or moderate, respectively), symptoms (moderate or high, respectively), and overall survival (low for each treatment).[17]
- The general steps in therapy of PV according to ELN recommendations is summarized in Table 11.

Table 11 ELN Recommendations for Use of Cytoreductive Therapies for PV

Step in Therapy	Treatment Alternatives	Considerations
Low-risk PV, initial *cytoreductive* therapy	PegIFN alfa-2a	RopegIFN alfa-2b is the only IFN alfa product approved for PV in the EU and US. The ELN recommends either formulation of pegylated IFN alfa.
	RopegIFN alfa-2b	IFN alfa controls hematocrit and achieves molecular response (high quality evidence), and delays or reduces transformation of PV into myelofibrosis and does not increase the risk of secondary skin cancer (moderate quality); therefore, it is preferred over hydroxyurea in patients < 60 y old. Screen patients pretreatment for subclinical thyroid dysfunction and autoimmune and neuropsychiatric disorders. Avoid use of IFN alfa in severe psychiatric disorders. Use of pegIFN alfa-2a is based on evidence for ropegIFN alfa-2b in low-risk PV.
	Hydroxyurea	Hydroxyurea is preferred in patients > 60 y of age. Prevents 2 thrombotic events / 100 patient-years overall in PV population. Increased risk of disease transformation in patients with progressive leukocytosis or increased spleen size. Increases risk of secondary skin cancer; associated with anemia, neutropenia, skin ulcers, hyperpigmentation. Resistance to hydroxyurea develops in 10% of patients.[6]
Hydroxyurea inadequate response or intolerance*	PegIFN alfa-2a	Selection of either IFN alfa or ruxolitinib should be individualized based on clinical features, especially age, spleen size, symptoms, history of skin cancers, and patient preferences. Ruxolitinib may be preferred over IFN alfa in patients previously treated with hydroxyurea who have clinically relevant splenomegaly. Ruxolitinib had higher risks of herpes zoster infection, recurrent infections, or secondary cancers / NMSC than comparator therapies (i.e., best available treatment, phlebotomy, or IFN alfa).
	RopegIFN alfa-2b	
	Ruxolitinib	

Source: 17

IFN alfa, Recombinant interferon alfa (either peginterferon alfa-2a or ropeginterferon alfa-2b); NMSC, Nonmelanoma skin cancer; QE, Quality of evidence; SR, Strength of recommendation

* A switch from hydroxyurea to alternative cytoreductive therapy should be considered in patients who have a high and persistent symptom burden despite moderate to high doses of hydroxyurea (> 1500 mg/day). Symptomatic splenomegaly and microvascular symptoms are also deemed relevant for considering a switch in therapy.

Projected Place in Therapy

- **Epidemiology and Prevalence of PV**. PV is a rare, chronic myeloproliferative neoplasm manifested by clonal proliferation of hematopoietic cells, mainly erythrocytes but also leukocytes and platelets. Genetic mutations usually involve the *JAK2*^{V617F} mutation. Thromboembolism and hemorrhagic events are the main complications, and PV can progress to acute myeloid leukemia and myelofibrosis. The incidence of PV has been estimated to be 0.01 to 2.61 per 100,000 per year.[18]
- **Place in Therapy Based on Medical Society Guidelines**. For low-risk PV, the NCCN recommends adding ropegIFN alfa-2b-njft to low-dose aspirin and phlebotomy when potential indications for cytoreductive therapy are present.[16] In high-risk PV, ropegIFN alfa-2b-njft is a less preferred alternative to hydroxyurea or pegIFN alfa-2a for cytoreductive therapy. In inadequate responders to initial cytoreductive therapies (hydroxyurea or pegIFN alfa), a clinical trial or ruxolitinib is the preferred second-line therapy while ropegIFN-alfa-2b-njft, hydroxyurea, and pegIFN alfa-2a are other alternatives, if not previously used.
- **Potential Place in Therapy Based on the Evidence**. No comparative trials were available to inform whether there are clinically important differences in efficacy, safety, or tolerability between ropegIFN alfa-2b and pegIFN alfa-2a in the treatment of patients with PV. RopegIFN alfa-2b offers a more convenient dosing frequency (Q2W with potential to reduce to Q4W after 1 year in hematologically stable

patients) as compared with the once weekly administration of pegIFN alfa-2a. Very low quality evidence from the PROUD-PV and CONTI-PV trials support the use of ropegIFN alfa-2b over hydroxyurea in patients with primarily early PV without splenomegaly. In subgroup analyses, more robust responses with ropegIFN alfa-2b vs hydroxyurea were seen in patients aged < 60 years than in those ≥ 60 years. These subgroup results and the findings of the Low-PV trial[5] support the use of ropegIFN alfa-2b-njft over hydroxyurea or phlebotomy in patients with low-risk PV. In addition, concerns about risk of malignancies with hydroxyurea favor the use of ropegIFN alfa-2b in younger patients. Based on the NCCN guidelines for PV, the main difference between ropegIFN alfa-2b-njft and pegIFN alfa-2a is its unique role in the treatment of patients with low-risk PV who have potential indications for cytoreductive therapy; neither hydroxyurea nor pegIFN alfa has a comparable place in therapy. However, according to the ELN guidelines, any one of three IFN alfa-2 products (pegIFN alfa-2a or -2b or ropegIFN alfa-2b) may be used for patients with low-risk PV who require cytoreductive therapy, with hydroxyurea preferred in patients > 60 years.

- **Potential Place in Therapy in VHA**. RopegIFN alfa-2b-njft may be used as a less preferred (higher-cost) alternative to pegIFN alfa-2a in patients with PV, including those with low-risk PV (< 60 years of age with no history of thrombosis) who are symptomatic and have potential indications for cytoreductive therapy. Both pegIFN alfa-2a and ropegIFN alfa-2b-njft should generally be avoided in pregnant patients and patients of childbearing potential not on contraception; however, their use in pregnancy can be considered after weighing risks vs benefits on a case-by-case basis.

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