

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**125276**

**OTHER ACTION LETTER(s)**



Our STN: BLA 125276/0

**COMPLETE RESPONSE**

September 17, 2008

Hoffmann-La Roche, Inc.  
340 Kingsland Street  
Nutley, New Jersey 07110-1199

Attention: Matthew Lamb, Pharm. D.  
Director, Global Regulatory Affairs

Dear Dr. Lamb:

Please refer to your biologics license application, dated and received November 19, 2008, submitted under section 351 of the Public Health Service Act for Actemra (tocilizumab).

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

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reason for this action and, where possible, our recommendations to address this issue.

**NONCLINICAL**

1. Although requested in the responses for the pre-BLA meeting which was scheduled for October 12, 2007, you have not submitted reports of peri-natal and post-natal developmental toxicology studies nor have you provided adequate justification for why such studies are not possible. To resolve this issue, you must submit reports of such studies using either the monkey or the surrogate model.
2. You have not provided adequate justification as to why the fertility studies in the surrogate model are not possible. Although adequate fertility studies are not feasible in the primate model, you do have a mouse homologous product that can be used to characterize the potential effects on fertility. Therefore, to resolve this issue, you must submit reports of fertility studies in the mouse model.

### LABELING

3. The proper name and dosage form should be presented consistently in all labeling and labels as “tocilizumab injection, solution, concentrate.” For information on dosage form terminology, see the CDER Data Standards Manual, <http://www.fda.gov/cder/dsm/DRG/drg00201.htm>.
4. Carton and immediate container labels should include a statement that the product must be diluted before use. For example, “CONCENTRATED – Must Be Diluted” or “FOR IV INFUSION ONLY AFTER DILUTION.”
5. Add the following bolded statement or appropriate alternative to the carton and immediate container labels per 21 CFR 208.24(d): **“ATTENTION PROVIDER: Each patient is required to receive the enclosed Medication Guide.”**

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>.

### DEBARMENT CERTIFICATION

6. Submit a signed copy of the debarment certification.

### FINANCIAL DISCLOSURE

7. Explain why the financial disclosure information submitted on July 23, 2008, was not included with the original application.
8. Explain why Box 3 was checked on the form FDA 3454 submitted on July 23, 2008, for those investigators for whom financial disclosure information was not submitted. This box is for studies sponsored by a firm or party other than the applicant.
9. Explain the due diligence steps taken to locate investigators for whom financial disclosure information was not obtained. For these investigators, you should provide information on those reportable interests which can be ascertained from H-LR’s files, i.e., whether any financial arrangements whereby the value of compensation to the investigator could be affected by the outcome of the study; whether the investigators have any proprietary interests in the product; and whether the investigators received any reportable significant payments of other sorts.

### FACILITY INSPECTIONS

During a recent inspection of the Chugai Pharmaceutical manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

### **SAFETY UPDATE**

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies for the proposed indication using the same format as the initial submission.
  - Present tabulations of the new safety data combined with the initial data.
  - Include tables that compare frequencies of adverse events in the initial data with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the initial data.
6. Provide updated exposure information for the clinical trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

### **RISK EVALUATION AND MITIGATION STRATEGIES (REMS) REQUIREMENTS**

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a REMS if the FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Actemra (tocilizumab) to ensure that the benefits of the drug outweigh the risks, including, but not limited to the risk of serious infection, gastrointestinal perforation, neutropenia, elevation in lipid parameters, and changes in liver function.

Your proposed REMS must contain a Medication Guide, a communication plan, elements to assure safe use, an implementation system, and a timetable for the submission of assessments. We will provide you further guidance on developing the REMS in a future letter.

### **OTHER**

While not approvability issues, we have the following requests for additional information:

- A. You have not submitted the results of carcinogenicity studies with either tocilizumab or the homologous protein. The application states that “The MR 16-1 antibody is also not an appropriate reagent to be used in long-term carcinogenicity studies, as this antibody is a rat monoclonal anti-mouse IL-6R antibody and is considered to be immunogenic in long-term in vivo studies in mice.” Submit data to support this statement in order to support your conclusion that this option for carcinogenicity assessment is not viable.
- B. As described in ICH S6, to assess in the extrapolation of the toxicology program findings to humans, submit a summary table comparing the binding affinity of tocilizumab to both the human and monkey sIL-6R and mIL-6R and a comparison of the functional potency of tocilizumab at the human and monkey IL-6R with references to the studies from which the data were obtained.
- C. You have not adequately assessed the risk-benefit ratio for your choice of recommending the 8-mg/kg dose. Overall, this dose does not appear to provide a significant benefit for most patients compared to the 4-mg/kg dose. While there may be some subpopulations or individuals that would achieve greater benefit from the higher dose, there also appear to be possible safety concerns that are dose related. In addition, the increased efficacy associated with the higher dose appears to be primarily driven by the product’s effect on the CRP levels. The actual clinical components of the ACR20 demonstrate less of an advantage for the higher dose. You should further evaluate the benefit-risk balance of recommending only the 8-mg/kg dose, or consider recommending starting with the lower dose, and increasing to the higher dose as needed and as tolerated.
- D. Provide more information on the proposed questionnaire for collecting adverse event data and the timeframe for following up on serious adverse events including infections. Also, collect information on pre-existing conditions or other factors that might pre-dispose the patient to a serious adverse event including infections, and what treatments were tried and the extent of those treatment successes.

- E. Provide the following additional details regarding your proposed pharmacoepidemiology board:
- i. The criteria used for the admission of the members to the board and total number of board members.
  - ii. The governance of the board.
  - iii. The information on what data will be provided to the board, by whom and how often the board will evaluate the data.
  - iv. The criteria the board will use to determine the risk of an adverse event and whether or not a risk mitigation needs to be implemented.
  - v. The criteria the board will use to “assess the sufficiency of risk management measures.”
  - vi. The information about the board’s decisions and Roche’s responses will be reported to the FDA
  - vii. The format and the frequency this information will be communicated to the FDA; for example, by a special report, the next periodic report or annual report.
- F. Provide information on what will trigger a study in the registries or claims database; for example, how much of an increase in the reporting rate of an adverse event.
- G. Describe and provide a protocol(s) for the potential studies that use the registry and claims data. Specifically address the issues of case identification, ascertainment, and validation, identification of a comparator group, measurement of exposure(s), confounders, loss to follow-up and sample size.

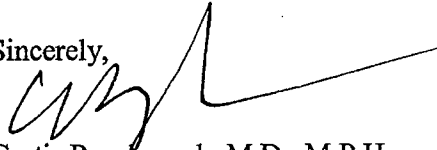
Within one year after the date of this letter, you are required to resubmit or withdraw the application. If you do not take any of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). A resubmission must fully address all the deficiencies listed, and will start a new review cycle. A partial response to this letter may not be reviewed and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application can be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry on *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/cder/guidance/2125fnl.htm> ).

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

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

Sincerely,

A handwritten signature in black ink, appearing to read 'C. Rosebraugh', with a long horizontal stroke extending to the right.

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

Director

Office of Drug Evaluation II

Center for Drug Evaluation and Research