CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125276

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Division of Risk Management

Date:	January 8, 2010
To:	Bob A. Rappaport, M.D., Director Division of Anesthesia, Analgesia, and Rheumatology Products
Through:	Claudia Karwoski, Pharm.D., Director Division of Risk Management (DRISK)
From:	DRISK Scientific Lead: Kathryn O'Connell, M.D., Ph.D., Medical Officer (DRISK) Mary Dempsey, Risk Management Coordinator (DRISK) Suzanne Berkman Robottom, Pharm.D., Team Leader (DRISK/OSE) Christopher Wheeler, Pharm.D., Safety Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE)
Subject:	Final DRISK review of REMS dated January 8, 2010
Drug Names/Sponsor:	ACTEMRA (tocilizumab)/Hoffman-La Roche, Inc.
Application Type/Number/Submission #:	BLA STN 1252760
OSE RCM #:	2009-1376

1 BACKGROUND

On November 14, 2008, DAARP issued a Complete Response for Actemra. The CR informed the sponsor that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for ACTEMRA. The letter specified that the REMS consist of a Medication Guide, Communication Plan, and the following Elements to Assure Safe Use (ETASU):

- A plan to ensure ACTEMRA is prescribed by prescribers who have particular training or experience or who are specially certified
- A plan to ensure that ACTEMRA is only dispensed or administered through prescribers or healthcare settings that are specially certified
- A plan to ensure that each patient using ACTEMRA is subject to monitoring of ALT, AST, bilirubin, neutrophils, platelets, and lipids and has his/her dose adjusted as per the recommendations in the ACTEMRA label, if any laboratory abnormalities are present

The CR letter specified laboratory monitoring of ALT, AST, neutrophils, and platelets every 4 to 8 weeks, with lipid monitoring 4 to 8 weeks after the first infusion, then at approximately 6 month intervals.

The CR letter also specified that the implementation system should minimally include:

- A database of certified prescribers and healthcare settings that links specified serious adverse events of interest to the prescribers and healthcare settings reporting the adverse event
- Monitoring of distribution and prescription data to ensure that ACTEMRA is shipped to, prescribed by, and administered by certified entities in at least 95% of all cases
- Monitoring of dispensing facilities to ensure that ACTEMRA is dispensed after verification of patient counseling and laboratory work
- Monitoring for specified adverse events of interest using an adverse event form that has been developed and disseminated to certified prescribers and certified healthcare settings

In a Complete Response submission dated July 8, 2009, Hoffmann-La Roche proposed a REMS including all of the components stipulated in the November 14, 2008 letter.

After further internal evaluation and discussion, the Office of Surveillance and Epidemiology (OSE) and DAARP confirmed that a REMS is necessary to ensure the safe use of Actemra (tocilizumab), but that ETASU and the implementation system are not warranted at this time. Specifically, we believe that educating healthcare practitioners about the labeled recommendations for close monitoring of the laboratory parameters and prompt recognition of the critical values is necessary to help ensure safe use of Actemra (tocilizumab). However, we also determined that the ETASU and implementation system were not necessary. Although changes in hematologic, hepatobilliary, and lipid laboratory values could potentially lead to serious adverse outcomes, the laboratory abnormalities observed in the

trials did not result in adverse clinical outcomes and, in the majority of cases, were reversible upon timely dose reduction, interruption, or discontinuation of Actemra. FDA, to date, has not required ETASU for laboratory abnormalities without evidence that the abnormalities result in serious adverse events. In addition, the adverse events and observed laboratory abnormalities in the tocilizumab clinical trials are similar to those observed with other products used to treat rheumatoid arthritis. Hoffman La Roche's proposed recommendations for monitoring and dose adjustment are similar to well established clinical practices in rheumatoid arthritis, and we have no reason to believe that the Actemra recommendations would not be routinely adopted.

Therefore, the sponsor was formally notified on November 10, 2009 that the REMS for Actemra would consist of a Medication Guide, a communication plan, and a timetable for submission of assessments.

2 MATERIAL REVIEWED

- Complete Response Letter with REMS notification signed November 8, 2008.
- REMS Retraction Letter signed November 10, 2009.
- Roche's Proposed REMS submission dated July 8, 2009 and received in EDR July 23, 2009. This submission and a previous draft were the subjects of DRISK interim reviews #1, #2, and #3 dated May 23, July 28, and December 14, 2009.
- Roche's revised REMS and REMS Supporting Document dated November 16, 2009, with subsequent WORD versions received via email for editing purposes.
- Roche's emailed revised REMS and Supporting Document dated December 22, 2009.
- Roche's revised REMS and Supporting Document dated January 2010, submitted January 8, 2010.

3 SPONSORS' PROPOSED REMS

3.1 Goal

As stated by the sponsor, the goals of the ACTEMRA REMS are:

To inform healthcare providers about the risks of serious infections, gastrointestinal perforations, changes in liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, elevations in lipid

parameters in peripheral blood, demyelinating disorders, and malignancies associated with ACTEMRA®.

To inform patients about the serious risks associated with ACTEMRA® treatment.

Review Comment: These goals are consistent with the REMS request letter.

3.2 REMS Elements

The proposed REMS includes a Medication Guide (MG), a Communication Plan, and a timetable for submission of assessments. The information needed for assessment of the REMS is included in REMS Supporting Document. Each element is described below and the final REMS is appended.

3.2.1 Medication Guide

The sponsor states that, in accordance with 21 CFR 208.24, a Medication Guide will be included in each ACTEMRA® vial package. This Medication Guide should be dispensed to each patient by the infusion site immediately prior to each ACTEMRA® administration. The Medication Guide will also be available via sales representatives, the ACTEMRA® patient and professional websites, and a toll-free product information line (1-800-ACTEMRA).

The Medication Guide is appended as Attachment A.

Review Comment: The Medication Guide has been reviewed separately (S. Mills completed on December 8, 2009). Inclusion of a Medication Guide is consistent with the REMS request letter.

3.2.2 Communication Plan

The sponsor proposes to implement a communication plan to the following healthcare providers:

Rheumatologists and rheumatology healthcare providers who are likely to prescribe ACTEMRA®

Infectious disease specialists who may be consulted about serious infection

Gastroenterologists and hepatologists who may be consulted about gastrointestinal perforation, hepatic disease, or hepatic impairment

- Family practitioners, general practitioners, osteopaths, internists, and internal medicine specialists who may be consulted about serious infections, gastrointestinal perforations, changes in liver function, decreases in peripheral neutrophil counts, decreases in platelet counts,

elevations in lipid parameters in peripheral blood, demyelinating disorders, and malignancies associated with ACTEMRA®

Emergency medicine specialists who may treat serious infections, gastrointestinal perforations, and changes in liver function

Neurologists who may treat demyelinating disorders

Oncologists who may treat malignancies

Elements of the communication plan include the following:

1. A Dear Healthcare Provider Letter (Attachment B) will be distributed to rheumatologists, gastroenterologists, hepatologists, neurologists, oncologists, infectious disease specialists, family medicine specialists, internal medicine specialists, emergency medicine specialists, and infusion sites. This letter will be distributed within 60 days of product approval.

A Professional Label and a copy of the Medication Guide will also be distributed in this communication.

2. A Dear Pharmacist letter (Attachment C) will be distributed to pharmacists. This letter will be distributed within 60 days of product approval.
3. Dissemination of information about the known and potential risks associated with ACTEMRA to healthcare providers through certain professional societies' scientific meetings and journals:

   a) For display as a panel/poster and distribution as printed material at major convention meetings of rheumatologists and other healthcare professionals specializing in rheumatology where the company has a sponsored booth

   b) For quarterly presentation as a printed information piece in *Arthritis and Rheumatism*, *The Rheumatologist*, *Clinical Infectious Diseases*, *Clinical Gastroenterology and Hepatology*, *American Family Physician*, *Annals of Internal Medicine*, *Annals of Emergency Medicine* and *Neurology* for 3 years

   c) For quarterly presentation as a printed information piece in the *Journal of Clinical Oncology* for 5 years

The REMS journal information pieces are appended as Attachments D, E, F, G, H, I, and J.

Review Comment: The attached documents for the Communication Plan are acceptable.

3.2.3 Timetable for Submission of Assessments

REMS assessments will be submitted to FDA at 18 months, 3 years, and 7 years after approval. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date so that it will be received by the FDA on or before the due date.

Review Comment: This schedule is acceptable.

4 Information Needed for Assessments

The ACTEMRA REMS assessments will include the following:

- Evaluations of healthcare providers' understanding and patients' understanding of the risks of ACTEMRA
- A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- A report on failures to adhere to Medication Guide distribution and dispensing requirements and corrective actions taken to address noncompliance
- A summary of all reported serious risks with an analysis of adverse event reporting by prescriber type (e.g., dermatologist, nurse, internist, oncologist), when available
- 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

4.1 Survey Protocols

The sponsor has submitted survey protocols in order to assess healthcare provider and patient understanding aspect of the REMS assessment.

Review Comment: This REMS assessment as outlined in the Supporting Document is consistent with what was requested. The survey protocols are under review by DRISK and comments, if necessary, will be provided under separate cover.

5 Discussion and Conclusion

The Sponsor has appropriately responded to all Agency comments. The Division of Risk Management in the Office of Surveillance and Epidemiology finds the elements of the proposed REMS for Actemra acceptable as appended here. DRISK recommends approval of the Actemara REMS as submitted on January 8, 2010.

Comments regarding the submitted survey protocols will be provided in a separate review.

6 **Appendix** (REMS and Attachments)

BLA 125276/0

ACTEMRA® (tocilizumab)

Human interleukin-6 receptor inhibitor

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of the ACTEMRA® REMS are:

- To inform healthcare providers about the risks of serious infections, gastrointestinal perforations, changes in liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, elevations in lipid parameters in peripheral blood, demyelinating disorders, and malignancies associated with ACTEMRA®.
- To inform patients about the serious risks associated with ACTEMRA® treatment.

II. REMS ELEMENTS

A. Medication Guide (FDCA Section 505-1 (e)(2))

In accordance with 21 CFR 208.24, a Medication Guide will be included in each ACTEMRA® vial package. This Medication Guide should be dispensed to each patient by the infusion site immediately prior to each ACTEMRA® administration.

The Medication Guide will also be available via sales representatives, the ACTEMRA® patient and professional websites, and a toll-free product information line (1-800-ACTEMRA).

Please see the appended Medication Guide (Attachment A).

B. Communication Plan (FDCA Section 505-1(e)(3))

Genentech, A Member of the Roche Group, will implement a communication plan to the following healthcare providers:

Rheumatologists and rheumatology healthcare providers who are likely to prescribe ACTEMRA®

Infectious disease specialists who may be consulted about serious infection

Gastroenterologists and hepatologists who may be consulted about gastrointestinal perforation, hepatic disease, or hepatic impairment

Family practitioners, general practitioners, osteopaths, internists, and internal medicine specialists who may be consulted about serious infections, gastrointestinal perforations, changes in liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, elevations in lipid parameters in peripheral blood, demyelinating disorders, and malignancies associated with Actemra®

Emergency medicine specialists who may treat serious infections, gastrointestinal perforations, and changes in liver function

Neurologists who may treat demyelinating disorders

Oncologists who may treat malignancies

Elements of the communication plan include the following:

1. A Dear Healthcare Provider Letter (see Attachment B) will be distributed to rheumatologists, gastroenterologists, hepatologists, neurologists, oncologists, infectious disease specialists, family medicine specialists, internal medicine specialists, emergency medicine specialists, and infusion sites. This letter will be distributed within 60 days of product approval.

A Professional Label and a copy of the Medication Guide will also be distributed in this communication.

2. A Dear Pharmacist letter (see Attachment C) will be distributed to pharmacists. This letter will be distributed within 60 days of product approval.
3. Dissemination of information about the known and potential risks associated with ACTEMRA® to healthcare providers through certain professional societies' scientific meetings and journals:

   d) For display as a panel/poster and distribution as printed material at major convention meetings of rheumatologists and other healthcare professionals specializing in rheumatology where the company has a sponsored booth for 1 year following approval.

   e) For quarterly presentation as a printed information piece in *Arthritis and Rheumatism*, *The Rheumatologist*, *Clinical Infectious Diseases*, *Clinical*

Gastroenterology and Hepatology, *American Family Physician*, *Annals of Internal Medicine*, *Annals of Emergency Medicine* and *Neurology* for 3 years

f) For quarterly presentation as a printed information piece in the *Journal of Clinical Oncology* for 5 years

The REMS journal information pieces are appended to this document (see Attachments D, E, F, G, H, I, and J)

C. Timetable for Submission of Assessments

REMS assessments will be submitted to FDA at 18 months, 3 years, and 7 years after approval. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date so that it will be received by the FDA on or before the due date.

ATTACHMENT A: MEDICATION GUIDE

The Medication Guide was reviewed separately and is not appended here.

ATTACHMENT B: DEAR HEALTHCARE PROVIDER LETTER

Genentech
A Member of the Roche Group

January 2010

IMPORTANT SAFETY INFORMATION
Regarding ACTEMRA® (tocilizumab)

Dear Healthcare Provider:

The purpose of this letter is to inform you of important safety information for ACTEMRA® (tocilizumab), a new interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more TNF antagonist therapies.

ACTEMRA targets IL-6. FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for ACTEMRA to ensure that the benefits of the drug outweigh the potential risks of serious infections, gastrointestinal perforations, changes in liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, elevations in lipid parameters in peripheral blood, demyelinating disorders and malignancies.

IMPORTANT SAFETY INFORMATION ON KNOWN AND POTENTIAL RISKS

Serious Infections

- Patients treated with ACTEMRA are at increased risk for developing serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral and other opportunistic infections. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.
- ACTEMRA should not be administered during an active infection, including localized infections. If a serious infection develops, ACTEMRA should be interrupted until the infection is controlled.
- Prior to initiating ACTEMRA, a test for latent TB should be performed. If the test is positive, treatment for TB should be started prior to starting ACTEMRA. All patients should be monitored for active TB during treatment, even if the initial latent TB test is negative.

Gastrointestinal Perforations

- Events of gastrointestinal (GI) perforations have been reported in Phase III clinical trials, primarily as complications of diverticulitis, including generalized purulent peritonitis, lower GI perforation, fistula and abscess. ACTEMRA should be used with caution in patients who may be at increased risk for GI perforation. Patients

presenting with new-onset abdominal symptoms should be evaluated promptly for early identification of GI perforation.

- During the six-month Phase III clinical trials, the overall rate of GI perforations was 0.26 events per 100 patient-years with ACTEMRA therapy versus no events for control.
- Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids or methotrexate.

Potential Risk of Demyelinating Disorders

- The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies. Patients should be closely monitored for signs and symptoms potentially indicative of demyelinating disorders. Prescribers should exercise caution in considering the use of ACTEMRA in patients with preexisting or recent onset demyelinating disorders.

Potential Risk of Malignancies

- The impact of treatment with ACTEMRA on the development of malignancies is not known, but malignancies were observed in clinical studies. ACTEMRA is an immunosuppressant and treatment with immunosuppressants may result in an increased risk of malignancies.

IMPORTANT INFORMATION ON LABORATORY ABNORMALITIES

Hepatic transaminases, lipids, neutrophils and platelets should be monitored, as abnormalities in these parameters were associated with ACTEMRA treatment in Phase III clinical trials. Prior to initiating treatment with ACTEMRA, it is recommended that appropriate baseline laboratory parameters be measured. While on ACTEMRA, liver aminotransferases (ALT, AST), neutrophil counts and platelet counts should be measured every 4 to 8 weeks. Total cholesterol and low-density lipoproteins should be measured 4 to 8 weeks after the first infusion and every 6 months thereafter. Dosage modifications may be required if laboratory abnormalities occur. Please see the accompanying full Prescribing Information for more information.

REPORTING ADVERSE EVENTS

It is important that you report all serious adverse events that occur in patients being treated with ACTEMRA, even if you do not think there is a causal relationship. The information you provide about these events may inform therapy and monitoring decisions.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.* You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

FULL PRESCRIBING INFORMATION AND MEDICATION GUIDE

This letter is not a comprehensive description of the risks associated with the use of ACTEMRA. Please read the accompanying full Prescribing Information and Medication Guide for a complete description of these risks.

You are advised to discuss the risks that may be associated with ACTEMRA therapy with patients and their caregivers. The ACTEMRA Medication Guide must be provided to patients being treated with ACTEMRA before each infusion. This Medication Guide contains information that can be used to facilitate discussions about the known and potential risks of therapy. A copy is enclosed.

Should you require additional copies of the ACTEMRA Medication Guide, you may:

- Request copies from Genentech by calling the toll-free medical information line at 1-800-ACTEMRA (1-800-228-3672)
- Print copies of the Medication Guide from the ACTEMRA Web site at www.ACTEMRA.com

For more information, please call 1-800-ACTEMRA or visit www.ACTEMRA.com

Sincerely,

Hal Barron, MD
Chief Medical Officer, USA
Genentech, Inc.

Enclosure

ATTACHMENT C: DEAR PHARMACIST LETTER

Genentech
A Member of the Roche Group

January 2010

IMPORTANT SAFETY INFORMATION
Regarding ACTEMRA® (tocilizumab)

Dear Pharmacist:

The purpose of this letter is to inform you of important safety information for ACTEMRA® (tocilizumab), a new interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more TNF antagonist therapies.

ACTEMRA targets IL-6. FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for ACTEMRA to ensure that the benefits of the drug outweigh the potential risks of serious infections, gastrointestinal perforations, changes in liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, elevations in lipid parameters in peripheral blood, demyelinating disorders and malignancies.

MEDICATION GUIDE

The FDA requires that a copy of the enclosed ACTEMRA Medication Guide be distributed to each patient who receives ACTEMRA. An ACTEMRA Medication Guide will be packaged with every vial of ACTEMRA. You should ensure that each dispensed vial of ACTEMRA includes a Medication Guide.

Should you require additional copies of the ACTEMRA Medication Guide, you may:
- Request copies from Genentech by calling the toll-free medical information line at 1-800-ACTEMRA (1-800-228-3672)
- Print copies of the Medication Guide from the ACTEMRA Web site at www.ACTEMRA.com

IMPORTANT SAFETY INFORMATION ON KNOWN AND POTENTIAL RISKS

Serious Infections
- Patients treated with ACTEMRA are at increased risk for developing serious infections leading to hospitalization or death including tuberculosis (TB), bacterial,

invasive fungal, viral and other opportunistic infections. Most patients who developed these infections were taking concomitant immunosupressants such as methotrexate or corticosteroids.

- ACTEMRA should not be administered during an active infection, including localized infections. If a serious infection develops, ACTEMRA should be interrupted until the infection is controlled.
- Prior to initiating ACTEMRA, a test for latent TB should be performed. If the test is positive, treatment for TB should be started prior to starting ACTEMRA. All patients should be monitored for active TB during treatment, even if the initial latent TB test is negative.

Gastrointestinal Perforations

- Events of gastrointestinal (GI) perforations have been reported in Phase III clinical trials, primarily as complications of diverticulitis, including generalized purulent peritonitis, lower GI perforation, fistula and abscess. ACTEMRA should be used with caution in patients who may be at increased risk for GI perforation. Patients presenting with new-onset abdominal symptoms should be evaluated promptly for early identification of GI perforation.
- During the six-month controlled clinical trials, the overall rate of GI perforations was 0.26 events per 100 patient-years with ACTEMRA therapy versus no events for control.
- Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids or methotrexate.

Potential Risk of Demyelinating Disorders

- The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies. Patients should be closely monitored for signs and symptoms potentially indicative of demyelinating disorders. Prescribers should exercise caution in considering the use of ACTEMRA in patients with preexisting or recent onset demyelinating disorders.

Potential Risk of Malignancies

- The impact of treatment with ACTEMRA on the development of malignancies is not known, but malignancies were observed in clinical studies. ACTEMRA is an immunosuppressant and treatment with immunosuppressants may result in an increased risk of malignancies.

IMPORTANT INFORMATION ON LABORATORY ABNORMALITIES

Hepatic transaminases, lipids, neutrophils, and platelets should be monitored, as abnormalities in these parameters were associated with ACTEMRA treatment in Phase III clinical trials. Prior to initiating treatment with ACTEMRA, it is recommended that appropriate baseline laboratory parameters be measured. While on ACTEMRA, liver aminotransferases (ALT, AST), neutrophil counts and platelet counts should be measured every 4 to 8 weeks. Total cholesterol and low-density lipoproteins should be measured 4 to 8 weeks after the first infusion and every 6 months thereafter. Dosage modifications may be required if laboratory abnormalities occur. Please see the accompanying full Prescribing Information for more information.

REPORTING ADVERSE EVENTS

It is important that you report all serious adverse events that occur in patients being treated with ACTEMRA. If you become aware of a patient who has developed a serious adverse event while being treated with ACTEMRA, it is important that you report the case, even if you do not think there is a causal relationship. The information you provide about these events may inform therapy and monitoring decisions.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.* You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

This letter does not include a comprehensive description of the risks associated with the use of ACTEMRA. Please read the accompanying full Prescribing Information and Medication Guide for a complete description of these risks.

For more information, please call 1-800-ACTEMRA or visit www.ACTEMRA.com.

Sincerely,

Hal Barron, MD
Chief Medical Officer, USA
Genentech, Inc.

Enclosure

ATTACHMENT D: JOURNAL INFORMATION PIECE FOR EMERGENCY MEDICINE PHYSICIANS AND EMERGENCY MEDICAL SERVICES PROFESSIONALS

Important Safety Information for Emergency Medicine Physicians
About Potential Risks of Infection and Gastrointestional Perforation With ACTEMRA®

ACTEMRA® (tocilizumab) is a new interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies. **Emergency medicine physicians** should be aware of important safety information regarding ACTEMRA.

Serious infections: Patients treated with ACTEMRA are at increased risk for developing serious infections leading to hospitalization or death. These infections include tuberculosis (TB), bacterial, invasive fungal, viral and other opportunistic infections.

Gastrointestional perforations: Gastrointestinal (GI) perforations have been reported in Phase III clinical trials, primarily as complications of diverticulitis. Reported perforations have involved generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids or methotrexate. Patients presenting with new-onset abdominal symptoms should be evaluated promptly for early identification of GI perforation.

In addition to these adverse events, patients treated with ACTEMRA may have elevated hepatic transaminases and lipids, and decreased neutrophils and platelet counts. Dosage modifications may be required if laboratory abnormalities occur. Please see the full Prescribing Information for more information.

Reporting Adverse Events
It is important that you report all serious adverse events that occur in patients being treated with ACTEMRA, even if you do not think there is a causal relationship. The information that you provide about these events may inform therapy and monitoring decisions for future patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting*. You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Please visit www.ACTEMRA.com for full Prescribing Information and Medication Guide.

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ATTACHMENT E: JOURNAL INFORMATION PIECE FOR GASTROENTEROLOGISTS AND HEPATOLOGISTS

Important Safety Information for Gastroenterologists and Hepatologists About Potential Risks of Gastrointestional Perforation and Transaminase Elevations With ACTEMRA®

ACTEMRA® (tocilizumab) is a new interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies. **Gastroenterologists** and **hepatologists** should be aware of important safety information regarding ACTEMRA.

Gastrointestional perforations: Gastrointestinal (GI) perforation has been reported in Phase III clinical trials, primarily as complications of diverticulitis, including generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids or methotrexate. ACTEMRA should be used with caution in patients who may be at increased risk for GI perforation. Patients presenting with new-onset abdominal symptoms should be evaluated promptly for early identification of GI perforation.

Transaminase elevations: Treatment with ACTEMRA was associated with a higher incidence of transaminase elevations in Phase III clinical trials. These elevations did not result in apparent permanent or clinically evident hepatic injury with modification of the treatment regimen, which resulted in a decrease or normalization of liver enzymes. Patients receiving ACTEMRA should be monitored for elevated transaminase levels and dose modifications may be necessary. When clinically indicated, other liver function tests, such as bilirubin, should be considered. Please see the full Prescribing Information for more information.

Reporting Adverse Events
It is important that you report any serious gastrointestinal adverse events, including GI perforation, hepatic disease or hepatic impairment, that occur in a patient being treated with ACTEMRA, even if you do not think there is a causal relationship. The information that you, as a gastroenterologist or hepatologist, provide about these events may inform therapy and monitoring decisions for future patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.* You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Please visit www.ACTEMRA.com for full Prescribing Information and Medication Guide.

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ATTACHMENT F: JOURNAL INFORMATION PIECE FOR INFECTIOUS DISEASE SPECIALISTS

Important Safety Information for Infectious Disease Specialists About Potential Risks of Infections With ACTEMRA®

ACTEMRA® (tocilizumab) is a new interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more TNF antagonist therapies. **Infectious disease specialists** should be aware of important safety information regarding ACTEMRA.

Serious infections: Patients treated with ACTEMRA are at increased risk for developing serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral and other opportunistic infections.

ACTEMRA should not be administered during an active infection, including localized infections. If a serious infection develops, ACTEMRA should be interrupted until the infection is controlled.

Reporting Adverse Events
It is important that you report all serious infections that occur in patients being treated with ACTEMRA, even if you do not think there is a causal relationship. The information that you, as an infectious disease specialist, provide about these events may inform therapy and monitoring decisions for future patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.* You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Please visit www.ACTEMRA.com for full Prescribing Information and Medication Guide.

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ATTACHMENT G: JOURNAL INFORMATION PIECE FOR INTERNISTS AND INTERNAL MEDICINE SUBSPECIALISTS

Important Safety Information for Physicians About Risks in Patients Receiving ACTEMRA®

ACTEMRA® (tocilizumab) is a new interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more TNF antagonist therapies. Physicians should be aware of important information regarding safety and laboratory monitoring recommendations for ACTEMRA.

Serious infections: Patients treated with ACTEMRA are at increased risk for developing *serious infections* leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral and other opportunistic infections.

Gastrointestinal perforations: Gastrointestinal (GI) perforations have been reported in Phase III clinical trials, primarily as complications of diverticulitis, including generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids or methotrexate. ACTEMRA should be used with caution in patients who may be at increased risk for GI perforation. Patients presenting with new-onset abdominal symptoms should be evaluated promptly for early identification of GI perforation.

Demyelinating disorders: The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies. Patients should be closely monitored for signs and symptoms potentially indicative of demyelinating disorders. Prescribers should exercise caution in considering the use of ACTEMRA in patients with preexisting or recent onset demyelinating disorders.

Malignancies: Malignancies were observed in clinical studies of ACTEMRA. The impact of treatment with ACTEMRA on the development of the malignancies is not known, but malignancy is a known risk of biological products that suppress the immune system. ACTEMRA is an immunosuppressant and may increase the risk of malignancies.

Laboratory abnormalities: Hepatic transaminases, lipids, neutrophils and platelets should be monitored, as abnormalities in these parameters were associated with ACTEMRA treatment in Phase III clinical trials. Dosage modifications may be required if laboratory abnormalities occur. Please see the full Prescribing Information for more information.

Reporting Adverse Events
It is important that you report all serious adverse events that occur in patients being treated with ACTEMRA, even if you do not think there is a causal relationship. As an ACTEMRA-prescribing rheumatologist, the information you provide about these events may inform therapy and monitoring decisions for future patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.* You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Please visit www.ACTEMRA.com for full Prescribing Information and Medication Guide.

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ATTACHMENT H: JOURNAL INFORMATION PIECE FOR NEUROLOGISTS

Important Safety Information for Neurologists About Demyelinating Disorders in Co-managing Rheumatoid Arthritis Patients Receiving ACTEMRA®

ACTEMRA® (tocilizumab) is a new interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more TNF antagonist therapies. **Neurologists** co-managing RA patients should be aware of important safety information regarding treatment with ACTEMRA.

Demyelinating disorders: The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies. Patients should be closely monitored for signs and symptoms potentially indicative of demyelinating disorders. Prescribers should exercise caution in considering the use of ACTEMRA in patients with preexisting or recent onset demyelinating disorders.

Reporting Adverse Events
It is important that you report any serious neurologic adverse event, including demyelinating disorders, that occurs in a patient being treated with ACTEMRA, even if you do not think there is a causal relationship. The information that you, as a neurologist, provide about these events may inform therapy and monitoring decisions for future RA patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting*. You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

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ATTACHMENT I: JOURNAL INFORMATION PIECE FOR ONCOLOGISTS

Important Safety Information for Oncologists
About Malignancy Risk With ACTEMRA®

ACTEMRA® (tocilizumab) is a new interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more TNF antagonist therapies. **Oncologists** should be aware of important safety information about ACTEMRA.

Malignancies were observed in clinical studies of ACTEMRA. The impact of treatment with ACTEMRA on the development of the malignancies is not known, but malignancy is a known risk of biological products that suppress the immune system. ACTEMRA is an immunosuppressant and may increase the risk of malignancies.

Reporting Adverse Events
If you are consulted to a see a patient with cancer at any time after receiving ACTEMRA therapy, it is important that you report the case, even if you do not think there is a causal relationship. The information that you, as an oncologist, provide about these events may inform therapy and monitoring decisions for future patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.* You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

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ATTACHMENT J: JOURNAL INFORMATION PIECE FOR RHEUMATOLOGISTS

Important Safety Information for Rheumatologists About Risks in Patients Receiving ACTEMRA®

ACTEMRA® (tocilizumab) is a new interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more TNF antagonist therapies. Rheumatologists should be aware of important information regarding safety and laboratory monitoring recommendations for ACTEMRA.

Serious infections: Patients treated with ACTEMRA are at increased risk for developing *serious infections* leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral and other opportunistic infections.

Gastrointestinal perforations: Gastrointestinal (GI) perforations have been reported in Phase III clinical trials, primarily as complications of diverticulitis, including generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids or methotrexate. ACTEMRA should be used with caution in patients who may be at increased risk for GI perforation. Patients presenting with new-onset abdominal symptoms should be evaluated promptly for early identification of GI perforation.

Demyelinating disorders: The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies. Patients should be closely monitored for signs and symptoms potentially indicative of demyelinating disorders. Prescribers should exercise caution in considering the use of ACTEMRA in patients with preexisting or recent onset demyelinating disorders.

Malignancies: Malignancies were observed in clinical studies of ACTEMRA. The impact of treatment with ACTEMRA on the development of the malignancies is not known, but malignancy is a known risk of biological products that suppress the immune system. ACTEMRA is an immunosuppressant and may increase the risk of malignancies.

Laboratory abnormalities: Hepatic transaminases, lipids, neutrophils and platelets should be monitored, as abnormalities in these parameters were associated with ACTEMRA treatment in Phase III clinical trials. Dosage modifications may be required if laboratory abnormalities occur. Please see the full Prescribing Information for more information.

Reporting Adverse Events
It is important that you report all serious adverse events that occur in patients being treated with ACTEMRA, even if you do not think there is a causal relationship. As an ACTEMRA-prescribing rheumatologist, the information you provide about these events may inform therapy and monitoring decisions for future patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.* You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 13, 2008
To:	Bob Rappaport, M.D. Director Division of Analgesics, Anesthetics, & Rheumatology Products, (HFD-170)
Thru:	Solomon Iyasu, MD, MPH, Director Division of Epidemiology (DEpi), HFD-460
From:	Carolyn A McCloskey, MD, MPH, Epidemiologist Division of Epidemiology (DEpi), HFD-460, Mail Stop 3411
Subject:	Actemra (tocilizumab) RiskMap Review
Drug Name(s):	Actemra (tocilizumab)
Submission Number:	Original submission
Application Type/Number:	BLA No. 125276
Applicant/sponsor:	Roche
OSE RCM #:	2008-357

TABLE OF CONTENTS

1 INTRODUCTION

The Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) requested a review of the proposed "Risk Management Plan" submission before approving the new BLA for Actemra/tocilizumab (TCZ) for the treatment of adult onset moderate to severe active rheumatoid arthritis (RA). TCZ is a new product, a recombinant humanized anti-human monoclonal antibody against the interleukin 6 receptor (IL-6R) which is the first in its class. The "Risk Management Plan" (RMP) document includes information on TCZ safety risks (identified and potential), and the sponsor's plan for managing safety issues with TCZ. The RMP includes proposed labeling and pharmacovigilance activities which include adverse event (AE) monitoring and collection, institution of a pharmacovigilance board, development of questionnaires to capture information of serious infections, and monitoring safety in ongoing or planned studies using data from registries and claims databases.

2 MATERIAL REVIEWED

The materials reviewed were:

1. Section 2.7.4, "Summary of Clinical Safety" for 'Actemra (tocilizumab), treatment of RA' (Original BLA, Item 8, pages 1 – 271 of mostly text and pages 272 – 10,646 of tables)
2. The 'Risk Management Plan for Actemra (tocilizumab) for the Treatment of Rheumatoid Arthritis in Adult Patients with Moderately to Severely Active Disease' (Original BLA, Item 8, pages 1 – 38) provided with the consult request.
3. Sections 5 and 6, '5. Overview of Safety' and '6. Benefits and Risks Conclusions' (Original BLA, Item 8, pages 33 – 60)

3 RESULTS OF REVIEW

3.1 CLINICAL TRIAL SAFETY INFORMATION

The "Summary of Clinical Safety" for Actemra/tocilizumab (TCZ) includes safety data from five adequate and well-controlled, double blind, international, Phase III studies in adult patients with moderate to severe active RA who had an inadequate response to methotrexate (MTX), other disease modifying antirheumatic drugs (DMARDs), or anti-tumor necrosis factor (TNF) therapies while on MTX (WA17822, WA17823, WA17824, WA18062, WA18063). These clinical trials studied TCZ used alone or in combination with MTX or with other non- DMARDs (TCZ 8 mg/kg alone, TCZ 4 and 8 mg/kg+MTX, TCZ 8 mg/kg+DMARD). The comparator groups received placebo +DMARD or MTX. The safety analyses were conducted using pooled data from these 5 studies ('pooled 6 month studies') and the long-term safety information is from ongoing open-label extensions of two of these studies (WA18695, WA18696). Additional safety information from Japan and Europe was collected from Chugai Pharmaceutical Co. Ltd, a co-development partner with the sponsor.

There were several situations where the TCZ dose was allowed to be changed or stopped. Those patients who did not have an adequate response to TCZ were allowed an increase in their TCZ dose to 8 mg/kg from 4 mg/kg or to 4 mg/kg from placebo, plus they were allowed to have intra-articular or to increase their oral dose of corticosteroids. TCZ was stopped temporarily for ALT or AST ≥3 x ULN (upper limits of normal) or for clinical signs of toxicity or infections. TCZ was stopped permanently for a second missed dose of TCZ for ALT or AST ≥3 x ULN, consecutive missed doses for ALT or AST elevations, ALT or AST >5 x ULN, total bilirubin

>2.5mg/dL or unconjugated bilirubin >2 x ULN, or absolute neutrophil count (ANC) <0.5 x 10^9/L, or drug toxicity or severe infection (determined by the investigator). Other changes to the protocol included prohibition of immunization with a live or attenuated vaccine and, due to serious gastrointestinal (GI) events, exclusion of patients with GI conditions that might predispose to GI perforations including Crohn's disease and ulcerative colitis.

There were 4098 patients participating in the safety studies and 3728 patients received at least one dose of TCZ. There were 2439 patients who continued in the long-term safety extension studies designed to follow patients up to 5 years. Of those treated with TCZ, 2958 of them were treated for 6 months, 1537 continued treatment for 12 months, 678 for 18 months and 11 for 27 months. The five controlled Phase III studies included RA patients with early disease, MTX-naïve patients, partial responders to standard non-biologic DMARDs, and non-responders to anti-tumor necrosis factor (TNF) agents.

For analyses, of the 4,098 patients included in the pooled and long-term safety studies, the comparator groups consisted of 1170 patients on placebo+MTX or DMARD and 284 on MTX monotherapy. The treatment groups consisted of 2644 patients on TCZ with or without MTX or DMARD:

- 774 on TCZ 4 mg/kg+MTX,
- 1582 on TCZ 8 mg/kg+MTX or DMARD,
- 288 on TCZ 8 mg/kg monotherapy;

It is not clear why so many patients were excluded from the 3728 TCZ-treated patients for the safety analyses. The cumulative dose of TCZ ranged from 0.1 to 2.2 years, mean 0.83 years and median 0.73 years.

Infections were the most common adverse events (AE) in the TCZ monotherapy and combination therapy groups and in the MTX group but the rate of infections was higher in the TCZ groups than in the MTX group (no statistical calculations were reported). The AEs that were more frequent in the TCZ 8 mg/kg group than the MTX group were abdominal pain/discomfort, headache, dizziness, rash, pruritis, elevated blood pressure, neutropenia, leucopenia and hyperlipidemia; most of which were mild and transient. The combination TCZ groups also had a higher frequency of mouth ulcerations and elevated liver enzymes.

There were 26 (0.4%) deaths in all RA studies of 6315 patients (not just the safety studies) of which 21 (0.5%) deaths were in the safety trials of 4098 patients. There were 16 (0.6%) deaths in the TCZ group of 2644 and 5 (0.4%) in the control group of presumed 1170 patients, see Table 1. Eight of the TCZ deaths occurred within the first 6 months of treatment (3 cardiovascular, 1 post surgical infection, 1 GI hemorrhage, 1 suicide, 1 polyneuropathy and 1 unknown death). The other 8 TCZ deaths occurred after 6 months (4 infection, 1 diverticular perforation, 2 cardiovascular, 1 gastric cancer). The mortality rates by person-years (PY) were higher in the control groups (placebo + DMARD and MTX groups) than for the TCZ group, see Table 1. The overall TCZ death rate was 0.51 per 100 PY. Of note, in a RA study to estimate the relative risk of overall mortality rates in RA patients (not referenced), the mortality rate for RA patients on anti-TNF therapy was 1.6 per 100 PY and 3.5 per 100 PY for RA patients not on anti-TNF therapy.

Table 1. RA Studies' Mortality Rates, Per Patient and Per Person-Years (PY)

Study Type	Total Patients	Deaths (%)	Mortality Rate per 100 PY
All RA studies	6315	26 (0.4)	
Safety Studies, all patients	4098	21 (0.5)	
Safety Studies, TCZ group	2644 (3112 PY)	16 (0.6)	0.51
Safety Trials, TCZ, 1st 6 months		8	0.41
Safety Extension Studies, Long Term		8	0.42
Safety Trials, Control group	1170	5 (0.4)	
Safety Trials, Placebo + DMARD			0.80
Safety Trials, MTX			0.75
RA Mortality Study, anti-TNF Therapy			1.6
RA Mortality Study, not on anti-TNF			3.5

The most common reasons for withdrawal of TCZ were elevated liver function tests and neutropenia as required by the protocol. These withdrawals were more frequent in the TCZ combination group followed by the MTX group and lastly the TCZ monotherapy group. For patients withdrawn due to infections, the most common infection was pneumonia.

The most common reasons for dose modification or interruption of TCZ were infections (mostly upper respiratory infections), elevated liver enzymes and GI disorders. The dose changes were more frequent in the TCZ monotherapy than the MTX group and lastly in the TCZ combination groups.

There were two opportunistic infections, *Mycobacterium avium* complex infection and *Pneumoncystis jirovecii* pneumonia, both in patients who received TCZ in the 6 month pooled safety data.

OSE Comments: The safety profile of TCZ appears to be acceptable within the limitations of the clinical trials which excluded many RA patients with co-morbid disease conditions. TCZ was stopped or the dose reduced for ALT or AST elevations and for very low ANCs. Once on the market, TCZ may be given to patients with the excluded conditions who may not be monitored as closely as in the trials and who may not have a change in TCZ dose based on the lab results.

3.2 Proposed Labeling and Pharmacovigilance Plan

Roche proposes two parts to the "The Risk Management Plan" for Actemra (Tocilizumab), 1), prescriber and patient labeling and 2), pharmacovigilance.

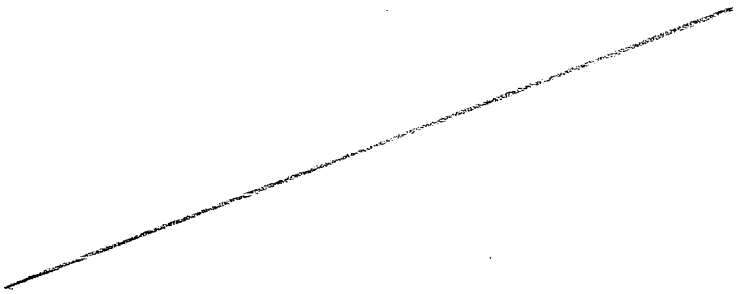
3.2.1 Labeling

The proposed labeling for the warnings section includes "serious infections", "serious hypersensitivity reactions" (including anaphylaxis), "neutropenia", and "elevated hepatic transaminases". Also, as relates to infections, the proposed dosage modifications section states that the TCZ should be "interrupted... until the infection is controlled". The proposed vaccinations section states that "vaccines should not be given concurrently with Actemra...". Other AEs in the proposed AE section include "elevated lipid levels", "immunogenicity", and, in the proposed drug interactions section, "CYP450 normalization" including drug interactions such

as with warfarin and cyclosporine. The proposed pregnancy section includes "Pregnancy Category C" and a registry phone number.

OSE Comments: The AEs are in the proposed labeling which includes the recommendation to "interrupt" TCZ if the patient develops a serious infection. The other dose modifications required in the clinical trials for ALT or AST elevations and very low ANC levels are not specifically mentioned in the proposed label. Of note, the advisory committee which met on July 29, 2008 had concerns with the liver function and lipid monitoring.

3.2.2 Pharmacovigilance



b(4)

3.2.2.1 Reporting

Current requirements for reporting of AEs are that serious and unlabeled AEs must be submitted as 15-day reports and labeled or non-serious AEs must be submitted as periodic reports quarterly (within 30 days of the close of the quarter) for the first three years after approval then annually. Serious AEs are defined as death, life-threatening, hospitalization or prolonged hospitalization, disability, or congenital anomaly. Roche acknowledged that they will submit "expedited" (15-day) and periodic AE reports (5.2.1 of RMP).

OSE Comments: Roche is proposing reporting as required by the FDA.

b(4)

3.2.2.3 Guided Questionnaires/Case Report Forms

The guided questionnaires or case report forms will be used to elicit specific information and standardize the collection of the information to help in the evaluation of cases of serious infections.

OSE Comments: No information was provided on these forms which apparently are for use upon Roche being notified of an AE, nor was there information on how often or how long the company will follow-up on serious infections. Enough detail should be solicited at each reporting or follow-up of an AE to determine any pre-existing conditions that might pre-dispose the patient to a serious infection, what factors might influence the emergence of the infection, what treatments were tried and the extent of their treatment success.

3.2.2.4 Clinical Trials and Observational Studies

The sponsor is continuing to evaluate safety risks by extending observation of ongoing clinical trials by 5 years, and, as needed, proposes to initiate additional clinical trials and implement observational studies in pre-existing registries and claims databases.

The ongoing clinical trials include the two long-term extension studies, a joint damage study, a simvastatin (CYP3A4 substrate) drug interaction study, and an ECG study. The planned studies include a children's safety and efficacy study in systemic-onset juvenile idiopathic arthritis and polyarticular juvenile idiopathic arthritis, and a vaccine safety and efficacy study in one of the ongoing open-label extension studies.

Data from existing patient registries will be considered for developing observational studies. The patient registries that already exist are:

- RA registries for patients receiving biologicals in the European Union (EU) (including the UK, Sweden, Germany, and Denmark) and in the US; and
- Pregnancy registries in the US (Organization of Teratology Information Specialists (OTIS)) and the EU (European Network of Teratology Information Services (ENTIS)).

Additional observational studies are proposed using claims databases with safety outcome either validated with medical record review or restricted to hospitalization data only. Proposed studies will include comparator cohorts of RA patients on other RA treatments including other biologicals. The outcome evaluated will focus on serious infections, serious hypersensitivity reactions, clinical manifestations of elevated hepatic transaminases, clinical manifestations of elevated lipids, malignancies (long latency periods), demyelinating disorders and pregnancy related issues. Proposed claims databases include United Health Care (UHC)/i3 and MarketScan in the US which include hospital prescriptions of biologicals.

OSE Comments:

Regarding the ongoing long-term open-label studies, these patients are all on TCZ and there is no proposed comparator group. The proposed duration is an additional 5 years of follow-up (the clinical trials were 6 months); however this might not be long enough for malignancies to develop such as those associated with anti-TNF therapies but 5 years may be adequate to identify promoters if they are known. The sample size of 2439 patients enrolled from the core 6 month safety trials is very small to detect rare adverse events and, as patients drop out over time, that number will decrease. Also, over time, new therapies may impact the management of RA patients and the small sample size will not provide enough power to detect significant differences in the incidences of adverse events. The sites for these continuing studies include Europe, South America and the USA although the number of US patients was not provided. Exclusion of certain patients with pre-existing conditions from the clinical trials (malignancies, infections, GI perforation conditions, etc.) pre-empt generalization to all patients. Once released on the market, the patients exposed to TCZ may include sicker patients or those with underlying conditions that might predispose them to drug interactions or adverse events.

Patient registries do not always provide comparator groups to fully study the risk of adverse events although disease specific registries may include patients on different treatments which could be compared if the sample size is large enough. Registries may offer some information on signal generation and prevalence of AEs. The existing registries are a benefit in that respect.

Claims databases have limitations in that claims are recorded based on which ICD-9 codes provide the most financial rewards, not necessarily which disease is of most concern; therefore, the codes need to be validated. In addition, claims databases usually do not have comprehensive information on prior health histories. However, Roche indicates that some claims databases contain biological treatment data and therefore may be helpful in studying TCZ AEs. Access to medical record reviews may also provide helpful information.

4 CONCLUSIONS

As presented by Roche, the adverse events (mostly infections, GI disorders, neutropenia, elevated liver function tests, and hyperlipidemia) associated with tocilizumab appear to be greatest for the TCZ combination therapy, less for the monotherapy and generally even less for MTX but the differences are small and the overall numbers of AEs identified are small. Roche proposes labeling and pharmacovigilance carried out through routine reporting of AEs and by analyzing data from ongoing studies or through pre-existing registries and claims data. Roche reports that the medical management of the AEs can be achieved by changes in dose, stopping the medication and by other medical interventions. Once marketed though, tocilizumab will be administered to greater numbers of patients and to patients with more complicated medical conditions than those in the clinical trials. At this time there is no apparent need for more risk management or pharmacovigilance activities but, as with any new treatment product, spontaneous reports of AEs noted in the clinical trials as well as AEs associated with other monoclonal antibody therapies should be monitored closely especially during the first several years on the market. Other components of a risk management/minimization plan should be considered if necessary as more is learned about the safety of tocilizumab.

The following suggested requests for information or questions to Roche regarding their proposed "Risk Management Plan" stem mainly from a request for more details:

- Will Roche include a notification to monitor liver function and lipid tests in the proposed label? If so, please provide proposed wording.
- Please provide more information on the proposed questionnaire for collecting AE data and how long the company will follow-up on serious AEs including infections. Please collect information on pre-existing conditions or other factors that might pre-dispose the patient to a serious AE including infections, what treatments were tried and the extent of those treatment successes.
- [redacted] b(4)
- [redacted] b(4)
- What criteria will the [redacted] use to determine the risk of an AE and whether or not a risk mitigation needs to be put in place. b(4)
- What criteria will the [redacted] use to "assess the sufficiency of risk management measures"? b(4)
- What will trigger a study in the registries or claims databases, for example how much of an increase in the reporting rate of an AE?

- Please describe and provide a protocol(s) for the potential studies that use registry and claims data. Specifically address the issues of case identification ,ascertainment and validation, identifying a comparator group, measurement of exposure(s), confounders, loss to follow-up, sample size, etc.
- What information about the pharmacoepidemiology board's decisions and Roche's responses will be reported to FDA? What format and how frequently will that information be communicated to the FDA (for example, by a special report, the next periodic report, or annual report)?
- Consider extending the follow-up of the ongoing continuation studies (WA18695, WA18696) to 10 years to better capture possible long latency AEs such as malignancies.

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Concur:

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