NEW DRUG APPROVAL

Brand Name	Vonjo™
Generic Name	pacritinib
Drug Manufacturer	CTI BioPharma Corp

New Drug Approval

FDA approval date: February 28, 2022

Review designation: Priority; Orphan

Type of review: Type 1 - New Molecular Entity; New Drug Application (NDA): 208712

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Myelofibrosis is a rare type of blood cancer in which the bone marrow (the soft, spongy tissue inside most bones) is replaced by fibrous scar tissue. It is considered a form of chronic leukemia. When myelofibrosis occurs on its own, it is called primary myelofibrosis. If it occurs as the result of a separate disease, it is known as secondary myelofibrosis (e.g., scar tissue in the bone marrow as a complication of an autoimmune disease).

The disease typically presents with anemia and other cytopenias, splenomegaly, and constitutional symptoms. It is diagnosed through assessment of the bone marrow; classic changes include the development of reticulin fibrosis.

In the most comprehensive epidemiologic study to date, the rate of incidence of myelofibrosis (MF) (including primary MF, Post-PV MF and Post-ET MF) was about 1.1 cases of MF per 100,000 adults per year in the US. Median survival is about 5-6 years from diagnosis and the disease typically affects the elderly with a median age at diagnosis of 65 years, although MF can occur at any age.

Males have a higher risk of MF with about 63% of new cases being diagnosed in male patients. High-risk characteristics include unfavorable karyotype (15%), thrombocytopenia at diagnosis (28%), and requiring blood transfusions at the time of referral to a treatment center (39%).

MF also has a 10-year risk of about 20% of conversion to a more aggressive disease such as acute myeloid leukemia (AML).

Efficacy

PERSIST-2

The efficacy of Vonjo™ in the treatment of patients with intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) MF was established in the PERSIST-2 trial. PERSIST-2 enrolled patients with intermediate or high-risk primary or secondary (postpolycythemia vera or post-essential thrombocythemia) MF with splenomegaly and a platelet count ≤100 × 109 /L. Both JAK2 naïve patients and patients with prior JAK2 inhibitor therapy were included. Patients were randomized 1:1:1 to receive Vonjo™ 400 mg once daily, Vonjo™ 200 mg twice daily, or best available therapy (BAT). BAT agents could be used alone, in combinations, sequentially, and intermittently, as clinically indicated by standards of care. BAT included any physician-selected treatment for MF and may have included ruxolitinib, hydroxyurea, glucocorticoids, erythropoietic agents, immunomodulatory agents, mercaptopurine, danazol, interferons, cytarabine, melphalan. BAT also included no treatment (“watch and wait”) or symptom-directed treatment without MF-specific treatment. In this trial, 311 patients were randomized to receive Vonjo™ 400 mg once daily (n=104), Vonjo™ 200

mg twice daily (n=107), or BAT (n=100). The Vonjo™ dose of 400 mg once daily was not established as safe and is not an approved dosage regimen. The demographic characteristics of the efficacy population were median age of 68 years (range 32 to 91), 55% male, 86% Caucasian, and 14% non-Caucasian. The Vonjo™ and BAT treatment arms were well balanced with respect to age, gender, race, ethnicity, body mass index, and geographic region. Sixty-eight percent of patients had primary MF, 20% had post-polycythemia vera MF, and 12% had post-essential thrombocythemia MF. Forty-six percent and 51% of patients in the Vonjo™ and BAT treatment arms, respectively, had received prior ruxolitinib therapy. The median baseline hemoglobin level was 9.5 g/dL and 23% of patients were red blood cell (RBC) transfusion dependent at study entry. The median baseline platelet count was 55 × 109 /L; 45% of patients had a platelet count< 50 × 109 /L. Patients had a baseline median spleen length of 14 cm assessed by magnetic resonance imaging (MRI) or computerized axial tomography (CAT). Efficacy was established in patients who received Vonjo™ 200 mg twice daily and had a platelet count< 50 x 109 (N=31).

The most common agents used in the BAT treatment arm in patients with baseline platelet counts<50 50 × 109 /L (N=32) were ruxolitinib (39%), watchful waiting (32%), and hydroxyurea (26%).

Spleen Volume Reduction

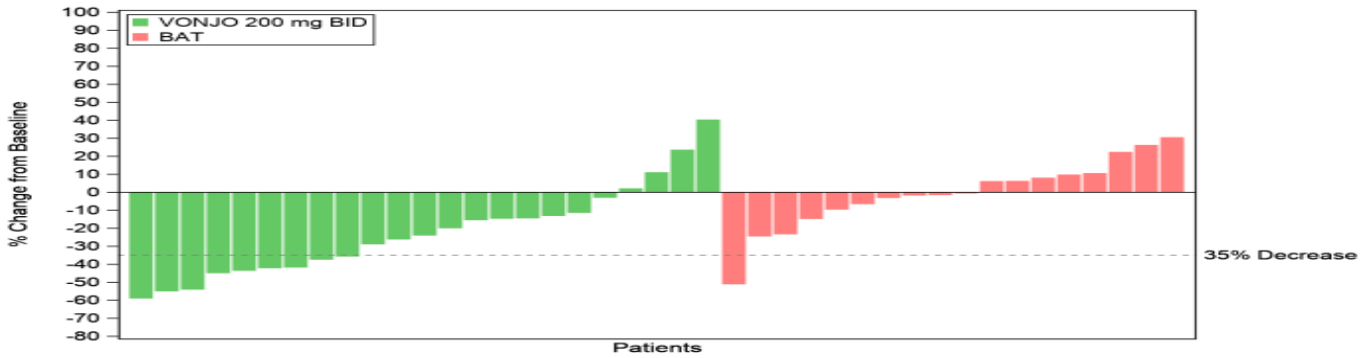
The efficacy of Vonjo™ in the treatment of patients with primary or secondary MF was established based upon the proportion of patients in the efficacy population receiving Vonjo™ 200 mg twice daily or BAT achieving ≥35% spleen volume reduction from baseline to Week 24 as measured by magnetic resonance imaging or computed tomography. Efficacy results for spleen volume reduction in patients with a platelet count.

Table 1: Percentage of Patients Achieving ≥35% Reduction in Spleen Volume from Baseline to Week 24 in the Phase 3 Study, PERSIST-2 (Efficacy Population)

Patient Population	VONJO 200mg Twice Daily N=31	Best Available Therapy N=32
Baseline Platelets <50 × 10^9/L	9 (29.0%)	1 (3.1%)
95% Confidence Interval (CI)	14.2, 48.0	0.1, 16.2
Difference (VONJO-BAT) 95% CI	25.9 (4.3,44.5)	

A waterfall plot of the percentage of change in spleen volume from baseline to Week 24 is presented in Figure 1 for the PERSIST-2 patients with baseline platelet counts.

Figure 1 Waterfall Plot of Median Percent Change From Baseline in Spleen Volume at Week 24 in Patients With <50 × 10^9/L Platelet Counts in PERSIST-2[a]



[a]Dropout rates in VONJO and BAT arms were 26% and 44%, 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%). Fatal adverse reactions occurred in 8% of patients receiving Vonjo™ 200 mg twice daily and in 9% of patients treated with 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.

Safety

ADVERSE EVENTS

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

WARNINGS & PRECAUTIONS

- Hemorrhage: Avoid use in patients with active bleeding and hold Vonjo™ prior to any planned surgical procedures. May require dose interruption, dose reduction or permanent discontinuation depending on severity.
- Diarrhea: Manage significant diarrhea with anti-diarrheals, dose reduction, or dose interruption.
- Thrombocytopenia: Manage by dose reduction or interruption.
- Prolonged QT Interval: Avoid use in patients with baseline QTc >480 msec. Interrupt and reduce Vonjo™ dosage in patients who have a QTcF >500 msec. Correct hypokalemia prior to and during Vonjo™ administration.
- Major Adverse Cardiac Events (MACE): Risk may be increased in current/past smokers and patients with other cardiovascular risk factors. Monitor for signs, evaluate and treat promptly.
- Thrombosis: Including deep venous thrombosis, pulmonary embolism, and arterial thrombosis may occur. Monitor for signs, evaluate and treat promptly.
- Secondary Malignancies: Lymphoma and other malignancies may occur. Past/current smokers may be at increased risk.
- Risk of Infection: Delay starting Vonjo™ until active serious infections have resolved. Observe for signs and symptoms of infection and manage promptly.

CONTRAINDICATIONS

Concomitant use of strong CYP3A4 inhibitors or inducers.

Clinical Pharmacology

MECHANISMS OF ACTION

Pacritinib is an oral kinase inhibitor with activity against wild type Janus associated kinase 2 (JAK2), mutant JAK2V617F, and FMS-like tyrosine kinase 3 (FLT3), which contribute to signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. MF is often associated with dysregulated JAK2 signaling. Pacritinib has higher inhibitory activity for JAK2 compared to JAK3 and TYK2. At clinically relevant concentrations, pacritinib does not inhibit JAK1. Pacritinib exhibits inhibitory activity against additional cellular kinases (such as CSF1R and IRAK1) the clinical relevance of which is unknown

Dose & Administration

ADULTS

200 mg orally twice daily.

PEDIATRICS

Safety and effectiveness in pediatric patients have not been established.

GERIATRICS

N/A

RENAL IMPAIRMENT

No dosage adjustments are needed. eGFR less than 30 mL/min: Use not recommended.

HEPATIC IMPAIRMENT

No dosage adjustments are needed. eGFR less than 30 mL/min: Use not recommended.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Capsules: 100 mg