

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**125472Orig1s000**

***Trade Name:*** Actemra

***Generic Name:*** tocilizumab

***Sponsor:*** Genentech, Inc.

***Approval Date:*** October 21, 2013

***Indications:*** For adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

# CENTER FOR DRUG EVALUATION AND RESEARCH

## 125472Orig1s000

### CONTENTS

#### Reviews / Information Included in this NDA Review.

<b>Approval Letter</b>	<b>X</b>
<b>Other Action Letters</b>	
<b>Labeling</b>	<b>X</b>
<b>REMS</b>	<b>X</b>
<b>Summary Review</b>	<b>X</b>
<b>Officer/Employee List</b>	<b>X</b>
<b>Office Director Memo</b>	
<b>Cross Discipline Team Leader Review</b>	<b>X</b>
<b>Medical Review(s)</b>	<b>X</b>
<b>Chemistry Review(s)</b>	<b>X</b>
<b>Environmental Assessment</b>	<b>X</b>
<b>Pharmacology Review(s)</b>	<b>X</b>
<b>Statistical Review(s)</b>	<b>X</b>
<b>Microbiology / Virology Review(s)</b>	<b>X</b>
<b>Clinical Pharmacology/Biopharmaceutics Review(s)</b>	<b>X</b>
<b>Other Reviews</b>	<b>X</b>
<b>Risk Assessment and Risk Mitigation Review(s)</b>	<b>X</b>
<b>Proprietary Name Review(s)</b>	<b>X</b>
<b>Administrative/Correspondence Document(s)</b>	<b>X</b>

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*APPLICATION NUMBER:*

**125472Orig1s000**

**APPROVAL LETTER**



BLA 125472/0

**BLA APPROVAL**

Genentech, Inc.  
A Member of the Roche Group  
1 DNA Way  
South San Francisco, CA 94080

Attention: Stuart Heminway, Program Director  
Regulatory Affairs

Dear Mr. Heminway:

Please refer to your Biologics License Application (BLA) dated December 21, 2012, received December 21, 2012, submitted under section 351(a) of the Public Health Service Act for Actemra (tocilizumab) Solution for Subcutaneous Injection.

We also refer to our approval letter dated October 21, 2013, which contained the following error: incorrect version of the carton and container labels.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain October 21, 2013, the date of the original approval letter.

We acknowledge receipt of your amendments dated January 22, February 14, March 12 and 14, April 22 and 23, May 15, 16, and 28, June 10 and 18, July 1, 10, 12, 15, 18, and 25, August 12, 13 (2), and 30, September 10, 15, 25, 26, and 30, and October 3 (3), 7, 8, 10 (3), 14, 17, and 18, 2013.

**LICENSING**

We have approved your BLA for Actemra (tocilizumab) Solution for Subcutaneous Injection, effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Actemra (tocilizumab) Solution for Subcutaneous Injection, under your existing Department of Health and Human Services U.S. License No. 1048. Actemra (tocilizumab) Solution for Subcutaneous Injection is indicated for adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

**MANUFACTURING LOCATIONS**

Under this license, you are approved to manufacture Actemra drug substance at Genentech in Oceanside, CA. The final formulated product will be manufactured and filled at (b) (4)

(b) (4) Labeling, assembly with the needle safety device and secondary packaging are performed by F. Hoffman-La Roche Ltd in Kaiseraugst, Switzerland. You may label your product with the proprietary name, Actemra, and will market it in single use 1 mL prefilled syringe.

### **DATING PERIOD**

The dating period for Actemra drug product shall be 30 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date (b) (4) of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4)

### **FDA LOT RELEASE**

You are not currently required to submit samples of future lots of Actemra to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Actemra or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

### **APPROVAL & LABELING**

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.

### **WAIVER OF HIGHLIGHTS SECTION**

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, 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, text for the instructions for use, 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" at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

In addition, within 14 days of the date of this letter, amend any pending supplement that includes labeling changes for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

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 carton and immediate container labels submitted on September 26, 2013, 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 “**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125472/0.**” Approval of this submission by FDA is not required before the labeling is used.

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

### **ADVISORY COMMITTEE**

Your application for Actemra (tocilizumab) Solution for Subcutaneous Injection was not referred to an FDA advisory committee because the efficacy and safety findings in the clinical program for the fixed dose subcutaneous formulation of tocilizumab were consistent with the findings from the intravenous (already approved) tocilizumab experience.

### **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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 2 years because necessary studies are impossible or highly impracticable. This is because there are small numbers of patients in this age group with the disease.

We are deferring submission of your pediatric study for ages 2 to 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 study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing study(ies). The status of this postmarketing study must be reported annually according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

1. Deferred pediatric study under PREA for the treatment of rheumatoid arthritis in pediatric patients ages 2 to 17 years of age.

Final Protocol Submission: March 20, 2013 (Submitted)  
Study Completion: March 31, 2016  
Final Report Submission: May 31, 2018

Submit the protocol(s) to your IND 11972 with a cross-reference letter to this BLA.

Reports of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA 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 COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitment:

2. Determine the (b) (4) volume needed to (b) (4).

The timetable you submitted on July 25, 2013 states that you will conduct this study according to the following schedule:

Final Report Submission: October 30, 2013

Submit clinical protocols to your IND 11972 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. 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.”**

**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 Actemra (tocilizumab) to ensure the benefits of the drug outweigh the serious risks of serious infections, gastro-intestinal perforations, changes in the liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, demyelinating disorders, malignancies, and elevations in lipid parameters in peripheral blood.

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

Your proposed REMS, submitted on October 18, 2013, and appended to this letter, is approved. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Actemra (tocilizumab) into interstate commerce.

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

- a. Evaluation of the prescribers’ understanding of the risks of ACTEMRA
- b. A summary of all reported serious risks with an analysis of adverse event reporting by prescriber type (e.g., rheumatologist, osteopath, infectious disease specialist, gastroenterologist, hepatologist, internal medicine specialist, hematology-oncology specialist, emergency medicine specialist, family medicine specialist, etc.), when available

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 1 or more such goals or such elements should be modified.

The timetable for submission of assessments for this REMS will be the same as that approved in the REMS for the Actemra (tocilizumab) intravenous solution which was approved on January 8, 2010, under BLA 125276. With the approval of BLA 125472, both the intravenous and subcutaneous products are included in the same REMS, known as the Actemra REMS.

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:

**BLA 125472 REMS CORRESPONDENCE  
(insert concise description of content in bold capital letters, e.g.,  
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT  
METHODOLOGY)**

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:

**BLA 125472 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR BLA 125472  
PROPOSED REMS MODIFICATION**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR BLA 125472  
REMS ASSESSMENT  
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 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  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), 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**

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Compliance Risk Management and Surveillance  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Compliance Risk Management and Surveillance  
10903 New Hampshire Avenue, Bldg. 51, Room 4206  
Silver Spring, MD 20903

**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>.

If you have any questions, call Philantha Bowen, Senior Regulatory Project Manager, at (301) 796-2466.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.  
Director  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**ENCLOSURES:**

Content of Labeling  
Carton and 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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SARAH K YIM  
10/21/2013  
Signing for Badrul Chowdhury, M.D., Ph.D.