

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125472Orig1s000

**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**

**ADDENDUM TO THE
PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)
MODIFICATION FOR ACTEMRA**

Date: October 16, 2013; *Revised October 17, 2013*

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: Actemra (tocilizumab) Injection via a Pre-Filled Syringe
Actemra (tocilizumab) Injection for Intravenous Infusion

Therapeutic Class: Human Interleukin-6 Receptor (IL-6) Inhibitor

Dosage and Route: - *Adult dosage, Rheumatoid Arthritis*: every 4 weeks - 4 mg/kg followed by 8 mg/kg based on clinical response
- *Pediatric dosage, Systemic Juvenile Idiopathic Arthritis (SJIA)*: every 2 weeks - 12 mg/kg in patients < 30 kilograms (kg) and 8 mg/kg in patients ≥ 30 kg
- *Pediatric dosage, Polyarticular (P-JIA)*: every 4 weeks - 10 mg/kg in patients < 30 kg and 8 mg/kg in patients ≥ 30 kg
- *Intravenous infusion* for Rheumatoid Arthritis, PJIA, and SJIA patients
- *Subcutaneous administration via a new proposed single-use, pre-filled syringe* proposed for treatment of adult RA

OND Review Division: Division of Pulmonary, Allergy and Rheumatology Products (DPAAP)

Application Type/Number: BLA 125-472/Supplement 00/Sequence 00 (received on December 21, 2012) and Sequence 036 (Amendment received on October 14, 2013)

Application Type/Number: BLA 125-276/Supplement 075 [REDACTED] (b) (4)
[REDACTED] and the Most Recent Modification approved
July/2013

PDUFA Date: October 21, 2013 for two applications:
- BLA 125-472 for the proposed SC route via a PFS
in RA (with new REMS)
- BLA 125-276 for a proposed REMS modification (to
incorporate the new proposed SC formulation/PFS)

Sponsor: Genentech, Inc (Genentech), a Member of the Roche
Group

OSE RCM #: 2013-312

This Addendum is to document the Division of Risk Management (DRISK) review of the applicant's response to the Agency's revisions to the proposed risk evaluation and mitigation strategy (REMS) modification for Actemra. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) sent three REMS Comments/Information Requests (IR) from the DRISK and the DPARP to the applicant (on October 1, 9, and 11, 2013, respectively). Each of the IRs clarified the Agency's revisions that the applicant must incorporate into the REMS Document and appended REMS materials for the proposed Actemra REMS modification to be acceptable to the Agency.

Background and Regulatory History

See the DRISK Proposed REMS Modification for Actemra Review written by Carolyn L. Yancey, M. D., DRISK (dated September 30, 2013) for the **Background and Regulatory History** of the new biologic license application (BLA) 125-472, Actemra proposed as a new subcutaneous (SC) formulation with a pre-filled syringe (PFS) for use in adults with rheumatoid arthritis (RA). This previous DRISK review also includes revisions to the most recent REMS modification (in BLA 125-276) with incorporation of the new proposed SC formulation with a PFS.

Results of Review

The applicant submitted an Amendment to the proposed REMS under BLA 125-472 with an updated REMS Document and appended REMS materials (received on October 14, 2013/Sequence 036) that included the Agency's most recent revisions to the proposed REMS and appended REMS materials. Brief summary of the applicant's revisions follows:

- The DRISK and the DGIEP agreed that since dissemination of the journal information pieces (specifically, for rheumatologists, gastroenterologists, hepatologists, neurologists, infectious disease specialists, family medicine specialists, internal medicine specialists, and emergency medicine specialists) has been completed, the REMS Document is revised to note that dissemination of the non-oncology journal information pieces was completed for 3 years following product approval [text to be inserted, "(completed January 2013)"].
 - o Description of the demyelinating disorders in Attachment G, Journal Information Piece for Neurologists, and Attachment F, Journal Information Piece for Internists and Internal Medicine subspecialists, is revised to be consistent with the substantially complete labeling for Actemra. Revised text is, "*Monitor* patients for signs and symptoms potentially indicative of demyelinating disorders."
- The *Prescriber Education Slide Deck* and the *Dear Healthcare Provider (DHCP) letter* are revised to include the new proposed SC formulation/PFS and revised labeling language for hypersensitivity reactions and for demyelinating disorders.
- All other revisions from the Agency have been incorporated in the **Attachments** to this **Addendum**.

The REMS Supporting Document is updated to be consistent the revisions to the REMS Document and appended materials.

Conclusion

The applicant's response to the Agency's REMS Comments/IR on the Amendment to the proposed REMS modification for Actemra (received on October 14, 2013 under BLA 125-472) is acceptable to the DRISK and the DPARP with one minor additional revision to the REMS Document, specifically, in the Communication Plan, insert "(completed January 2013)" following text about dissemination of the non-oncology journal information pieces. See the **Attachments** to this **Addendum**. No additional DRISK review is required.

Recommendations

The DRISK recommends acceptance of the applicant's response to the Agency's IR (received on October 14, 2013) and approval of the Amendment to the proposed REMS modification (BLA 125-472) following the applicant's incorporation of the minor edit to the REMS Document, insertion of "(completed January 2013)" following text about the dissemination of the non-oncology journal information pieces.

Comments To Be Communicated To The Applicant

The Amendment to the proposed Actemra REMS modification (received on October 14, 2013 under BLA 125-472) is acceptable to the Agency following incorporation of the text, "(completed January 2013)", following text about the dissemination of the non-oncology journal information pieces for 3 years following product approval.

Attachments to the Addendum

Initial REMS Approved: 01/08/2010



47 Page(s) have been Withheld in Full as b4
(CCI/TS) immediately following this page

**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**

**A Proposed Actemra Risk Evaluation and Mitigation Strategy (REMS)
Modification Review**

Date: September 25, 2013; *Revised on September 27, 2013*

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: Actemra (tocilizumab) Injection via a Pre-Filled Syringe
Actemra (tocilizumab) Injection for Intravenous Infusion

Therapeutic Class: Human Interleukin-6 Receptor (IL-6) Inhibitor

Dosage and Route: - *Adult dosage, Rheumatoid Arthritis*: every 4 weeks - 4 mg/kg followed by 8 mg/kg based on clinical response
- *Pediatric dosage, Systemic Juvenile Idiopathic Arthritis (SJIA)*: every 2 weeks - 12 mg/kg in patients < 30 kilograms (kg) and 8 mg/kg in patients ≥ 30 kg
- *Pediatric dosage, Polyarticular (P-JIA)*: every 4 weeks - 10 mg/kg in patients < 30 kg and 8 mg/kg in patients ≥ 30 kg
- *Intravenous infusion* for Rheumatoid Arthritis, PJIA, and SJIA patients
- *Subcutaneous administration via a new proposed single-use, pre-filled syringe* proposed for treatment of adult RA

OND Review Division: Division of Pulmonary, Allergy and Rheumatology Products (DPARP)

Application Type/Number: BLA 125-472/Supplement 00/Sequence 00 received on December 21, 2012

BLA 125-276/Supplement 075 (b) (4)

(b) (4)

PDUFA Date: October 21, 2013 for BLA 125-472 for the proposed SC route via a single-use, PFS in adult RA (with a REMS modification) *and* BLA 125-276 for a proposed REMS modification that includes the SC formulation/PFS

Sponsor: Genentech, Inc (Genentech), a Member of the Roche Group

OSE RCM #: 2013-312

- INTRODUCTION

This Division of Risk Management (DRISK) review evaluates Genentech's proposed risk evaluation and mitigation strategy for Actemra (tocilizumab) approved and marketed for adult patients with moderately to severely active rheumatoid arthritis (RA), Polyarticular Juvenile Idiopathic Arthritis (PJIA), and Systemic Juvenile Idiopathic Arthritis (SJIA). Genentech submitted a new biologic license application (BLA) 125-472 (received on December 21, 2012/Supplement (Suppl.) 00/Sequence 00) for a new proposed formulation of Actemra for subcutaneous (SC) administration via a new device, a single-use, pre-filled syringe (PFS) in adult patients with RA. The proposed REMS modification incorporates this new formulation and additional information recently incorporated in Actemra labeling (under the original Actemra BLA 125-276).

BACKGROUND

Tocilizumab (Actemra) is a monoclonal antibody of the IgG₁ subclass that binds to interleukin-6 (IL-6) receptor, thereby inhibiting the biologic activity of the cytokine, IL-6. Interleukin-6 is an important mediator of inflammation, including the production of acute phase reactants. Actemra Solution, approved for administration via intravenous (IV) infusion and SC injection, has the following approved indications for the treatment of:

- Adult patients with moderately to severely active RA who have had an inadequate response to one or more Disease Modifying Anti-Rheumatic Drugs (DMARDs), approved on January 8, 2010
- Patients 2 years of age and older with active PJIA, approved on April 15, 2011
- Patients 2 years of age and older with active SJIA, approved on April 29, 2013

See the cover page, of this review, for the different dosage and routes of administration for each Actemra indication (approved and proposed)

Approved Actemra REMS

The Agency determined that a REMS is necessary for Actemra to ensure that the benefits of Actemra outweigh the potential risks of serious infections, gastrointestinal perforations, hypersensitivity reactions, including anaphylaxis, changes in liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, elevation in lipid parameters in peripheral blood, demyelinating disorders and malignancies.

The current approved Actemra REMS (initially approved on January 8, 2010) includes a goal to inform healthcare providers about the serious risks associated with Actemra, a communication plan (that includes a *Dear Healthcare Provider (DHCP) letter*, a *Prescriber Education Slide Deck*, *journal information pieces*, and the *REMS website*), and a timetable for submission of assessments. See previous DRISK reviews in DARRTS for the background and regulatory history of the Actemra REMS Modifications (approved on April 15, 2011; June 20, 2012; October 11, 2012; April 29, 2013; July 2, 2013).

REGULATORY HISTORY

The regulatory history, specific to this review, follows:

New BLA 125-472

October 22, 2012:

(b) (4)

The sponsor also received feedback that the Instructions for use (IFU) and training for the PFS should be further optimized. Based on this feedback, the applicant has completed a Supplemental Human Factor Study (submitted on December 21, 2012).

October 31, 2012: Type B Meeting, Pre-BLA meeting concluded that the filing was deemed a BLA, therefore, for previously submitted non-clinical, and Chemistry and Manufacturing Controls (CMC) /technical information, reference is made to Genentech's BLA 125-276.

December 21, 2012: The applicant submitted a new BLA 125-472, Suppl. 00, supporting the use of Actemra SC for the treatment of adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs. This application seeks marketing approval for Actemra administered SC via a PFS.

The BLA 125-472 is a new BLA per the Bundling Policy (Guidance to ... a new route of ... formulation for the drug product (SE-3 ...). The *Bundling Policy* describes the Agency's policy regarding what constitutes a separate original application, amendment, or supplement.¹

As part of the application under the new BLA 125-472 for Actemra, the applicant submitted a proposed REMS using the Actemra REMS modification (approved on July 2, 2013 under BLA 125-276) and inserted new language that includes the new proposed SC formulation via a PFS.

August 12, 2013: The applicant submitted a proposed REMS modification, updated REMS documents to incorporate the SC dosage form of Actemra for adults with RA [Most Recent Modification for Actemra (under BLA 125-276) was used for this submission.]

- Update the "Most Recent Modification" date to Month/2013 (from July 2013) and addition of BLA 125-472.
- Removal of the expired journal information pieces (Attachments C – G and I) and reference to distribution of printed material at scientific meetings.
- Addition of language at the end of the following sentence, "This letter will be distributed within 60 days of approval of a new indication *or new dosage form*."
- Updates to the dosing, hypersensitivity/anaphylaxis language, and laboratory parameter monitoring information to match the current proposed SC USPI (submitted in the original BLA for Sc formulation).

¹ Refer to the *Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* <http://www.fda.gov/cder/guidance> for more information.

September 10, 2013: The applicant submitted separate MS word document for each of the REMS documents.

BLA 125-276 Actemra (tocilizumab)

June 28, 2013: The sponsor submitted the most recent REMS modification based on the 3-year REMS Assessment and advised that the sponsor insert minor revisions (e.g., delete (b) (4) from (b) (4) Prescribing Information”, revise the *Prescriber Education Slide Deck* “version date” and revise the Most Recent Modification date to be July 2013). See DARRTS for the DRISK Review written by Carolyn L. Yancey, M. D., Senior Medical Officer, DRISK, dated July 2, 2013.

July 2, 2013: The Agency approved the sponsor’s revised proposed REMS modification that incorporated all of the Agency’s requested revisions.

- MATERIALS REVIEWED

DATA AND INFORMATION SOURCES

The following materials, listed by document date, reviewed from BLA 125-472 (Suppl. 00) and sBLA 125-276 (Supplement 064) for the new proposed Actemra REMS and the proposed amendment to the Actemra REMS Modification, respectively, are:

BLA 125-472

December 21, 2012: BLA 125-472/Suppl. 00/Seq. 00, Actemra for a new proposed formulation for SC administration via a PFS in adult RA. The applicant submitted a new proposed Actemra REMS that includes the new formulation and route of administration.

August 12, 2013: Updated Proposed REMS modification that includes the SC dosage formulation.

September 10, 2013: The applicant submitted separate MS word documents based on the Agency’s request to resubmit all REMS documents (that were submitted in the REMS Modification dated August 13, 2013 to BLA 125-472).

September 18, 2013: The Division of Pulmonary, Allergy and Rheumatology Products (DPARP) latest version of the substantially complete Actemra labeling (BLA 125-472).

- RESULTS OF REVIEW OF A PROPOSED REMS MODIFICATION

The applicant’s proposed REMS modification for the original BLA 125-276 and for BLA 125-472 (new proposed SC formulation in RA) includes the following:

- REMS Document:

- a. Revises Most Recent Modification date to October/2013
- b. Adds the new BLA number, BLA 125-472, to the centered, upper-title of the Actemra REMS

- Appended REMS materials in the Communication Plan:

- a. The applicant did not propose any revisions to the proposed *Prescriber Education Slide Deck*. See **Section 6**, in this review, for revisions from the Agency that need to be incorporated in the *Prescriber Education Slide Deck*.
- b. Revises the *DHCP letter* and the *journal information pieces* to include:
 - i. IV administration and the weekly SC administration as inserted in labeling
 - ii. New text about the SJIA controlled trial with IV Actemra
 - iii. Post marketing events of hypersensitivity reactions, including anaphylaxis and death.
 - iv. Minor edits to the description of the potential risk of demyelinating disorders
 - v. New text regarding *Important Information on Laboratory Abnormalities*
 - vi. Removal of the word, (b) (4) from Prescribing Information
 - vii. Updates the version date of each appended REMS material

- **Timetable for Submission of Assessments**

- a. There is no change to the timetable for submission of assessments

- **REMS Assessment Plan**

- a. The applicant did not propose any modifications to the REMS assessment plan.

See the **Attachments**, to this review, for track changes to the single proposed REMS Document (that will include the two BLA numbers, 125-276 and 125-472 for Actemra) and the appended REMS materials.

- **DISCUSSION AND CONCLUSION**

The applicant's proposed Actemra REMS modification incorporates the new formulation for SC administration via a PFS in RA (under BLA 125-472 received on December 21, 2012) and additional information recently incorporated in the Actemra labeling (under the original BLA 125-276). There are minor additional revisions to the proposed REMS modification that the applicant must incorporate to be acceptable to the DRISK.

- **RECOMMENDATIONS**

The DRISK requests that the DPARP send the below comments and attached REMS appended materials as described in **Section 6**, of this review, to the applicant in a REMS Correspondence letter and copy the DRISK on this written communication. The DRISK requests that the DPARP request that the applicant submit the revised REMS Document and appended REM materials by close-of-business on October 1, 2013.

- **COMMENTS TO BE SENT TO THE SPONSOR**

The proposed Actemra REMS modification will be acceptable to the Agency following the applicant's incorporation of the Agency's revisions.

See the following comments and the track changes in the **Attachments**:

1. The REMS Document, insert the “Most Recent Modification” date as October/2013 in the second-line, left-side of the header. Delete “June” and the DD portion of the date.
2. Insert “and BLA 125-472” in the center header before “ACTEMRA® (tocilizumab)”
3. In the appended REMS materials in the communication plan:
 - a. *Prescriber Education Slide Deck*
 - i. Insert an updated “version date” in the lower-left corner of each slide
 - ii. Update the slide deck with the SC dosing information
 - iii. Update the slide deck to reflect the modified laboratory monitoring as revised in labeling
 - b. *Dear HealthCare Provider letter*
 - i. Insert an updated “version date” at the bottom of the final page of this letter.
 - ii. Delete all references to the product website, www.ACTEMRA.com. Only reference to the REMS website, www.ACTEMRAREMS.com, should appear in appended REMS materials. The exception is in the journal information pieces where you appropriately direct providers to the product website, www.ACTEMRA.com, for access the Prescribing Information and Medication Guide.
 - iii. Insert text in 1st bullet point, “for intravenous (IV) or every other week or weekly for subcutaneous (SC) administration.”
 - iv. Insert text in 3rd bullet point to read, “Children 2 years of age and older with active systemic Juvenile Idiopathic Arthritis (SJIA) with a recommended ACTEMRA dosing interval of every 2 weeks for IV administration.”
 - v. Insert text under “Hypersensitivity Reactions, Including Anaphylaxis” that is shown in track changes to align with revisions to Actemra labeling
 - vi. Insert text under “Potential Risk of Demyelinating Disorders” as noted in minor track changes.
 - vii. Insert text under “Important Information on Laboratory Abnormalities” to align with revisions to the Actemra labeling.
 - c. *Journal Information Pieces*
 - i. Insert the same track changes (as they apply to the specialty provider) in each journal information piece that are cited in track changes to the *DHCP letter*.
4. Timetable for Submission of Assessments
 - a. There are no changes to the approved timetable for submission of assessments.
5. REMS Assessment Plan

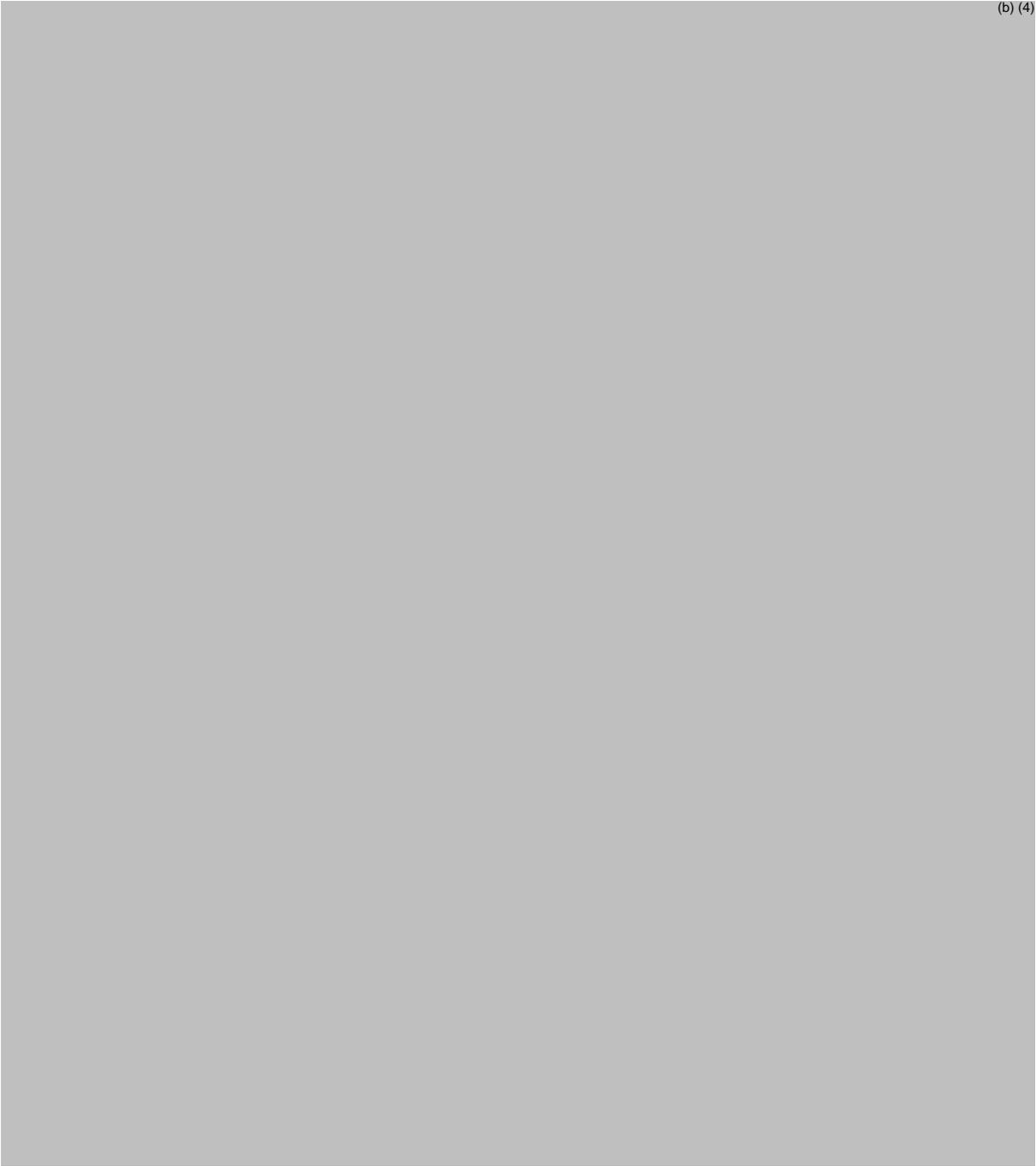
The REMS assessment plan is acceptable as approved.

6. You are reminded that the REMS Supporting Document must be consistent with the revised REMS Document.

Attachments

Initial REMS Approved: 01/08/2010

(b) (4)



53 Page(s) have been Withheld in Full as b4 (CCI/tS)
immediately following this page

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

10/17/2013

Addendum to proposed REMS modification for Actemra

CLAUDIA B MANZO

10/17/2013

concur

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF DRUG EVALUATION II
DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS (DPARP)

NDA/BLA #s: BLA#125472
Products: Actemra (tocilizumab) for Subcutaneous Injection
APPLICANT: Genentech
FROM: Sally Seymour, Deputy Director for Safety, DPARP
DATE: October 16, 2013

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Actemra to ensure that the benefits of the drug outweigh the serious risks of Actemra. In reaching this determination, we considered the following. The pre-marketing clinical review of studies with the intravenous Actemra product showed that serious risks were observed with the use of Actemra in clinical trials. The serious risks associated with Actemra included serious infections, gastro-intestinal perforations, changes in the liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, and elevations in lipid parameters in peripheral blood. Other serious adverse effects observed with use of Actemra included peripheral demyelinating disorders and malignancies. Because Actemra for subcutaneous administration has the same mechanism of action, these serious risks are assumed to also be associated with the subcutaneous formulation being approved under this BLA.

- A. The estimated number of patients in the United States with rheumatoid arthritis (RA) is 1.5 million. This estimate is based on data published in *Arthritis Rheum.* 2010 Jun;62(6):1576-82.
- B. RA is a chronic systemic progressive disease associated with synovial inflammation resulting in joint pain and swelling, autoantibody production (rheumatoid factor and anti-citrullinated

protein antibodies), bone erosions, joint space narrowing and joint destruction, and systemic features, including inflammation, cardiovascular, pulmonary, musculoskeletal, and other manifestations. Sustained RA activity results in irreversible joint destruction, functional impairment and increased morbidity and mortality, and significantly impacts society and the health care system. Actemra will be used to reduce the signs and symptoms of moderate to severe rheumatoid arthritis.

- C. Compared with placebo, Actemra has been shown to be effective for the above indication in clinical trials lasting 6 months or longer
- D. The expected duration of therapy with Actemra is chronic, life-long.
- E. During the review of the Actemra intravenous formulation application, we identified signals of serious risks, and because the subcutaneous formulation being approved under this application has the same mechanism of action, the risks are thought to be associated with both products. Those risks observed with the use of Actemra were serious infections, gastrointestinal perforations; and changes in the hematology, hepatobiliary, and lipid parameters. Occurrences of demyelinating disorders and malignancies have been observed with Actemra treatment, but their association with Actemra exposure remains unclear. Serious infections and gastrointestinal perforations are events that lead to hospitalizations and in severe cases may lead to fatal outcomes.

Abnormal elevations of the liver function tests (ALT, AST, and bilirubin) and decreases in the hematology parameters (neutrophils and platelets) were observed with Actemra treatment and were considered related to Actemra's mechanisms of action. Increases in total cholesterol and in low density lipoproteins (LDL) have also been observed with Actemra treatment; the mechanism for these elevations is not understood. Changes in the laboratory parameters were observed both upon initiation of treatment with Actemra and with continued use of the product.

In the majority of cases the changes were reversible upon timely dose reduction, or interruption, or discontinuation of Actemra treatment.

Elevations in liver function tests (LFTs) are considered biomarkers for liver injury and should be promptly recognized in the setting of chronic treatment with Actemra to prevent a serious liver injury, including liver failure. Severe decreases in neutrophil counts lead to insufficient host defenses and may result in an increased susceptibility to infections. Decreased platelet counts result in decreased ability to form clots translating into clinically evident bleeding. Elevations in lipid parameters such as cholesterol and LDLs are considered biomarkers of atherosclerosis and have been shown to be associated with an increased risk for cardiovascular and cerebrovascular thromboembolic events. Educating the healthcare practitioners to understand and adhere to the labeled recommendations for close monitoring of the laboratory parameters and to promptly recognize the critical values indicating toxicities of Actemra, will be necessary to help ensure safe use of Actemra and help prevent occurrence of serious adverse events.

F. Actemra is not a new molecular entity.

A REMS is already approved for the Actemra (tocilizumab) intravenous injection formulation and is being modified to add the Actemra subcutaneous formulation being approved today. The elements of the REMS are a communication plan and a timetable for submission of assessments of the REMS, which will remain the same as that approved on January 8, 2010 for the Actemra intravenous product.

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

/s/

SALLY M SEYMOUR
10/16/2013