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RESEARCH**

APPLICATION NUMBER:
BLA 125276/S049

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
Office of Medication Error Prevention and Risk Management**

Final Review of an Amendment to the Proposed Risk Evaluation and Mitigation Strategy (REMS) Modification for ACTEMRA

Date: September 26, 2012; *Revised October 3, 2012*

Reviewer(s): Carolyn L. Yancey, M. D., F. A. A. P., Senior Medical Officer, Risk Management Analyst, Division of Risk Management (DRISK)

Team Leader: Kendra Worthy, Pharm. D., DRISK

Division Director: Claudia Manzo, Pharm. D., DRISK

Drug Name(s): ACTEMRA (tocilizumab)

Therapeutic Class: Human Interleukin-6 Receptor Inhibitor

Dosage and Route: Adult dosage: 4 mg/kg every 4 weeks followed by an increase to 8 mg/kg every 4 weeks
Pediatric dosage: 12 mg/kg in patients less than 30 kg and 8 mg/kg in patients at or above 30 kg, every 2 weeks with systemic juvenile idiopathic arthritis

Application/Number: BLA 125-276/Supplement 049/Sequence 113, Amendment to A Pending Supplement Application: Revised Proposed REMS Modification for ACTEMRA (submitted September 20, 2012)

Application: Genentech, Inc.

OSE RCM: 2012-288

TSI: 108

EXECUTIVE SUMMARY

This Division of Risk Management (DRISK) review evaluates an amendment to the proposed Risk Evaluation and Mitigation Strategy (REMS) Modification for Actemra submitted on September 20, 2012 in the Supplemental Biologics License Application (sBLA) 125-276 submission (Supplement 049/ Sequence 113). The original proposed REMS Modification for Actemra was submitted in Supplement 049/Sequence 075 [dated December 13, 2011; amended on June 5, 2012 (Sequence 094)] for the proposed claim of use of Actemra in rheumatoid arthritis (RA) patients with an inadequate response to [REDACTED] (b) (4) population. This supplement also reports new cases of hypersensitivity reactions, including anaphylaxis, a known risk with infusion of Actemra.

The DRISK completed review of the applicant's amendment to the proposed REMS Modification for Actemra (Sequence 113) and concluded that the applicant incorporated all of the required revisions cited in the DRISK Interim Comments Review (dated September 14, 2012) ¹ as well as other appropriate minor revisions. See **Section 7, Attachments**, to this review, for the final clean version of the REMS Modification for Actemra and appended REMS materials including the REMS website-landing page.

1 INTRODUCTION

1.1 BACKGROUND

Details of the introduction, background, past regulatory history of Actemra, and the amendment to the proposed REMS Modification for Actemra (submitted on June 5, 2012; approved on June 20, 2012) are in the DRISK Interim Comments Review (dated September 14, 2012). ¹

The most recent modification for Actemra (approved on June 20, 2012) includes a communication plan and a timetable for submission of assessments of the REMS. Communication plan materials include a Dear Healthcare Provider letter, Prescriber Education Slide Deck, and journal information pieces for the professional journals of subspecialists likely to prescriber of Actemra.

1.2 REGULATORY HISTORY

Past regulatory history specific to review of the amendment to the proposed REMS Modification for Actemra (Sequence 113, dated September 20, 2012) follows:

- September 14, 2012: The DRISK completed an Interim Comments Review of the Proposed REMS Modification for Actemra (Supplement 049/Sequence 075, originally submitted on December 13, 2011; amended on June 5, 2012) and the Most Recent REMS Modification (approved on June 20, 2012).
- September 17, 2012: A REMS Information Request (IR) letter* was issued to the applicant with comments and required revisions in response to review of the proposed

¹ See DRISK Interim Comments Review on a Required REMS Modification for ACTEMRA, Set 1, (dated September 14, 2012) written by Carolyn L. Yancey, M.D., F.A.A.P., Senior Medical Officer, DRISK

REMS Modification for Actemra (dated December 13, 2011/Sequence 075; amended on June 5, 2012/Sequence 094) and conclusions in the DRISK Interim Comments Review, Set 1 (dated September 14, 2012).¹

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

The following material, listed by document date, reviewed from sBLA 125-276 (Supplement 049/Sequence 113) for an amendment to the proposed REMS Modification for Actemra is:

- September 20, 2012: The applicant submitted an Amendment To A Pending Application - Revised Proposed REMS for Actemra in a Prior Approval Supplement in response to the agency's REMS Information Request letter.*

2.2 OTHER MATERIALS REVIEWED TO INFORM THIS REVIEW

- September 12, 2012: The applicant submitted revised labeling for Actemra in Physician Labeling Rule (PLR) format. Changes include removal the claim for use of Actmerra in treatment of RA patients not responding to “at least one tumor-necrosis factor antagonist” based on approval of Supplement 046 (submitted on August 13, 2012) and updates to the Medication Guide (amendments submitted on August 20, 2012 and August 27, 2012).
- September 24, 2012: The Actemra Patient Labeling Review written by Sharon W. Williams, R.N., B.S.N., M.S.N., Division of Medical Policy Programs (DMPP)

2.3 ANALYSIS TECHNIQUE

The required Amendment to the Proposed REMS Modification for Actemra is reviewed for conformance with the DRISK required revisions (see **Section 1.2, Regulatory History** above).

3 APPLICANT'S AMENDMENT TO THE PROPOSED REMS MODIFICATION FOR ACTMERA

The applicant has submitted the following amendment to the proposed REMS Modification for Actemra (Sequence 113; dated September 20, 2012) in response to Agency comments:

1. In the REMS Document under the element, Communication Plan, insertion of “hypersensitivity reactions, including anaphylaxis” to the list of specific safety risks associated with Actemra described in the Prescriber Education Slide Deck.
2. In the Communication Plan materials, revisions include:
 - a. Insertion of the new claim for use of Actemra in “adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDS)” in the following appended REMS materials:
 - Dear Healthcare Provider letter (Attachment A)

- Prescriber Education Slide Deck (Attachment B)
 - Journal Information pieces (attachments C, D, E, F, G, H, and I)
 - REMS website, www.ACTEMRAREMS.com (Attachment J)
- b. Insertion of additional new safety data describing hypersensitivity reactions, including anaphylaxis, as reported in the long-term extension clinical studies and postmarketing safety data with Actemra, as well as infusion precautions during administration of Actemra is inserted in the following:
- Dear Healthcare Provider letter (Attachment A)
 - Prescriber Education Slide Deck (Attachment B)
 - Journal information pieces (Attachments C, and F)

The goals of the REMS, “to inform healthcare providers about the serious risks associated with ACTEMRA”, and the Timetable for Submission of REMS Assessments are the same as in the most recent modification approved June 20, 2012.

3.1 REMS ASSESSMENT PLAN

The applicant’s revised REMS assessment plan removes all items related to the Medication Guide and will include the following:

1. Evaluation of the prescribers’ understanding of the risks of ACTEMRA
2. A summary of all reported serious risks with an analysis of adverse event reporting by prescriber type (eg, rheumatologist, osteopath, infectious disease specialist, gastroenterologist, hepatologist, internal medicine specialist, hematology-oncology specialist, emergency medicine specialist, family medicine specialist, etc.), when available
3. Based on the information provided, an assessment and a conclusion of whether the REMS is meeting its goal and whether modifications to the REMS are needed

Rheumatologists account for greater than (b)(4)% of all Actemra prescribers (note: this information is supported by Wolters Kluwer claims data of filled prescriptions). Genentech concludes that rheumatologists are the appropriate representative sample of Actemra prescribers for the prescriber surveys.²

The timetable for submission of assessments will remain the same as that approved on January 8, 2010. The REMS assessment plan is summarized in the REMS Supporting Document and will be addressed in the REMS Approval letter (See **Section 6, Appended Information**, in this review).

3.2 REMS SUPPORTING DOCUMENT

The applicant’s revised REMS supporting document includes acceptable track changes with the following revisions:

² Pediatric rheumatologist account for (b)(4)% of all Actemra prescribers, primarily for treating systemic juvenile idiopathic arthritis

- Insertion of the claim for “... inadequate response to (b) (4),...” as stated in **Section 3**, above.
- Revised purpose of this submission (dated September 20, 2102) to update the REMS proposal (Document) and Supporting Document based on the DMARD-IR Supplemental BLA submission, the June 20, 2012 REMS Modification approval, and the FDA REMS Information Request dated September 17, 2012.
- Revisions that include insertion of “hypersensitivity reactions, including anaphylaxis” (as detailed in **Section 3**, above) to each appended REMS educational materials

4 DISCUSSION

The applicant’s amendment to the proposed REMS Modification for Actemra (dated September 20, 2012) in response to the Agency’s comments (dated September 17, 2012) includes the new claim for use of Actemra in patients with moderately to severely active RA who had inadequate response to DMARDs and informs prescribers about new safety data regarding hypersensitivity reactions, including anaphylaxis.

The REMS elements are unchanged; the above information inserted in the REMS Document and all appended REMS materials are included in the **Attachments** to this review. Revisions to the REMS Assessment Plan are consistent with revisions in the REMS Document and appended REMS materials. The revised REMS supporting document is consistent with the proposed amendments as summarized in **Section 3**, in this review. See **Section 7, Attachments**, in this review, for clean versions of the final REMS Modification for Actemra and all appended materials.

5 CONCLUSION

In conclusion, the amendment to the proposed REMS Modification for Actemra (submitted September 20, 2102) is acceptable to the DRISK and contains the agreed upon revisions to the REMS Document and appended REMS materials, including the REMS website landing page and the REMS assessment plan as stipulated by the Agency. The applicant has committed to update the appended REMS materials (as revised), to the REMS website-landing page.

6 APPENDED INFORMATION

The REMS assessment plan, as summarized in the REMS Supporting Document (submitted September 20, 2012, Sequence 113) will be included in the REMS approval letter.

The revised REMS assessments will include the following:

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

3. Based on the information provided, an assessment and a conclusion of whether the REMS is meeting its goal and whether modifications to the REMS are needed.

7 ATTACHMENTS

REMS Document

Appended REMS Material

(b)(4)

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/s/

CAROLYN L YANCEY

10/03/2012

Final Amendment to the Proposed REMS Modification for ACTEMRA (new claim for DMARD-IR in RA patients; additional safety data on hypersensitivity reactions, including anaphylaxis

CLAUDIA B MANZO

10/03/2012

concur

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

**Interim Comments on a Required Risk Evaluation and Mitigation Strategy (REMS)
Modification for ACTEMRA - Set # 1**

Date: September 5, 2012; *Revised September 14, 2012*

Reviewer(s): Carolyn L. Yancey, M.D., F.A.A.P., Senior Medical Officer, Risk Management Analyst, Division of Risk Management (DRISK)

Team Leader: Kendra Worthy, Pharm. D., DRISK

Division Director: Claudia Manzo, Pharm. D., DRISK

Drug Name(s): ACTEMRA (tocilizumab)

Therapeutic Class: Human Interleukin-6 Receptor Inhibitor

Dosage and Route: Adult dosage: 4 mg/kg every 4 weeks followed by an increase to 8 mg/kg every 4 weeks based on clinical response

Pediatric dosage: 12 mg/kg in patients less than 30 kg and 8 mg/kg in patients at or above 30 kg, every 2 weeks with systemic juvenile idiopathic arthritis

Application/Number: BLA 125-276/Supplement 049/Sequence 075 and 094: new controlled clinical studies and long-term data in support of ACTEMRA in patients with inadequate response to (b) (4) for adult patients with moderately to severely active rheumatoid arthritis

Applicant: Genentech, Inc.

OSE RCM #: 2012-288

TSI #: 1086

1 INTRODUCTION

This Division of Risk Management (DRISK) review evaluates the proposed risk evaluation and mitigation strategy modification for Actemra (tocilizumab) based on supplemental biologic licensing application (sBLA) 125-276, Supplement 049, Sequence 075 and 094 (submitted on December 13, 2011 and amended on June 5, 2012, respectively). This supplement contains data in support of the proposed claim, use of Actemra in rheumatoid arthritis (RA) patients with an inadequate response to (b) (4) population).¹

This sBLA also reports new cases of hypersensitivity reactions, including anaphylaxis observed in long-term extension clinical studies and postmarketing safety data, and therefore, requires a REMS Modification for Actemra.

2 BACKGROUND

Actemra is a first-in-class myeloma receptor antibody (MRA) and a recombinant humanized anti-human monoclonal antibody against soluble and membrane bound interleukin-6 receptor inhibitor. Increased soluble interleukin (sIL)-6 levels are associated with anti-inflammatory and autoimmune disorders including RA and juvenile idiopathic arthritis (systemic-type).

Actemra is approved for treatment of RA and systemic JIA (on January 8, 2010) as an intravenous (IV) infusion with weight-based dosing and frequency of administration that differ for adult and pediatric patients.

3 REGULATORY HISTORY

REMS

A REMS was determined to be necessary for Actemra to ensure that the benefits of therapeutic biologic product outweigh the risks of serious infection, gastrointestinal perforations, changes in the liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, elevations in lipid parameters in peripheral blood, and demyelinating disorders and malignancies.

The initial REMS for Actemra (approved on January 8, 2010) included a Medication Guide (MG), communication plan with a Dear Healthcare Provider (DHCP) letter, Dear Pharmacist letter and journal information pieces, and a timetable for submission of assessments.

- A REMS Modification (approved on April 15, 2011) during the review cycle for the indication of treatment of systemic juvenile idiopathic arthritis (sJIA) included removal of the MG as an element in the REMS. The MG remains as part of approved labeling. The communication plan educational materials and timetable for submission of assessments remained unchanged.

¹ This claim is under the approved indication for treatment of adult patients with moderately to severely active RA.

- A REMS Modification Notification letter issued to the applicant on September 12, 2011 was based on the 18-Month REMS assessment report (submitted on July 7, 2011).² The DRISK Review of this REMS assessment report determined that a prescriber educational slide deck be added to the communication plan materials based on the need to improve prescriber awareness of the risks of demyelination, malignancy, and lipid elevations and monitoring advice with Actemra. The Dear Pharmacist letter was removed from the communication plan materials as pharmacists are not among target healthcare providers for Actemra.²
- Additional comments on the proposed REMS Modification were issued to the applicant by the Agency on December 21, 2011; March 28, 2012; April 18, 2012; and May 31, 2012. *These submissions were concurrent with sBLA 125-276/S-049 (submitted on December 13 2012) and S-094 (submitted on June 5, 2012).*
- The REMS Modification was approved on June 20, 2012 based on the above required changes.

4 MATERIALS REVIEWED

The following materials, listed by document date, were reviewed from BLA 125-276 in regards to the proposed REMS Modification (submitted in Supplement 049/Sequence 075 and 094):

- December 13, 2012: The applicant submitted sBLA 125-276, Supplement 049/Seq-075, Actemra, a proposed REMS Modification
- June 5, 2012: The applicant submitted an amended proposed REMS Modification (Sequence-094) based on an Information Request letter from the Agency (dated May 31, 2012). This amendment to the proposed REMS Modification includes all prior required revisions.

Other materials informing this review are:

- November 15, 2011: The applicant submitted a Prior Approval Labeling Supplement with labeling revisions to the MG (as in the Supplement Approval letter, “(b) (4) (b) (4), bolding of all serious side effect (b) (4) to increase the prominence of these serious side effects with Actemra”)
- Supplemental Approval letter (dated August 13, 2012) for the Prior Approval Labeling Supplement (dated November 15, 2011, see above)
- Revised Proposed Labeling from the applicant (dated July 3, 2012)
- Information Request letter (dated August 28, 2012) was issued to the applicant. Based on the cases of anaphylaxis and serious hypersensitivity events identified by the applicant, the Agency requested that the applicant provide a minimum duration of time for monitoring these events (this duration should capture the time-period from the end of infusion through the potential first occurrence of signs and symptoms of hypersensitivity/anaphylaxis) that be potentially incorporated in labeling.

² Review of 18-Month REMS Assessment Report (dated August 30, 2011), written by Jodi Duckhorn, M.A. Social Science Analyst

5 RESULTS OF REVIEW OF THE PROPOSED REMS MODIFICATION

The applicant's proposed REMS Modification for Actemra (submitted on December 13, 2011/Sequence-049 and amended on June 5, 2012/Sequence-094) incorporated modifications being negotiated concurrently (from September 12, 2011, REMS Notification letter) and included revisions to the REMS Document and the appended REMS materials.^{3, 4, 5}

The DRISK requires additional revisions to include the new claim (DMARD-IR population) and additional cases of hypersensitivity reactions, including anaphylaxis to the Most Recent Approved REMS Modification (approved on June 20, 2012).

A summary of the proposed REMS Modification revisions completed by the applicant on June 20, 2012 follow:

- Revised the *Most Recent Modification Approval Date* to reflect June 20, 2012; updated Genentech's address from Nutley, New Jersey to South San Francisco, California
- Simplified the REMS goals to reflect "serious risks" rather than a list of 8 serious safety risks⁶
- Removed reference to an enclosed MG
- Revised communication plan materials as follows:
 - Deleted the Dear Pharmacist letter as pharmacists are not target providers of Actemra
 - Prescriber Educational Slide Deck includes safety information about "Hypersensitivity Reactions, Including Anaphylaxis"
 - Revised the alpha-assignments for each journal information piece
 - Revised the DHCP letter and all journal information pieces as follows:
 1. Removed text (*italicized*) about adult patients with moderately to severely active RA "who have had an inadequate response to one or more TNF antagonist therapies" with a recommended ACTEMRA dosing every 4 weeks.
 2. Removed list of 8 serious safety risks; refer to "serious risks"
 3. Removed reference to an enclosed copy of a MG

³ See DRISK REMS Modification Review (written on March 26, 2012) by Carolyn L. Yancey, M.D., F.A.A.P., Senior Medical Officer, DRISK

⁴ See DRISK Addendum REMS Modification Review (written on April 13, 2012) by Carolyn L. Yancey, M.D., F.A.A.P., Senior Medical Officer, DRISK

⁵ See DRISK Final REMS Modification Review (written on June 8, 2012) by Carolyn L. Yancey, M.D., F.A.A.P., Senior Medical Officer, DRISK

⁶ Safety risks with use of Actemra includes: serious infections, gastrointestinal perforations, changes in liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, elevations in lipid parameters in peripheral blood, demyelination disorders, and malignancies.

- Updated the timetable for submission of assessment to include the original REMS approval date
- The REMS assessment plan, updated in the REMS Supporting Document, reflects the above changes

6 CONCLUSIONS AND RECOMMENDATIONS FOR THE REVIEW DIVISION

This DRISK review concludes that the proposed REMS Modification (submitted December 13, 2011 and amended on June 5, 2012) based the concurrent REMS Modifications (cited in Section 5, of this review) are acceptable. Addition of the *new claim* for treatment of RA patients who had an inadequate response to DMARDs and the *new safety data* about hypersensitivity reactions, including anaphylaxis, must be completed by the applicant for a REMS Modification to be acceptable to the Agency.

The required revisions to the REMS Modification are summarized below and must be sent to the applicant as soon as possible to facilitate our review within the PDUFA deadline of October 12, 2012.

Appended to this review is the REMS Document and appended REMS materials including track changes (see **Attachments**).

7 COMMENTS TO BE SENT TO THE APPLICANT

The DRISK has the following required revisions on the proposed REMS Modification (originally submitted on December 13, 2011; amendment submitted on June 5, 2012):

1. The REMS Document requires minor edits: update the “Most Recent Modification: MM/DD/2012” in the upper left-hand corner of the first page of the REMS Document (see the **appended** REMS Document with track changes).
2. Communication Plan materials:
 - a. Revise the Dear Healthcare Provider (**Attachment A**) letter to include:
 1. New claim for adult patients with moderately to severely active RA who have had inadequate response to one or more DMARDs
 2. Add the header under IMPORTANT SAFETY INFORMATION ON KNOWN AND POTENTIAL RISKS, entitled, **Hypersensitivity Reactions, Including Anaphylaxis** (in bold-font) to follow the header entitled, **Gastrointestinal Perforations** (see appended Dear Healthcare Provider letter with track changes). Added language includes additional data about hypersensitivity reactions, including anaphylaxis and the number of events reported in the 6-month controlled trials, the all-exposure rheumatoid arthritis population, and in a single systemic juvenile idiopathic arthritis controlled-trial.
 - b. Revise the Prescriber Education Slide Deck as follows:

- Slide 2: Order the list of serious adverse events with Actemra to align with the order of safety risks in the WARNINGS and PRECAUTIONS Section of labeling.
 - Slide 3: Revise “Black Box Warning” to read, “Boxed Warning”
 - Following Slide 5, insert a new slide entitled, “Hypersensitivity Reactions, Including Anaphylaxis” with new safety data about these events (reported in sBLA 125-276/Supplement 049). See below comment about Slide 12.
 - Slide 12: Revised this slide to include new safety data about hypersensitivity reactions, including anaphylaxis and move Slide 12 up to follow Slide 5 (See above comment, 2. c.). Insert the same text used in the Agency’s revisions to the Dear Healthcare Provider letter (**Attachment A**) under the header, **Hypersensitivity Reactions, Including Anaphylaxis**, in Slide 12.
- c. Revise journal information pieces (**Attachments C and F**) to include a new header entitled, **Hypersensitivity Reactions, Including Anaphylaxis** (in bold font) in the journal information pieces to follow the header, **Gastrointestinal Perforations**. See track changes in **Attachments C**, Journal Information Piece for Emergency Medicine Physicians and Emergency Medical Services, and **Attachments F**, Journal Information Piece for Internists and Internal Medicine Subspecialists).
- d. On the REMS website for Actemra, www.ACTEMRAREMS.com, update the applicable revised materials to the appropriate links in the REMS website landing-page.

Ensure that all new language in the Attachments describing **Hypersensitivity Reactions, Including Anaphylaxis**, is consistent with the Agency’s proposed labeling and that the font-size is consistent throughout each revised appended material.

3. The timetable for submission of assessments is acceptable.
4. The REMS assessment plan is acceptable.
5. Revise the REMS Supporting Document to be consistent with revisions to the REMS Document.
6. General Comments
 - a. Resubmission Requirements and Instructions: Submit the revised proposed REMS for Actemra with the attached materials and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

- b. Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word document.

ATTACHMENTS

- **REMS Document**
- **Attachment A: DHCP letter**
- **Attachment C: Journal Information Piece for Emergency Medicine Physicians and Emergency Medicine Services Professionals**
- **Attachment F: Journal Information Piece for Internists and Internal Medicine Subspecialists**

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/s/

CAROLYN L YANCEY

09/16/2012

ACTEMRA REMS Modification Review, Interim Comments Review, Set # 1

CLAUDIA B MANZO

09/17/2012

concur

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

ADDENDUM: Revision to Comments To Be Sent To The Sponsor

**Required Revisions to a Proposed Risk Evaluation and Mitigation Strategy (REMS)
Modification for ACTEMRA Review Based on a REMS Assessment**

Date: April 5, 2012; *Accepted April 13, 2012*

Reviewer(s): Carolyn L. Yancey, M. D., F. A. A. P., Senior Medical Officer, Risk Management Analyst, Division of Risk Management (DRISK)

Anahita Tavakoli, M.A., Health Communications Analyst, DRISK

Team Leader: Kendra Worthy, Pharm. D., DRISK

Division Director: Claudia Manzo, Pharm. D., DRISK

Drug Name(s): ACTEMRA (tocilizumab) Injection for Intravenous Infusion

Therapeutic Class: Human Interleukin-6 Receptor Inhibitor

Dosage and Route: Adult dosage: every 4 weeks - 4 mg/kg followed by 8 mg/kg based on clinical response. Pediatric dosage: every 2 weeks - 12 mg/kg in patients < 30 kg and 8 mg/kg in patients ≥ 30 kg with systemic juvenile idiopathic arthritis

Application Type/Number: BLA 125-276 (Supplement (b) (4) Sponsor's amendments to the proposed REMS for Actemra Modification (submitted February 6, 2012)

Sponsor: Genentech, Inc.

OSE RCM #: 2012-288

TSI #: 1086

The Office of Surveillance and Epidemiology (OSE), the Division of Risk Management (DRISK), acknowledges error in **Section 4. Comments To Be Sent To The Sponsor**, in the appended DRISK review (Required Revisions to a Proposed Risk Evaluation and Mitigation Strategy (REMS) Modification for ACTEMRA Review Based on a REMS Assessment written by Carolyn L. Yancey, M.D., dated March 26, 2012).

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) is requested to communicate the following to the sponsor in regard to revisions to the proposed REMS Modification for Actemra and the REMS Supporting Document communicated by the Agency to the sponsor on March 28, 2012:

1. Disregard comment 2, c. concerning discussion about the REMS Assessment Plan in the REMS Document. This comment was made in error.
2. See the revisions to the REMS Supporting Document (see the **Attachment** including track changes). You are reminded that the REMS Supporting Document must be consistent with the revised REMS Document.
3. Submit the revised REMS Modification for Actemra with all appended REMS materials including the REMS website landing page and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all (each) revised document and/or appended material. Submit the REMS and REMS Supporting Document as two separate MS Word documents.

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**Department of Health and Human Services
Public Health Service
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Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

**Required Revisions to a Proposed Risk Evaluation and Mitigation Strategy (REMS)
Modification for ACTEMRA Review Based on a REMS Assessment**

Date: March 26, 2012

Reviewer(s): Carolyn L. Yancey, M.D., F.A.A.P., Senior Medical Officer, Risk Management Analyst, Division of Risk Management (DRISK)

Anahita Tavakoli, M.A., Health Communications Analyst, DRISK

Team Leader: Kendra Worthy, Pharm.D., DRISK

Division Director: Claudia Karwoski, Pharm.D., DRISK

Drug Name(s): ACTEMRA (tocilizumab) Injection for Intravenous Infusion

Therapeutic Class: Human Interleukin-6 Receptor Inhibitor

Dosage and Route: Adult dosage: every 4 weeks - 4 mg/kg followed by 8 mg/kg based on clinical response. Pediatric dosage: every 2 weeks - 12 mg/kg in patients < 30 kg and 8 mg/kg in patients ≥ 30 kg with systemic juvenile idiopathic arthritis

Application Type/Number: BLA 125-276 (Supplement (b) (4) Sponsor's amendments to the proposed REMS for Actemra Modification (submitted February 6, 2012)

Sponsor: Genentech, Inc.

OSE RCM #: 2012-288

TSI #: 1086

*** This document contains proprietary and confidential information that should not be released to the public. ***

CONTENTS

EXECUTIVE SUMMARY

1	INTRODUCTION	1
1.1	Background	1
1.2	Regulatory History	2
2	MATERIALS REVIEWED	2
2.1	Data and Information Sources	2
2.2	Analysis Techniques	2
3	DISCUSSION AND CONCLUSION	2
4	COMMENTS TO BE SENT TO THE SPONSOR	2
5	APPENDED INFORMATION	3
6	ATTACHMENTS	4

EXECUTIVE SUMMARY

This Office of Epidemiology and Surveillance (OSE), the Division of Risk Management (DRISK), review evaluates the required amendment to the proposed Risk Evaluation and Mitigation Strategy (REMS) Modification for Actemra submitted February 6, 2012 (Supplement (b) (4)). This submission is in response to the DRISK Interim Comments Review and a REMS Correspondence from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on December 21, 2011 that included a number of comments and revisions to the proposed REMS Modification for Actemra based on the REMS Assessment Report (dated July 7, 2011).^{1,2}

The original REMS for Actemra (approved January 8 2010) included a Medication Guide, a communication plan, and timetable for submission of assessments. The Medication Guide (MG) was removed from the REMS (April 15, 2011) and remains part of approved labeling. The currently approved REMS for Actemra includes the two remaining elements cited above.

The sponsor's amendment to the proposed REMS Modification for Actemra (Sequence (b) (4)) incorporates the majority of comments and revisions in the December 21, 2011 DRISK review. The proposed REMS Assessment Plan is consistent with required revisions to the proposed REMS Modification for Actemra.

To address the DRISK's comments that the sponsor must improve prescriber awareness of the risk of demyelination, malignancy, and lipid-monitoring advice (based on the 18-Month REMS Assessment review²). Genentech proposes a prescriber re-education slide deck that Genentech Rheumatology Medical Science Liaisons will use to improve education about key safety risks with Actemra (as cited above) to rheumatology prescribers of Actemra. Additional revisions are required to the proposed prescriber slide deck and the REMS Document to be acceptable to the DRISK and DPARP. See **Section 4, Comments To Be Sent To The Sponsor.**

5 INTRODUCTION

5.1 BACKGROUND

The introduction, background, regulatory history, and comments on the proposed REMS Modification for Actemra, including DRISK comments and rationale for required revisions to the original REMS for Actemra based on the 18-Month REMS Assessment, are detailed in previous DRISK reviews.^{1,2}

¹ Interim Comments on Required Amendments to a Proposed REMS Modification Based on a REMS Assessment Review (dated December 21, 2011) by Carolyn L. Yancey, MD, FAAP, Senior Medical Officer, DRISK

² Actemra REMS Assessment Review (dated August 30, 2011) written by Jodi Duckhorn, M.A., Senior Social Science analyst, DRISK and Therese Cvetkovich, M.D., Senior Medical Officer, REMS Assessment Reviewer, DRISK

5.2 REGULATORY HISTORY

The past regulatory history specific to this review of the amendment to the proposed REMS Modification for Actemra (Supplement (b)(4)) follows:

- February 6, 2012: The sponsor submitted an amendment to a proposed REMS Modification for Actemra based on DRISK Interim Comments Review (dated December 21, 2011)

6 MATERIALS REVIEWED

6.1 DATA AND INFORMATION SOURCES

The following materials, listed by document date, reviewed from BLA 125-276 (Supplement (b)(4)) for the required amendments to the proposed REMS Modification for Actemra are:

- February 6, 2012: (Sequence (b)(4)) The sponsor submitted an amendment to the proposed REMS Modification in response to Agency comments (dated December 21, 2011)

6.2 ANALYSIS TECHNIQUES

The required amendment to a proposed REMS Modification for Actemra is reviewed for conformance with the DRISK Interim Comments (dated December 21, 2011).¹

7 DISCUSSION AND CONCLUSION

The applicant submitted required amendments to the proposed REMS Modification for Actemra on February 6, 2012 (Sequence (b)(4)) in response to Agency comments (see the **Executive Summary**, in this review). In general, the proposed REMS Modification amendment includes agreed upon revisions to the REMS Document as stipulated by the Agency.

There are additional required revisions to the proposed REMS Document and the proposed prescriber re-education slide deck (to improve rheumatology prescriber understanding specific risks associated with Actemra) that the sponsor must complete for the amendment to the proposed REMS Modification for Actemra to be acceptable to the DRISK and the DPARP (see the **Executive Summary**). Additional required revisions to the proposed prescriber re-education slide deck will be forthcoming from the DPARP and included in an Agency letter to the sponsor.

The REMS Assessment Plan, as summarized in the REMS Supporting Document (Sequence (b)(4)) is consistent with the amended proposed REMS Modification for Actemra and will be included in the REMS Modification Approval letter following completion of all required revisions. See **Section 5, Comments for the DPARP** in this review, for the proposed REMS Assessment Plan.

8 COMMENTS TO BE SENT TO THE SPONSOR

The DPARP is requested to place the following comments to the sponsor in a REMS Correspondence letter and copy DRISK on the letter when it is sent to the sponsor. The

DRISK defers to the DPARP for additional revisions to the Prescriber Educational Slide Deck.

Complete the following amendments to the proposed REMS for ACTEMRA:

See the track changes to the attached REMS Document and appended REMS materials corresponding to the comments below:

1. Insert the complete date of the original REMS approval, 01/08/10, in the header.
2. In the communication plan:
 - a. Insert the Prescriber Education Slide Deck under II. A. 2.
Note: Additional revisions to the proposed Prescriber Education Slide Deck will be forthcoming from the Division of Pulmonary, Allergy and Rheumatology Products.
 - b. Edit information about the ACTEMRA REMS program website to be concise, to include a timeframe for an ACTEMRA REMS program website to exist.
 - c. Remove text about the REMS Assessment Plan from the REMS in the communication plan. This information is not required in a REMS Document (see track changes in the **Attachment**). The REMS Assessment Plan, as detailed in the REMS Supporting Document (Supplement (b) (4)) is acceptable to the DRISK and DPARP.
3. Append the Prescriber Education Slide Deck to the REMS.
4. Append the Actemra REMS website screenshot to the REMS. Add a link titled, Prescriber Education Slide Deck, on the Actmera REMS website landing page screenshot.
5. You are reminded that the REMS Supporting Document must be consistent with the revised REMS Document (see track changes in the **Attachment**)
6. Resubmit the revised REMS, the appended REMS materials including the revised Prescriber Education Slide Deck, and a revised Actemra REMS Website landing page screenshot for review by the Division of Risk Management and the Division of Pulmonary, Allergy and Rheumatology Products.

9 COMMENTS FOR THE DPARP

The REMS Assessment Plan, as summarized in the REMS Supporting Document (submitted February 6, 2012/Sequence (b) (4)) will be included in the REMS Modification Approval letter after the sponsor completes all required revisions. The prescriber survey methods and instrument should be provided to FDA for review at least 90 days before the implementation of the prescriber survey.

The revised ACTEMRA REMS assessments will include the following:

1. Evaluation of prescriber's understanding of the risks of ACTEMRA
2. A summary of all reported serious risks with an analysis of adverse event reporting by prescriber type (eg, rheumatologist, osteopath, infectious disease

specialist, gastroenterologist, hepatologist, internal medicine specialist, hematology-oncology specialist, emergency medicine specialist, family medicine specialist, etc.), when available

3. Based on the information provided, an assessment and a conclusion of whether the REMS is meeting its goal and whether modifications to the REMS are needed

10 ATTACHMENTS

(b)(4)

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CAROLYN L YANCEY

04/13/2012

ADDENDUM to REMS MODIFICATION for ACTEMRA BLA 125276 Supplement 049

CLAUDIA B MANZO

04/13/2012

concur