

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125276

APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

STN: BL 125276

BLA APPROVAL
January 8, 2010

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

Attention: Mary B. Sliwowski, Ph.D.
V.P., Regulatory CMC and Information Systems

Dear Dr. Sliwowski:

Please refer to your biologics license application (BLA), dated and received November 19, 2007, submitted under section 351 of the Public Health Service Act for Actemra (tocilizumab).

We acknowledge receipt of your submissions dated December 20, 2007, January 4, 10, and 31, February 13, 18, and 28, March 19, 20, and 26, April 2, 8, 11, 24, and 25, May 23, June 12, 13 and 30, July 1, 7, 8, 11, 14, 15, 16, 17, 19, and 23 (2), August 5, 8 (2), 11 (2), 15, and 26, September 2, 5, 15, 16, and 29, October 7, 23, 27, 28, and 29, and December 19, 2008, July 8, November 4 and 25, and December 9 and 30, 2009, and January 2 and 6, 2010.

The July 8, 2009, submission constituted a complete response to our September 17, 2008, action letter.

We have completed our review of this application, as amended, and your biologics license application for Actemra (tocilizumab) is approved. You are hereby authorized to introduce into, or deliver for introduction into, interstate commerce Actemra (tocilizumab) under your existing Department of Health and Human Services U.S. License No. 1048. Actemra (tocilizumab) is indicated for the treatment of adult patients with moderately-to severely-active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies.

Under this license, you are approved to manufacture tocilizumab drug substance at Chugai Pharma Manufacturing Co., Ltd., in Utsunomiya, Tochigi, Japan. The final formulated drug product will be manufactured and filled at Chugai Pharma Manufacturing Co., Ltd., Utsunomiya, Japan. The final formulated drug product will be packaged and labeled at Hoffmann-La Roche Ltd., Kaiseraugst, Switzerland. You may label your product with the proprietary name Actemra and will market it as a 4-mL single-use vial containing 80 mg tocilizumab (20 mg/mL), a 10-mL single-use vial containing 200 mg tocilizumab (20 mg/mL), and a 20-mL single-use vial containing 400 mg tocilizumab (20 mg/mL).

The dating period for Actemra (tocilizumab) shall be 24 months from the date of manufacture when stored at 2-8 °C. The date of manufacture shall be defined as the date of _____ of the formulated drug product. The dating period for your drug substance shall be 24 months when stored at less than or equal to -50 °C. We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

b(4)

You currently are not 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.

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging, or labeling of Actemra (tocilizumab), or in the manufacturing facilities.

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 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling and Medication Guide. The content of labeling should be provided by submitting a link to your SPL file submitted to the drug establishment registration and labeling system. The drug establishment and labeling system will transmit the labeling to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved STN BL 125276/0.**"

Pursuant to 21 CFR 201.57(c)(18), patient labeling must be reprinted immediately following the last section of labeling or, alternatively, accompany the prescription drug labeling.

CARTON AND CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed draft labels 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*. 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 STN 125276/0.**" Approval of this submission by FDA is not required before the labeling is used.

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

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 because necessary studies are impossible or highly impracticable. This is because juvenile idiopathic arthritis (JIA) polyarticular subtype most often occurs in children ages ≥ 2 years and older and is infrequent in children ages 0 to < 2 years.

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

Your deferred pediatric study required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.70 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

1. Assessment of pharmacokinetic (PK/PD) parameters and dosing, efficacy, safety, tolerance and immunogenicity in the pediatric population ages ≥ 2 years to < 17 years with polyarticular JIA.

Protocol Submission: October 16, 2009
Final Report Submission: March 31, 2014

Submit final study reports to your BLA 125276. Use the following designator to prominently label all submissions:

REQUIRED PEDIATRIC ASSESSMENT

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)).

Your final proposed REMS, submitted on January 6, 2010, 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.

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

- a. Evaluations of healthcare providers' understanding and patients' understanding of the risks of Actemra (tocilizumab).
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- c. A report on failures to adhere to Medication Guide distribution and dispensing requirements, and corrective actions taken to address noncompliance.
- d. A summary of all reported serious risks with 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.
- e. Based on the information provided, an assessment and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 601.70 and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

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 FDCA.

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 STN 125276 REMS ASSESSMENT

**NEW SUPPLEMENT FOR BLA STN 125276
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR BLA STN 125276
REMS ASSESSMENT
PROPOSED REMS MODIFICATION *(if included)***

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

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) 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 (section 505(o)(3)(A)).

Data from the clinical development program for Actemra (tocilizumab) demonstrate that treatment with Actemra is associated with episodes of hypertension and an increase in all lipid parameters, with an average increase of 30 mg/dL in total cholesterol, 20 mg/dL in LDL, 5 mg/dL in HDL, and 30-40 mg/dL in triglycerides. Since elevation in blood pressure and lipids, especially LDL, are considered risk factors for the development of serious cardiovascular outcomes, these data indicate the potential for an increase in cardiovascular events associated with Actemra treatment. In addition, since the long-term risks of Actemra are unknown, further investigation of the long-term safety of Actemra will be essential for the chronic treatment setting.

Because Actemra inhibits IL-6 activity, it is immunosuppressive, and also may specifically impair the ability of B cells to differentiate into immunoglobulin-secreting cells. Therefore, there are plausible biological mechanisms as reason to suspect that Actemra treatment may impair immune responses to vaccination.

Animal data suggest that tocilizumab increased the incidence of abortion and embryofetal death at doses above therapeutic human levels. It is not known whether embryofetal exposure to therapeutic doses in humans could negatively impact pregnancy outcomes.

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 unexpected risks of serious cardiovascular events, long-term serious risks of Actemra, serious outcomes resulting from the potential of Actemra to interfere with host responses to vaccinations, or negative pregnancy outcomes related to Actemra.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to identify these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following postmarketing clinical studies:

2. Pregnancy registry to evaluate pregnancy outcomes for women exposed to Actemra (tocilizumab) during pregnancy. Utilize the established Organization of Teratology Information Specialists (OTIS) pregnancy registry to evaluate pregnancy outcomes.

The timetable you submitted on December 18, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission: July 30, 2010
Study Completion Date: December 31, 2016
Final Report Submission: December 31, 2017

3. Long-term, observational study of patients who continue to be treated with tocilizumab in the open-label part of the treatment trials WA18695 and WA18696 to evaluate long-term serious risks of Actemra and to accrue safety data on at least 1000-1500 patients treated for 5 years.

The timetable you submitted on December 18, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission: December 17, 2009
Study Completion Date: June 30, 2013
Final Report Submission: June 30, 2014

Finally, we have determined that only clinical trials (rather than nonclinical or observational studies) will be sufficient to assess the two potential issues of unexpected risks of serious cardiovascular events and serious outcomes resulting from treatment-related interference with host responses to vaccinations.

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

4. A randomized, controlled trial to rule out a moderate increase in the risk of serious cardiovascular events with tocilizumab, e.g., stroke, non-fatal MI, cardiovascular death.

The timetable you submitted on December 18, 2009, states that you will conduct this trial according to the following timetable:

Final Protocol Submission: July 30, 2010
Study Completion Date: February 28, 2018
Final Report Submission: February 28, 2019

5. A randomized trial to study the effects of tocilizumab on therapeutic vaccines. B cell-dependent antigens (e.g., pneumococcal polysaccharide vaccine) and T cell-dependent antigens (e.g., tetanus toxoid) will be evaluated.

The timetable you submitted on December 18, 2009, states that you will conduct this trial according to the following timetable:

Final Protocol Submission: April 30, 2010
Study Completion Date: October 31, 2013
Final Report Submission: November 30, 2012

Submit the protocols to your IND, with a cross-reference letter to this BLA, STN 125276. Submit all final reports to this BLA. Use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study requirements 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 601.70, 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 601.70 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 601.70. 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.

PROMOTIONAL MATERIALS

You may submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this BLA and to the following address:

MedWatch, HFD-001
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20852-9787

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 4203
Silver Spring, MD 20992-0002

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 important 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 the drug development and marketing application review process. 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, contact the Division of Anesthesia, Analgesia and Rheumatology Products.

OTHER

Please refer to

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, contact the Regulatory Project Manager, Sharon Turner-Rinehardt, at (301) 796-2254.

Sincerely,



/Curtis J. Rosebraugh, M.D., M.P.H./

Curtis J. Rosebraugh, M.D., M.P.H.

Director

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Enclosures (4):

REMS documents

Package Insert

Medication Guide

Carton and Immediate-Container Labels