CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

202192Orig1s000

Trade Name: Jakafi Tablets

Generic Name: ruxolitinib

Sponsor: Incyte Corporation

Approval Date: November 16, 2011

Indications: Treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, postpolycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202192

NDA APPROVAL

Incyte Corporation
Attention: Ronald C. Falcone, Ph.D.
Vice President, Regulatory Affairs
Rt 141 & Henry Clay Road, E336
Wilmington, DE 19880-0336

Dear Dr. Falcone:

Please refer to your New Drug Application (NDA) dated June 3, 2011, received June 3, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Jakafi™ (ruxolitinib) Tablets.

We acknowledge receipt of your amendments dated June 10; July 8 and 12; August 1, 4, 5, 12, 18, 24, 29, and 30; September 12, 14, 27, 28, and 30; October 5, 12, 19, 20, 21, and 31; and November 2, 2011.

This new drug application provides for the use of Jakafi™ (ruxolitinib) Tablets for the treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on October 20, 2011, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 202192**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

CHEMISTRY, CONTROLS AND MANUFACTURING

A 24-month expiration dating period is granted for the drug product (5 mg, 10 mg, 15 mg, 20 mg, and 25 mg) when stored at USP controlled room temperature 20-25ºC (68-77ºF); excursions permitted to 15-30ºC (59-86ºF).

ADVISORY COMMITTEE

Your application for Jakafi™ (ruxolitinib) Tablets was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of myelosuppression with longer-term exposure to Jakafi™ (ruxolitinib) Tablets therapy and to monitor safety findings occurring in the context of drug discontinuation to determine if specific cautions are necessary during drug discontinuation.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of myelosuppression with longterm exposure and safety findings in the context of drug discontinuation.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1838-1 Provide safety findings related to the interval of drug discontinuation in at least 75 patients previously entered on INCB-351 to determine if specific cautions are appropriate to describe discontinuation strategies.

The timetable you submitted on November 14, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	07/2009
Trial Completion:	08/2012
Final Report Submission:	10/2013

1838-2 Provide safety findings related to the interval of drug discontinuation in at least 75 patients previously entered on INCB-352 to determine if specific cautions are appropriate to describe discontinuation strategies.

The timetable you submitted on November 14, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	05/2010
Trial Completion:	08/2012
Final Report Submission:	10/2013

1838-3 Collect and analyze safety information on myelosuppression for up to 144 weeks of therapy following randomization in the patients entered on INCB-351 who are continuing on therapy past 24 weeks.

The timetable you submitted on November 14, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	07/2009
Trial Completion:	03/2013
Final Report Submission:	12/2013

1838-4 Collect and analyze safety information on myelosuppression for up to 144 weeks of therapy following randomization in the patients entered on INCB-352 who are continuing on therapy past 48 weeks.

The timetable you submitted on November 14, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	05/2010
Trial Completion:	03/2013
Final Report Submission:	12/2013

Submit the protocols to your IND 077456, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

1838-5 Provide longer-term efficacy and safety outcomes of current clinical trial INCB-351 to provide at least 3 year follow-up data.

The timetable you submitted on November 14, 2011, states that you will conduct

this trial according to the following schedule:

Final Protocol Submission:	07/2009
Trial Completion:	08/2013
Final Report Submission:	08/2014

1838-6 Provide longer-term efficacy and safety outcomes of current clinical trial INCB-352 to provide at least 3 year follow-up data.

The timetable you submitted on November 14, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	05/2010
Trial Completion:	08/2013
Final Report Submission:	08/2014

Submit clinical protocols to your IND 077456 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence.**"

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more

information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Amy Baird, Regulatory Project Manager, at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Office Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD PAZDUR
11/16/2011