

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203214Orig1s000**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 203214/Original 1

**NDA APPROVAL**

Pfizer Inc.  
445 Eastern Point Road  
Groton, CT 06340

Attention: Nickie V. Kilgore, D.V.M.  
Director  
Worldwide Regulatory Strategy

Dear Dr. Kilgore:

Please refer to your New Drug Application (NDA) dated October 21, 2011, received October 21, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xeljanz (tofacitinib) Tablets, 5 mg.

We acknowledge receipt of your amendments dated October 25, and December 16 and 20, 2011, and January 13 and 31, February 1, 8, 16, and 20, March 20, 22, 23, 28 (2), and 30, April 3, 10, 23, and 30, May 21, 22, and 24, June 5, 8, 11, 15 (2), 19, 22, and 25, July 6, 16, and 20, August 1, 2, 10, 13, and 14, September 5, October 2, 16, 23, and 29 (2), and November 2 and 5 (2), 2012.

NDA 203214 provides for the use of Xeljanz (tofacitinib) Tablets for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate, to be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs). For administrative purposes, we have designated this NDA as follows:

- NDA 203214/Original 1 – 5 mg twice daily
- [REDACTED] (b) (4)

The subject of this action letter is NDA 203214/Original 1. [REDACTED] (b) (4)

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, Medication Guide). 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* available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

## **CARTON AND IMMEDIATE-CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels submitted on August 14, 2012, 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 203214/Original 1.**” 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 it is available.

## **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.

We are waiving the pediatric study requirement for ages 0 to < 2 years of age because necessary studies are impossible or highly impracticable as polyarticular juvenile idiopathic arthritis (JIA) is not diagnosed in children < 2 years of age.

We are deferring submission of your pediatric study for ages 2 through 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1934-1 A multiple-dose pharmacokinetic trial in children from 2 to less than 18 years of age with juvenile idiopathic arthritis (JIA)

Final Protocol Submission: November 2012  
Trial Completion: March 2014  
Final Report Submission: September 2014

1934-2 A randomized withdrawal, double-blind, placebo-controlled trial to evaluate the efficacy and safety of tofacitinib in children from 2 to less than 18 years of age with polyarticular-course juvenile idiopathic arthritis.

Final Protocol Submission: March 2014  
Trial Completion: March 2017  
Final Report Submission: September 2017

Submit the protocols to your IND 070903, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

#### **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.

The clinical development program showed that treatment with Xeljanz (tofacitinib) is associated with an increase in cholesterol levels, which raises the concern of an increase in cardiovascular adverse events with Xeljanz (tofacitinib) therapy. An increase in serious infections and malignancy was also noted in the Xeljanz (tofacitinib) clinical development program.

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 assess signals of the serious

risks of cardiovascular adverse events, serious infections, including opportunistic infections, and malignancy with Xeljanz (tofacitinib).

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 these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess signals of the aforementioned risks.

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

- 1934-3      Controlled clinical trial to evaluate the long term safety of tofacitinib in patients with rheumatoid arthritis. The trial should include two doses of tofacitinib and an active comparator. The trial should be of sufficient size and duration to evaluate safety events of interest, including cardiovascular adverse events, opportunistic infections, and malignancy.

The timetable you submitted on August 2, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:    March 2013  
Trial Completion:                December 2019  
Final Report Submission:      June 2020

Submit the protocol(s) to your IND 070903, 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.

## **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Xeljanz (tofacitinib) to ensure the benefits of the drug outweigh the risks of serious infections, including opportunistic infections, tuberculosis, malignancy, increase in cholesterol, and decrease in blood counts.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR part 208. Pursuant to 21 CFR part 208, FDA has determined that Xeljanz (tofacitinib) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of tofacitinib. FDA has determined that Xeljanz (tofacitinib) is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Xeljanz (tofacitinib). Under 21 CFR part 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Xeljanz (tofacitinib).

We have also determined that a communication plan is necessary to support implementation of the REMS.

Your proposed REMS, submitted on November 5, 2012, and appended to this letter, is approved. The REMS consists of a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Xeljanz (tofacitinib) into interstate commerce.

The REMS assessment plan should include, but is not limited to, the following:

1. A survey of the patients' knowledge and understanding of the serious risks of tofacitinib.
2. A survey of the prescribers' knowledge and understanding of the serious risks of tofacitinib.
3. A survey of the pharmacists' knowledge and understanding of the serious risks of tofacitinib.
4. An assessment and conclusions regarding the success of the REMS in meeting the stated goals.
5. An assessment of the communication plan including:

- a. The source(s) of the list of healthcare professionals to whom the DHCPL and Dear Pharmacist Letter are distributed
- b. Journal information pieces published, including date and journal name, volume, and issue.
- c. The date of launch of the communication plan (DHCPL, Dear Pharmacist Letter, website, and journal information pieces
- d. The number of recipients of the DCHP and Dear Pharmacist letters
- e. Date(s) of distribution of the DHCP and Dear Pharmacist letters
- f. The number of returned and refused letters

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 203214 REMS CORRESPONDENCE**  
***(insert concise description of content in bold capital letters, e.g.,***  
**UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT**  
**METHODOLOGY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 203214 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 203214  
PROPOSED REMS MODIFICATION  
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR NDA 203214  
REMS ASSESSMENT  
PROPOSED REMS MODIFICATION (*if included*)**

If you do not submit electronically, please send five copies of REMS-related submissions.

**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 (OPDP)  
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>.

**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 Philantha Montgomery Bowen, Senior Regulatory Project Management Officer, at (301) 796-2466.

Sincerely,

*{See appended electronic signature page}*

Curtis J. Rosebraugh, M.D., M.P.H.  
Director  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosures:

Content of Labeling  
Carton and Immediate-Container Labeling  
REMS

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CURTIS J ROSEBRAUGH  
11/06/2012