CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208712Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	208712
PDUFA Goal Date	11/30/2021
OSE RCM #	2016-114
Reviewer Name(s)	Ingrid N. Chapman, Pharm.D., BCPS[a]
Team Leader	Naomi Boston, Pharm.D.
Associate Director for REMS Design and Evaluation	Laura Zendel, Pharm.D., BCPS
Review Completion Date	November 29, 2021
Subject	Evaluation of Need for a REMS
Established Name	Pacritinib
Trade Name	Vonjo
Name of Applicant	CTI BioPharma Corp
Therapeutic Class	Kinase Inhibitor
Formulation(s)	100 mg capsules for oral administration
Dosing Regimen	200 mg by mouth twice daily

[a] At the time of this review Dr. Chapman was on extended leave from the Agency.

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity, (NME) Vonjo (pacritinib) is necessary to ensure the benefits outweigh its risks. CTI BioPharma Corp. submitted a New Drug Application (NDA) 208712 for pacritinib with the proposed indication: for the treatment of adult patients with intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis. The FDA approved indication will be: for the treatment of adults with intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF) with a platelet count below 50×10^9/L. This indication will be approved under accelerated approval based on spleen volume reduction (SVR). The serious risks determined to be associated with pacritinib include diarrhea, thrombocytopenia, and hemorrhage. The Applicant did not submit a proposed REMS or risk management plan with this application.

The Division of Risk Management (DRM) and the Division of Nonmalignant Hematology (DNH) agree that a REMS is not needed to ensure the benefits of pacritinib outweigh its risks. The efficacy of pacritinib in the indicated patient population was established based on 29% (n = 9) of patients achieving a reduction in SVR greater than or equal to 35%, compared to 3.1% (n = 1) of patients in the best available therapy (BAT) group which was statistically significant. However, the Applicant's clinical trial did not meet statistical significance with the prespecified secondary endpoint, a reduction in Total Symptom Score (TSS) by week 24. Pacritinib at a dose of 200 mg twice daily meets accelerated approval criteria based on the potential to address an unmet medical need in patients with intermediate or high-risk primary or secondary MF that have a platelet count below 50×10^9/L. A confirmatory trial will be required to provide clear evidence for the effect of pacritinib 200mg twice daily for SVR and TSS.

Pacritinib will primarily be prescribed by hematologists and oncologists. These prescribers will likely have experience in monitoring and managing the adverse events of diarrhea, thrombocytopenia, and hemorrhage seen with pacritinib therapy. These risks will be addressed in the warnings and precautions section of the pacritinib prescribing information, and in the patient information, which will assist with communicating the risks to patients.

1 Introduction

This review evaluates whether a REMS for the NME, Vonjo (pacritinib) is necessary to ensure the benefits outweigh its risks.[b] CTI BioPharma Corp., submitted a NDA 208712 for pacritinib with the proposed indication: for the treatment of adult patients with intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis.[1] The FDA approved indication will be: for the treatment of adults with intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF) with a platelet count below 50×10^9/L.[2] This application is under review in the DNH. The Applicant did not submit a proposed REMS or risk management plan with this application.

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

2 Background

2.1 PRODUCT INFORMATION

Vonjo (pacritinib), a NME, is an oral kinase inhibitor with activity against wild type Janus Associated Kinase 2 (JAK2), mutant JAK2, and FMS-like tyrosine kinase 3 (FTL3).[2] Pacritinib inhibits the phosphorylation of signal transducer and activator of transcription 5 (STAT5) proteins in a dose-dependent manner in patients expressing the JAK2 mutation.[2] Pacritinib will be available as 100 mg capsules for oral administration with a recommended dose of 200mg orally twice daily. The FDA approved indication will be for the treatment of adults with intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF) with a platelet count below 50×10^9/L. Treatment with pacritinib is continued as long as clinical benefit is observed or until unacceptable toxicity occurs.[c] Pacritinib is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 208712 relevant to this review:

- 08/05/2014: Fast Track Designation granted for pacritinib under IND 078406 for the treatment of intermediate and high-risk myelofibrosis.
- 03/30/2021: The final rolling submission for NDA 208712, pacritinib, for the treatment of intermediate and high-risk myelofibrosis was received.
- 08/13/2021: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. There were no discussions of safety issues that may require a REMS for pacritinib.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Myelofibrosis (MF), a type of chronic myeloproliferative neoplasm, is a rare condition in which the bone marrow is replaced by fibrous scar tissue.[3] The pathogenesis of this disease is based primarily on hyperactivation of the Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathway. This causes uncontrolled myeloproliferation and abnormal release of proinflammatory cytokines.[4] Most patients with MF carry mutations in three "driver" genes, with JAK2 mutations seen in 60% of cases.[4] Primary myelofibrosis (PMF) occurs in approximately 1.5 cases per 100,000 people in the U.S. annually.[d] PMF occurs mainly in middle aged and older adults with the median age at presentation being 67 years.[3] If MF is the result of a separate disease (i.e., polycythemia vera or essential thrombocytopenia), it is referred to as secondary MF. Patients who present with secondary MF (more commonly known as post-PV and Post-ET MF) may exhibit a substantially different disease compared to patients with PMF in terms of clinical presentation, cytogenetic abnormalities, molecular background, and prognosis. The clinical manifestations of MF is most often characterized by progressive

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

splenomegaly,[4] and may include other clinical symptoms such as anemia, thrombocytopenia, hepatomegaly, portal hypertension, thrombotic events, fever, night sweats, severe fatigue, bone and joint tenderness/pain. People with PMF are at risk for premature death due to disease progression, leukemic transformation, thrombo-hemorrhagic complications, and infections.[5,e]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

There are various tools used to determine risk stratification (prognosis) for patients with MF. This is important as management of PMF and secondary MF is informed by risk stratification and the presence of symptoms. Non-pharmacologic treatment for MF includes allogeneic hematopoietic cell transplantation. For patients with higher-risk PMF (poor prognosis), transplantation can prolong survival and offers the possibility of cure for patients who are medically eligible. [6]

Selection of pharmacologic therapy is based on the patient's symptoms, blood counts, kidney and liver function, preference, and the clinician's experience. Ruxolitinib (Jakafi) and fedratinib (Inrebic) are the two FDA-approved treatment options for myelofibrosis. Hydroxyurea is often prescribed off-label to relieve moderate splenomegaly and other proliferative manifestations (thrombocytosis and leukocytosis) but is less efficacious than FDA-approved treatment options ruxolitinib and fedratinib. Both ruxolitinib and fedratinib can further lower the level of platelets, thereby requiring dosing interruptions and modification for patients with platelet counts less than 50×10^9/L. Therefore, there is an unmet medical need for an effective therapy for patients with MF who have platelet counts below 50×10^9/L. [7] See Table 1 for further details on the FDA-approved therapies for MF.

Table 1:[7,9,9] FDA-Approved Therapies for the Treatment of Myelofibrosis

Drug (Approval Date)	Indication	Dosing and Administration	Important Safety & Tolerability Issues	Risk Management Approaches
Jakafi – ruxolitinib[8] (11/16/2011)	Treatment of intermediate or high-risk myelofibrosis in adults, including primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis.	Initial dosage: 5 mg to 20 mg by mouth twice daily (based on platelet count) Maximum dose: 25 mg by mouth twice daily.	**Warnings & Precautions** Hematologic toxicity Infections Withdrawal syndrome Lipid abnormalities Cardiac effects Thrombosis Secondary malignancy	Labeling – Warnings & Precautions and Patient Information

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

Inrebic – fedratinib[9] (08/16/2019)	Treatment of intermediate-2 or high-risk primary or secondary (post polycythemia vera or post-essential thrombocythemia) myelofibrosis in adults.	400 mg by mouth once daily (in patients with a baseline platelet count ≥50,000/mm^3)	**Boxed Warning** Encephalopathy, including Wernicke Encephalopathy **Warnings & Precautions** Encephalopathy Hematologic toxicity Gastrointestinal toxicity Hepatoxicity	Labeling – Boxed Warning, Warnings & Precautions and Medication Guide

4 Benefit Assessment

The efficacy of pacritinib for the treatment of patients with intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocytopenia) MF was demonstrated in PERSIST-2 (PAC326; NCT # NCT02055781). PERSIST-2 was a Phase 3, global, multicenter (96 study sites), randomized, controlled study of 311 patients receiving pacritinib 400mg once daily (n = 104), pacritinib 200mg twice daily (n = 107), and best available therapy (BAT, n = 100). BAT included any physician-selected treatment for MF based on the current standard of care for this disease and may have included watch and wait or symptom-directed treatment, single or combination therapy.[2,10] The study enrolled patients with intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) MF with baseline platelet counts ≤100 × 10^9/L. This study also included JAK2 treatment naïve and JAK2 treatment experienced patients.[10]

Of note, enrollment was stopped early in patients randomized to receive the 400mg once daily dose of pacritinib due to a clinical hold that resulted from discovery of a numerical disadvantage in on-study deaths in the 400 mg once daily arm in the PERSIST-1 trial. In addition, the 200 mg twice daily dose of pacritinib was found to be numerically superior in efficacy compared to the 400 mg once daily dose; likely driven by higher rates of dose interruptions and reductions seen in the 400mg once daily arm.[10]

Of the 311 patients included in PERSIST-2, 63 of these patients had baseline platelet counts less than 50x10^9/L. The efficacy and safety of pacritinib was established in this subset of the randomized population, in which patients either received pacritinib 200 mg twice daily (n = 31) or BAT (n = 32).[2,10] Common treatments in the BAT arm included ruxolitinib (39%), watchful waiting (32%), and hydroxyurea (26%).[2] The efficacy of pacritinib was based on the proportion of patients in the efficacy population who achieved ≥35% spleen volume reduction from baseline by week 24 as measured by magnetic resonance imaging or computed tomography.[2] The prespecified secondary endpoint was a reduction in Total Symptom Score (TSS) by week 24.

Twenty-nine percent (n = 9) of patients receiving pacritinib 200 mg twice daily achieved ≥35% reduction in SVR from baseline to the 24th week compared to 3.1% (n = 1) in the BAT group. This result was statistically significant. Twenty-six percent (n = 8) of patients in the pacritinib arm had a reduction of ≥50% reduction in their TSS from baseline to the 24th week of therapy compared to 9% (n = 3) of patients in the BAT group. This result did not reach statistical significance.[10]

TSS is an established measure of the benefit of therapy in patients with MF, while SVR only implies a

benefit.[10] Since statistical significance was only achieved in the SVR endpoint, the clinical review team will grant accelerated approval for pacritinib 200 mg twice daily in the indicated population. A confirmatory trial will be required to provide clear evidence for the effect of pacritinib 200mg twice daily for SVR and TSS.[10]

5 Risk Assessment & Safe-Use Conditions

The safety profile of pacritinib was derived from the PERSIST-2 study (n = 106), which includes all patients who received pacritinib 200 mg by mouth twice daily. The 400 mg once daily dose of pacritinib was not established to be safe due to higher rates of deaths associated with bleeding, congestive heart failure and cardiac arrest. No further information on this cohort of patients is provided.[2,10] Fifty-four percent of the patients in the 200 mg twice daily cohort completed at least 24 weeks of pacritinib therapy. Serious adverse reactions were reported in 47% of patients receiving pacritinib with the most frequent being anemia (9%), thrombocytopenia (6%), cardiac failure (4%), pyrexia (4%), and squamous cell carcinoma of skin (3%).[2,10] Fatal adverse reactions occurred in 8% of patients receiving pacritinib and included disease progression, multiorgan failure, central nervous system lesion, cerebral hemorrhage, menorrhagia, and acute myeloid leukemia.[2,10]

Key risks associated with pacritinib 200 mg twice daily include diarrhea, thrombocytopenia, and bleeding events (hemorrhage).[10,f] These risks will be communicated in the warnings and precautions section of the prescribing information.

5.1 DIARRHEA

Diarrhea was reported in approximately 48% of patients receiving pacritinib, with a median time to resolution of 2 weeks. Forty-one percent of patients reported diarrhea in the first 8 weeks of treatment, 15% in weeks 8 through 16, and 8% in weeks 16 through 24. Recommendations are to manage diarrhea with antidiarrheal medications, fluid replacement, and to interrupt or modify the dose of pacritinib.[2]

5.2 THROMBOCYTOPENIA

Thrombocytopenia of Grade 3 and higher occurred in 34% of patients receiving pacritinib. This included patients with pre-existing moderate to severe thrombocytopenia. Recommendations in the prescribing information are to interrupt pacritinib therapy in patients with clinically significant or worsening of thrombocytopenia that lasts for more than seven days (b) (4).[2]

5.3 HEMORRHAGE

Serious (11%) and fatal (2%) hemorrhages occurred in pacritinib-treated patients; bleeding events occurred in 15% of patients.[2] Recommendations are to avoid pacritinib use in patients with active bleeding and to hold pacritinib seven days prior to any planned surgical or invasive procedures. In addition, platelet counts should be assessed periodically as clinically indicated.

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

6 Expected Postmarket Use

Pacritinib will be prescribed primarily in the outpatient setting. Hematologists and oncologists will be the primary prescribers of pacritinib. These prescribers are likely familiar with managing patients with MF, as well as the associated adverse events that may occur with treatment such as diarrhea, thrombocytopenia and hemorrhage.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities beyond labeling and routine pharmacovigilance for pacritinib.

8 Discussion of Need for a REMS

When evaluating the need for a REMS, factors such as the seriousness of disease, the estimated patient population, current treatment options, the expected benefit, the potential risks, as well as the possible prescribing population are taken into consideration.

Myelofibrosis (MF), a type of chronic myeloproliferative neoplasm, is a rare condition in which the bone marrow is replaced by fibrous scar tissue with primary clinical features of splenomegaly, thrombocytopenia, and other clinical symptoms that can severely impact a patient's quality of life. Patients presenting with more advanced forms of MF such as secondary MF are at risk for premature death due to disease progression, leukemic transformation, thrombo-hemorrhagic complications, and infections. Primary myelofibrosis (PMF) occurs in approximately 1.5 cases per 100,000 people in the U.S. annually. FDA-approved treatment options include ruxolitinib and fedratinib. Both ruxolitinib and fedratinib can further lower the level of platelets, thereby requiring dosing interruptions and modification for patients with platelet counts less than 50×10^9/L. Hydroxyurea is often prescribed off-label to relieve moderate splenomegaly and other proliferative manifestations (thrombocytosis and leukocytosis) but is less efficacious than FDA-approved treatment options. In some patients, a watch and wait approach is used to prevent exposure to adverse events that may be associated with MF therapy.

In the pivotal trial for pacritinib, PERSIST-2, 29% (n = 9) of patients receiving pacritinib 200 mg orally twice daily achieved a statistically significant $\geq$35% reduction in SVR from baseline to the 24th week of therapy compared to 3.1% (n = 1) in the BAT group. Twenty-six percent (n = 8) of patients in the pacritinib arm had a reduction of $\geq$50% reduction in their TSS from baseline to the 24th week of therapy compared to 9% (n = 3) of patients in the BAT group. This result did not reach statistical significance.

The review team recommends accelerated approval for pacritinib based on the results of the PERSIST-2 trial. TSS is an established measure of the benefit of therapy in patients with MF, while SVR only implies a benefit.[10] Since statistical significance was only achieved in the SVR endpoint, the clinical review team will only grant accelerated approval for pacritinib 200 mg twice daily in the indicated population. A post marketing requirement (PMR) for a confirmatory trial will be required to provide clear evidence for the effect of pacritinib 200mg twice daily for SVR and TSS. The trial results showed a benefit for therapy, and

provides an unmet medical need in patients with intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocytopenia) MF with baseline platelet counts below 50 x 10^9/L.

Key risks associated with pacritinib 200 mg twice daily include diarrhea, thrombocytopenia, and bleeding events (hemorrhage). The pacritinib label will not include a boxed warning for any risk. The key risks identified will be addressed in the warnings and precautions section of the prescribing information, as well as in the patient information section to communicate these risks to patients. Hematologists and oncologists will likely be the primary prescribers for pacritinib. The keys risks associated with pacritinib therapy are not any that are new or unusual seen in therapy for MF. These prescribers will likely be familiar with monitoring and managing the adverse events associated with pacritinib therapy.

Based on the available data and the consideration of factors for determining the need for a REMS, this reviewer recommends that a REMS is not necessary for the approval of pacritinib.

9 Conclusion

Based on the available data from the prescribing information and from the integrated review, DRM and DNH agree that a REMS is not necessary for pacritinib to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 REFERENCES

[1] CTI BioPharma Corp. Vonjo (pacritinib). NDA 208712. Prescribing Information, draft. March 30, 2021

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