VONJO™
(pacritinib) capsules

Now Approved.

INDICATION: VONJO™ (pacritinib) is indicated for the treatment of adults with intermediate or high-risk primary or secondary (post-polycythemia vera [PPV] or post-essential thrombocythemia [PET]) myelofibrosis (MF) with a platelet 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(s).

VONJO is available as 100 mg capsules, for oral use.

Important Safety Information

CONTRAINDICATIONS

VONJO is contraindicated in patients concomitantly using strong CYP3A4 inhibitors or inducers as these medications can significantly alter exposure to pacritinib, which may increase the risk of adverse reactions or impair efficacy.

WARNINGS AND PRECAUTIONS

Hemorrhage: Serious (11%) and fatal (2%) hemorrhages have occurred in VONJO-treated patients with platelet counts <100 x 10^9/L. Serious (13%) and fatal (2%) hemorrhages have occurred in VONJO-treated patients with platelet counts <50 x 10^9/L. Grade ≥3 bleeding events (defined as requiring transfusion or invasive intervention) occurred in 15% of patients treated with VONJO compared to 7% of patients treated with control arm. Due to hemorrhage, VONJO dose reductions, dose interruptions, or permanent discontinuations occurred in 3%, 3%, and 5% of patients, respectively. Avoid use of VONJO in patients with active bleeding and hold VONJO 7 days prior to any planned surgical or invasive procedures.

Assess platelet counts periodically, as clinically indicated. Manage hemorrhage using treatment interruption and medical intervention. In the case of severe bleeding, hold VONJO until hemorrhage resolves. When the bleeding has resolved, restart treatment at 50% of the last given dose. If the bleeding recurs, discontinue treatment with VONJO. In the event of life-threatening bleeding, discontinue VONJO.

Diarrhea: VONJO caused diarrhea in approximately 48% of patients compared to 15% of patients treated with the control arm. The median time to resolution in VONJO-treated patients was 2 weeks. The incidence of reported diarrhea decreased over time with 41% of patients reporting diarrhea in the first 8 weeks of treatment, 15% in Weeks 8-16, and 8% in Weeks 16-24. Diarrhea resulted in treatment interruption in 3% of VONJO-treated patients. None of the VONJO-treated patients reported diarrhea that resulted in treatment discontinuation. Serious diarrhea adverse reactions occurred in 2% of patients treated with VONJO compared to none in the control arm. **(cont. on the back)**

Please see Important Safety Information continued on the back and full Prescribing Information enclosed inside.

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Important Safety Information (cont.)

VONJO™ (pacritinib) capsules

WARNINGS AND PRECAUTIONS (cont.)

Diarrhea (cont.): Control preexisting diarrhea before starting VONJO treatment. Manage diarrhea with antidiarrheal medications, fluid replacement, and dose modification. Treat diarrhea with antidiarrheal medications promptly at the first onset of symptoms. Interrupt or reduce VONJO dose in patients with significant diarrhea despite optimal supportive care. In patients with Grade 3 or 4 diarrhea, hold VONJO until it resolves to Grade ≤1 or baseline, and restart VONJO at the last given dose. Intensify antidiarrheal regimen and provide fluid replacement. For recurrent diarrhea, hold VONJO until the diarrhea resolves to Grade ≤1 or baseline, and restart VONJO at 50% of the last given dose once the toxicity has resolved. Concomitant antidiarrheal treatment is required for patients restarting VONJO.

Thrombocytopenia: VONJO can cause thrombocytopenia. VONJO dosing was reduced due to worsening thrombocytopenia in 2% of patients with preexisting moderate to severe thrombocytopenia (platelet count <100 x 10^9/L). VONJO dosing was reduced due to worsening thrombocytopenia in 2% of patients with preexisting severe thrombocytopenia (platelet count <50 x 10^9/L). Monitor platelet count prior to VONJO treatment and as clinically indicated during treatment. Interrupt VONJO in patients with clinically significant worsening of thrombocytopenia that lasts for more than 7 days. Restart VONJO at 50% of the last given dose once the toxicity has resolved. If toxicity recurs, hold VONJO. Restart VONJO at 50% of the last given dose once the toxicity has resolved.

Prolonged QT Interval: VONJO can cause prolongation of the QTc interval. QTc prolongation of >500 msec was higher in VONJO-treated patients than in patients in the control arm (1.4% vs 1%). QTc increase from baseline by 60 msec or higher was greater in VONJO-treated patients than in control arm patients (1.9% vs 1%). Adverse reactions of QTc prolongation were reported for 3.8% of VONJO-treated patients and 2% of control arm patients. No cases of torsades de pointes were reported.

Avoid use of VONJO in patients with a baseline QTc of >480 msec. Avoid use of drugs with significant potential for QTc prolongation in combination with VONJO. Correct hypokalemia prior to and during VONJO treatment. Manage QTc prolongation using VONJO interruption and electrolyte management. In the case of QTc prolongation >500 msec or >60 msec from baseline, hold VONJO. If QTc prolongation resolves to ≤480 msec or baseline within 1 week, restart VONJO at the same dose. If time to resolution is >1 week, restart VONJO at a reduced dose.

Major Adverse Cardiac Events (MACE): Another Janus associated kinase (JAK) inhibitor has increased the risk of MACE, including cardiovascular death, myocardial infarction, and stroke (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which VONJO is not indicated.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with VONJO, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur.

Thrombosis: Another JAK inhibitor has increased the risk of thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which VONJO is not indicated. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately.

Secondary Malignancies: Another JAK inhibitor has increased the risk of lymphoma and other malignancies, excluding non-melanoma skin cancer (NMSC), (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which VONJO is not indicated. Patients who are current or past smokers are at additional increased risk.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with VONJO, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers.

Risk of Infection: Another JAK inhibitor has increased the risk of serious infections (compared to best available therapy) in patients with myeloproliferative neoplasms. Serious bacterial, mycobacterial, fungal, and viral infections may occur in patients treated with VONJO. Delay starting therapy with VONJO until active serious infections have resolved. Observe patients receiving VONJO for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines.

DRUG INTERACTIONS

Effect of Other Drugs on VONJO: VONJO is predominantly metabolized by CYP3A4. Coadministration of VONJO with strong CYP3A4 inhibitors or inducers are contraindicated. Avoid concomitant use of VONJO with moderate CYP3A4 inhibitors or inducers.

Effect of VONJO on Other Drugs: VONJO is an inhibitor of CYP1A2, CYP3A4, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic cation transporter 1 (OCT1) in vitro. Concomitant administration of VONJO with these substrates may increase their plasma concentrations. Avoid coadministration of VONJO with drugs that are sensitive substrates of CYP1A2, CYP3A4, P-gp, BCRP, or OCT1.

ADVERSE REACTIONS

Fatal adverse reactions occurred in 8% of patients receiving VONJO 200 mg twice daily and in 9% of patients treated with best available therapy (BAT). The fatal adverse reactions among patients treated with VONJO 200 mg twice daily included events of disease progression (3%), and multiorgan failure, cerebral hemorrhage, meningorrhagia, and acute myeloid leukemia in <1% of patients each, respectively.

Serious adverse reactions occurred in 47% of patients treated with VONJO 200 mg twice daily and in 31% of patients treated with BAT. The most frequent serious adverse reactions occurring in ≥3% patients receiving VONJO 200 mg twice daily were anemia (8%), thrombocytopenia (6%), pneumonia (6%), cardiac failure (4%), disease progression (3%), pyrexia (3%), and squamous cell carcinoma of skin (3%).

Permanent discontinuation due to an adverse reaction occurred in 15% of patients receiving VONJO 200 mg twice daily compared to 12% of patients treated with BAT. The most frequent reasons for permanent discontinuation in ≥2% of patients receiving VONJO 200 mg twice daily included anemia (3%) and thrombocytopenia (2%).

The most common adverse reactions in ≥20% of patients (N=106) were diarrhea, thrombocytopenia, nausea, anemia, and peripheral edema.

USE IN SPECIFIC POPULATIONS

Pregnancy: There are no available data on VONJO use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Advise pregnant women of the potential risk to a fetus. Consider the benefits and risks of VONJO for the mother and possible risks to the fetus when prescribing VONJO to a pregnant woman.

Lactation: There are no data on the presence of pacritinib in either human or animal milk, the effects on the breastfed child, or the effects on milk production. It is not known whether VONJO is excreted in human milk. Because of the potential for serious adverse reactions in the breastfed child, advise patients that breastfeeding is not recommended during treatment with VONJO, and for 2 weeks after the last dose.

Infertility: Pacritinib reduced male mating and fertility indices in BALB/c mice. Pacritinib may impair male fertility in humans.

Pediatric Use: The safety and effectiveness of VONJO in pediatric patients have not been established.

Hepatic Impairment: Administration of a single dose of VONJO 400 mg to subjects with hepatic impairment resulted in a decrease in the geometric mean area under the concentration curve (AUC) of pacritinib by 8.5%, 36%, and 45% in subjects with mild [Child-Pugh A], moderate [Child-Pugh B], or severe hepatic impairment [Child-Pugh C], respectively, compared to subjects with normal hepatic function. Avoid use of VONJO in patients with moderate [Child-Pugh B] or severe hepatic impairment [Child-Pugh C].

Renal Impairment: Administration of a single dose of VONJO 400 mg to subjects with renal impairment resulted in approximately 30% increase in maximal concentration (C_{max}) and AUC of pacritinib in subjects with eGFR 15 to 29 mL/min and eGFR <15 mL/min on hemodialysis compared to subjects with normal renal function (eGFR ≥90 mL/min). Avoid use of VONJO in patients with eGFR <30 mL/min.

Please see the full Prescribing Information enclosed inside.

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