CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202192Orig1s000

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA/BLA # **Supplement #**	202192
Applicant Name	Incyte Corporation
Date of Submission	June 3, 2011
PDUFA Goal Date	December 4, 2011
Proprietary Name / **Established (USAN) Name**	Jakafi™/ruxolitinib phosphate
Dosage Forms / Strength	5 mg, 10 mg , 15 mg, 20 mg, and 25 mg
Proposed Indications	Jakafi is a kinase inhibitor indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Albert Deisseroth, M.D., Ph.D.
Statistical Review	Hong Lu, Ph.D., Mark Rothman, Ph.D., Rajeshwari Sridhara, Ph.D.
Pharmacology Toxicology Review	Wei Chen, Ph.D., Haleh Saber, Ph.D.
ONDQA – CMC and Biopharmaceutic Reviews	Tien Mien Chen, Ph.D., Sue-Ching Lin, Ph.D., Joyce Crich, Ph.D., Janice Brown, Ph.D., Richard T. Lostritto, Ph.D.
Microbiology Review	John Metcalfe, Ph.D.
Clinical Pharmacology Review	Joe Grillo, Pharm.D., Jian Wang, Pharm.D., Julie Bullock, Pharm.D.
OPDP/DDTCP	Adora E. Nu, James Dvorsky
OSI/DGCPC	Anothony Orencia, M.D., Lauren Iacono-Connors, Ph.D., Jean Mulinde, M.D.
OMPI/DMPP	Latonia Ford, BSN, MBA, LaShawn M. Griffiths, BSN, MSHS-PH
OSE/DMEPA	Lissa Owens, Pharm.D., Carlos Mena-Grillasca, RPh, Carol Holquist, RPh
IRT/QT	Qianyu Dang, Joanne Zhang, Jeffry Florian, Monica L. Fiszman, Norman L. Stockbridge, M.D.

OND=Office of New Drugs
ONDQA=Office of New Drug Quality Assessment
OPDP/DDTCP=Office of Prescription Drug Promotion/Division of Direct-to-Consumer Promotion
OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance
OMPI/DMPP=Office of Medical Policy Initiatives/Division of Medical Policy Programs
OSE/DMEPA= Office of Surveillance and Epidemiology/ Division of Medication Error Prevention and Risk Management
IRT/QT=Interdisciplinary Review Team for QT Studies
CDTL=Cross-Discipline Team Leader

1. Introduction

Jakafi™ (ruxolitinib) is the first of a new class of kinase inhibitors (JAK1 and JAK2 kinases) that signal pathways involved in myeloid cell proliferation. It is the first therapeutic agent that decreases splenomegaly and ameliorates symptoms in primary or secondary myelofibrosis. This NDA is supported by results of trials that enrolled patients with myelofibrosis who needed treatment (intermediate-2 risk and high risk classifications).

2. Background

Approximately 455 patients with myelofibrosis and 162 patients with other diseases (polycythemia vera, essential thrombocythemia, multiple myeloma, and prostate cancer) have been been treated with ruxolitinib. Primary myelofibrosis is a chronic myeloproliferative disorder of unknown etiology characterized by progressive bone marrow fibrosis, extramedullary hematopoiesis, a leukoerythroblastic peripheral blood picture, splenomegaly, hepatomegaly and constitutional symptoms. JAK2 mutations have been described in about 50% of patients. This NDA, which was submitted on June 3, 2011, contains the results of two large, randomized trials with reduction of splenomegaly as the primary endpoint. A key secondary endpoint in the primary double-blinded trial was reduction of myelofibrosis-associated symptoms.

3. CMC

The CMC review team recommends that this application be approved with acceptability of the manufacturing of the drug product and drug substance. Stability testing supports an expiry of 24 months when stored at USP controlled room temperature of 20-25°C (68-77°F); excursions are permitted to 15-30°C (59-86°F). Additionally, the microbiology reviewer has concluded that there are no outstanding microbiology or sterility issues that preclude approval.

4. Nonclinical Pharmacology/Toxicology

There are no pharmacology/toxicology issues that preclude the approval of ruxolitinib. Toxicities were mostly related to pharmacology of the drug, with lymphoid depletion, and reduced size of thymus and spleen being the primary adverse effects. When administered during the period of organogenesis, ruxolitinib was not teratogenic to rats or rabbits. Reduced fetal weight and/or increased post-implantation loss were seen in animals only at doses that resulted in maternal mortalities. In a designated fertility study, ruxolitinib did not impair male or female fertility but resulted in increased post-implantation loss.

Ruxolitinib was not genotoxic when tested *in vitro* or *in vivo* for mutagenic or clastogenic potential. When tested in a 6-month carcinogenicity study in Tg.rasH2 transgenic mouse, ruxolitinib was not carcinogenic. A 2-year carcinogenicity study in rat is ongoing. Considering the results of reproduction toxicology studies together with the negative results reported in the genetic toxicology studies, the Applicant's proposed Category C for pregnancy is acceptable.

5. Clinical Pharmacology

The Clinical Pharmacology team recommended approval, and there are no issues that would preclude approval from this discipline. Food does not affect ruxolitinib exposure. Ruxolitinib is eliminated almost completely by oxidative metabolism (primarily by CYP3A4) with a terminal elimination half-life of approximately 3 hours (5.8 hours for ruxolitinib plus metabolites). Active metabolites contribute approximately 18% of the overall ruxolitinib activity. Ruxolitinib and its M18 metabolite are unlikely inhibitors of the major CYP and transporter pathways.

Ruxolitinib is not a potent inducer of CYP isozymes and an unlikely P-gp substrate. Ruxolitinib dose should be adjusted for thrombocytopenia, hepatic impairment and moderate or severe renal impairment.

6. Clinical/Statistical-Efficacy

This NDA is supported by two randomized controlled trials in patients with intermediate or high risk myelofibrosis comparing ruxolitinib to placebo (Study 1) or to best available therapy (Study 2).

Study 1 was a double-blind, randomized, placebo-controlled study allocating 309 patients (1:1) to either ruxolitinib (15-20 mg orally twice daily) or placebo. Fifty percent of patients had primary myelofibrosis, 31% post-polycythemia vera myelofibrosis and 18% post-essential thrombocythemia myelofibrosis. Study 2 was an open-label trial allocating 219 patients (2:1) to either ruxolitinib (15-20 mg orally twice daily) or best available therapy. Fifty-three percent of patients had primary myelofibrosis, 31% post-polycythemia vera myelofibrosis, and 16% post-essential thrombocythemia myelofibrosis. The ruxolitinib starting dose in both trials was based on the entry platelet counts.

Ruxolitinib treatment in both trials continued as long as the patients continued to benefit or until unacceptable toxicity. The primary endpoint was a comparison of the proportion of patients in the two arms who achieved a ≥35% reduction in spleen volume (by CAT scan or MRI) after 24 weeks (Study 1) or after 48 weeks of treatment (Study 2)

Both randomized trials achieved their pre-specified primary endpoints. In Study 1, 42% versus 1% of patients on the ruxolitinib and placebo arms, respectively, experienced a ≥ 35% reduction of spleen volume at 24 weeks ($p<0.0001$, Chi-square and Fisher's exact test). In Study 2, 29% versus 0% of patients on the ruxolitinib and best available therapy arms, respectively, experienced a ≥ 35% reduction of spleen volume at 48 weeks ($p<0.0001$, Cochran-Mantel-Haenszel test).

The key secondary endpoint for Study 1 was to determine the difference between the proportion of patients on ruxolitinib versus placebo who experienced ≥50% reduction of a total symptom score. This symptom score evaluated abdominal discomfort, pain under left ribs, night sweats, itching, bone/muscle pain and early satiety at 24 weeks compared to baseline. The percentage of patients who achieved a ≥50% reduction of the total symptom score at 24 weeks was 46% versus 5% on the ruxolitinib and placebo arms, respectively ($p<0.0001$, Chi-square test).

The key secondary endpoint on Study 2 was to determine the difference between the two arms in the proportion of patients who achieved a ≥35% reduction in spleen volume (by CAT scan or MRI) at 24 weeks of treatment. A ≥35% reduction in spleen volume occurred in 32% of the patients on the ruxolotinib arm and 0% on the best available therapy arm ($p <0.0001$, Chochran-Mantel-Haenszel test). At the time of approval, 75% of the patients on Study 1 and 67% on Study 2 who achieved a ≥35% reduction in spleen volume maintained this reduction in spleen volume.

The results of Study 1 and Study 2 are shown in Tables 1 and 2 below.

Table 1-Efficacy Results for Study 1 (INCB-351)

Treatment Arm	Ruxolitinib	Placebo	P value
Patients Randomized	N=155	N=154	
Primary Endpoint	N=155	N=153	

% SVR ≥35% at week 24	41.9%	0.7%#	P<0.0001*
Key Secondary Endpoint	N=148&	N=154	
%↓TSS by ≥50% week 24	45.9%	5.3%	P<0.0001**

*By Fisher's exact test; ** by Chi-square test; &NR=data not recorded or available.
This patient died (105-002) from disease progression 4 days after this measurement. It was not determined if this patient had a splenic infarct which could have accounted for the rapid reduction in the splenic volume in this patient.

Table 2-Outcome of Primary and Key Secondary Endpoint for Study 2 (INCB-352)

	Ruxolitinib	BAT*	P-value
Number randomized	N=146	N=73	
Primary Endpoint: % SVR ≥35% at 48 weeks	29%	0%	<0.0001
Key Secondary Endpoint: % SVR ≥35% at 24 weeks	32%	0%	<0.0001

*Best available therapy.

7. Safety

A total of 617 patients had been exposed to ruxolitinib; however, only patients with MF (509) were reviewed for safety. Patients with prostate cancer, multiple myeloma, polycythemia vera, and essential thrombocythemia were omitted from this analysis. The median duration of continuous therapy in patients initially started on ruxolitinib in the two Phase 3 trials and all Phase 2 trials was 14.8 months.
Among adverse reactions, thrombocytopenia and anemia require close monitoring and treatment. The degree of thrombocytopenia was used to determine the starting dose and for dose adjustments. Platelet transfusions were administered to 4.7% of patients receiving ruxolitinib and to 4.0% of patients receiving placebo. RBC transfusions were administered to 60% of patients treated with ruxolitinib and 38% receiving placebo. Neutropenia resulted in ruxolitinib discontinuation or dose reduction in 1.0% of patients. Headaches, dizziness and confusion were more common in ruxolitinib-treated patients.

Elevations of ALT, AST and cholesterol were more common in ruxolitinib-treated patients than in placebo controls. They were mostly Grade 1.

The most common adverse drug reactions observed in ≥1% of the patients treated with ruxolitinib included thrombocytopenia, anemia, bruising, dizziness and headache. Adverse drug reactions (grade 3 or greater) increased on the ruxolitinib arm compared to the placebo arm in Study 1 were thrombocytopenia (13% versus 1%) and anemia (45% versus 19%). Similar results were observed in Study 2.

8. Advisory Committee Meeting

An Oncology Drugs Advisory Committee did not occur because the benefits of ruxolitinib in spleen volume reduction and symptom control are evident in the results of two adequate and well-controlled trials, while adverse reactions appear to be manageable.

9. Pediatrics

Ruxolitinib has been granted Orphan Drug Status for myelofibrosis.

10. Other Relevant Regulatory Issues

OSI/DGCPC conducted inspections at two of the eighty-nine clinical sites, in which the pivotal clinical trial were performed. The overall assessment was that the studies appear to have been conducted adequately, and the data generated appear acceptable in support of the application.

IRT/QT concluded that no significant QTc prolongation effect of ruxolitinib was detected in the TQT study. There are no other unresolved relevant regulatory issues.

11. Labeling

OSE/DMEPA approved the proprietary name request. OSE/DMEPA made labeling (including to the Patient Package Insert) recommendations to help prevent medication errors, and agreed with the revised label and labeling, including carton and container labels.

OMPI/DMPP concluded that Patient Package Insert is acceptable with the recommended changes. A Patient Counseling Information section and a Patient Information section are included in the labeling and were approved by OMPI/DMPP.

12. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Full Approval
- Risk Benefit Assessment

The following table is from the Clinical Review.

Benefit-Risk Assessment Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition: MF Clinical Manifestations Median Survival (all groups) Survival high risk Survival intermediate-2 Approved available therapy	 Splenomegaly and symptoms which disrupt quality of life 57 months 27 months 48 months No approved therapy	MF is a serious, life-threatening condition in which death is due to evolution into AML (12%), bleeding (11%), portal hypertension (7%), and liver insufficiency (9%).
Unmet Medical Need: Therapy: Off label use of interferon-alpha, anagrelide, dexamethasone, hydroxyurea, erythropoietin, thalidomide, splenic radiation, and allografts.	Allograft is the only curative therapy (7-year survival is 60%). Only a fraction of patients with MF are eligible. All other therapies are palliative and have significant side effects.	For most patients, there is no curative therapy, and no effective treatment which reduces symptoms and splenomegaly for a long time. There is an unmet medical need in MF.
Clinical Benefit: 2 randomized, well controlled trials were conducted with reproducible results.	42% and 29% of ruxolitinib treated patients in the two trials displayed ≥35% reduction of splenic volume. In the pivotal phase III trial, 46% of patients experienced ≥50% reduction in total symptom score. Long term benefit and toxicity unknown.	Two large well controlled and well designed trials met efficacy endpoints when measured at 24 and 48 weeks of therapy. Uncertain is the how long benefits will last beyond the 24 and 48 weeks and what will be the toxicity of long-term treatment.

Risks: Early deaths (≤28 days) SAEs AEs ↓platelets (Grade 3) ↓platelets (no Grade 4) Bleeding Anemia (Grade 3) Anemia (Grade 4) Infections AEs leading to discontinuation AEs leading to dose reduction	Ruxolitinib Arms Not increased Not increased Increased Not increased Not increased Increased Increased Not increased Not increased Increased	Thrombocytopenia was successfully managed by a dose adjustment schedule. Anemia was managed by RBC transfusions. The risks of long term therapy have not been characterized.
Risk Management: Need of studies for toxicity of long-term therapy.	Two phase III trials showed significant benefit and minimal risks for up to 48 weeks of treatment. Need PMC for longer term follow-up of response duration and toxicity.	PMR for follow-up (for 3 years after randomization) of phase III trial populations for myelosuppression PMC for post-marketing follow-up of efficacy and safety outcomes of current randomized trials and to report on discontinuation of at least 150 patients previously entered onto the randomized trials to determine if specific cautions are appropriate to describe discontinuation strategies.

The benefits and risks of ruxolitinib were also discussed in the Division Director's Summary Review and Clinical Reviews. The review team found the risk-benefit assessment to be acceptable. This application is supported by the results of two well designed, well controlled, randomized trials of ruxolitinib in patients with MF demonstrating a clinically significant benefit with ruxolitinib. The major side effect of thrombocytopenia can be limited by dose adjustments.
In conclusion, I concur with the review team's recommendation for approval.

- Recommendation for Postmarketing Risk Management Activities

None.

- Recommendation for other Postmarketing Study Commitments

See action letter for Postmarketing Requirements and Commitments.

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/s/

TAMY E KIM
11/16/2011

RICHARD PAZDUR
11/16/2011