

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125276

SUMMARY REVIEW



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

Summary Review for Regulatory Action

Date	December 29, 2009
From	Bob A. Rappaport, M.D. <i>Bob A. Rappaport</i> Director Division of Anesthesia, Analgesia and Rheumatology Products
Subject	Division Director Summary Review
BLA #	125276
Supplement #	0
Applicant Name	Hoffmann-LaRoche
Date of Submission	July 9, 2009
PDUFA Goal Date	January 9, 2010
Proprietary Name / Established (USAN) Name	Actemra Tocilizumab
Dosage Forms / Strength	Injectable, 20 mg/mL aqueous solution for intravenous injection
Proposed Indication	For the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to or could not tolerate one or more disease modifying anti-rheumatic drugs (DMARDs).
Recommendation for action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Sarah Okada, M.D.
Statistical Review	Joan Buenconsejo, Ph.D.; Dionne Price, Ph.D.; Thomas Permutt, Ph.D.
Pharmacology Toxicology Review	Asoke Mukherjee, Ph.D.; R. Daniel Mellon, Ph.D.
OBP Quality Review	Gerald M. Feldman, Ph.D.; Marjorie A. Shapiro, Ph.D.; Kathleen A. Clouse, Ph.D.
Microbiology Review	N/A
Clinical Pharmacology Review	Lei Zhang, Ph.D.; Suresh Doddapaneni, Ph.D.; Venkatesh Atul Bhattaram, Ph.D.; Jogarao Gobburu, Ph.D.
Division of Cardiorenal Products	Shari L. Targum, M.D.; Norman Stockbridge, M.D., Ph.D.
Division of Metabolic and Endocrine Products	Eileen Craig, M.D.; Eric Colman, M.D.
DDMAC	Michelle Safarik, PA-C
DSI	Susan Leibenhaut, M.D.
CDTL Review	Jeffrey Siegel, M.D.
OSE IO	John R. Senior, M.D.
OSE/DMEPA	Tara Turner, Pharm.D.; Linda Kim-Jung, Pharm.D.; Denise Toyer, Pharm.D.
OSE/DAEA	N/A
OSE/DRISK	Kathryn O'Connell, M.D., Ph.D.; Suzanne Berkman Robottom, Pharm.D.
OSE/DEPI	N/A

OBP=Office of Biotechnology Products
OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK= Division of Risk Management
DAEA=Division of Adverse Event Analysis
CDTL=Cross-Discipline Team Leader
DEPI= Division of Epidemiology

1. Introduction

Actemra is an aqueous solution for intravenous injection of tocilizumab, a monoclonal antibody that binds to the interleukin-6 (IL-6) receptor, inhibiting the biological activity of IL-6 and thereby reducing the production of acute phase reactants that are thought to play a role in the underlying inflammatory pathophysiology of rheumatoid arthritis. This is a "first in class"

BLA 125276 Actemra

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Division Director Summary Basis for Recommendation of Approval Action
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product submitted by Hoffmann-La Roche for licensure as BLA 125276. IL-6 also acts as a growth factor for certain cells and regulates cells of the immune system.

Actemra was approved in Japan in April 2005 for the treatment of multicentric Castleman's disease. In April 2008, tocilizumab was approved in Japan for the treatment of adult RA, systemic juvenile idiopathic arthritis (SJIA) and polyarticular juvenile idiopathic arthritis (PJIA).

b(4)

2. Background

The sponsor has submitted data from an extensive Phase 3 development program. While the efficacy of Actemra appears to have been clearly established, a number of safety signals arose during review of the application. These safety signals include serious infections, gastrointestinal perforations, central and peripheral demyelinating disorders, and laboratory evidence of hepatotoxicity, elevated lipids and decreases in neutrophil and platelet counts. Based on the fact that this is a first in class product, and because of the safety concerns documented during the review, this application was presented to the members of the Arthritis Advisory Committee at an open public meeting on July 29, 2008.

In my review of the original application (Appendix 1), I recommended a Complete Response action, based on nonclinical deficiencies and the need for a Risk Evaluation and Mitigation Strategy (REMS) to assure that the benefits of the product outweighed the risks. On September 17, 2008, a Complete Response (CR) letter (Appendix 2) was issued for this application. The letter cited a number of deficiencies:

1. Peri- and post-natal developmental toxicology studies in either monkey or a surrogate model were not submitted with the application and would be necessary for approval.
2. Fertility studies in the mouse were not submitted with the application and would be necessary for approval.
3. Certain labeling changes would be required prior to approval.
4. A signed copy of the debarment certification must be submitted prior to approval.
5. Certain questions regarding the Financial Disclosure section of the application would require clarification prior to approval.
6. Inspection of the Chugai Pharma Manufacturing Company facility in Japan documented numerous deficiencies requiring resolution before approval of the application would be possible.
7. A REMS would be needed before the application could be approved.

In addition, a number of other requests for information were delineated in the CR letter (see Appendix 2 for the complete list). In the sponsor's response to the CR letter they have adequately addressed all of the deficiencies and provided all necessary information to merit approval. After extensive internal discussion, the division modified the REMS to eliminate the Elements to Assure Safe Use as discussed below in Section 13.

3. CMC

Major deficiencies at the Chugai Pharma Manufacturing Company facility in Japan included infestation, failure of sterile processes and the use of _____ in one testing procedure. The company corrected these deficiencies and Drs. Hughes and Suvarna have concluded that the establishment may now be classified as acceptable from a CGMP perspective.

b(4)

I agree with the review team that there are no outstanding CMC issues that would preclude approval.

4. Nonclinical Pharmacology/Toxicology

As noted above, the CR letter stated that peri- and pre-natal developmental toxicology studies, and a fertility study would be required before the application could be approved. The sponsor was also asked to submit additional data to support their contention that carcinogenicity could not be performed for this product. On page 5 of his supervisory review, Dr. Mellon states:

...the Applicant conducted a pre- and post natal development study and fertility and early embryonic development studies in both the male and female mouse using the MR16-1 homologous protein (IgG1).

Dr. Mellon then concludes on page 6 of his review:

Therefore, the studies adequately characterized the potential impact of IL-6R blockade on both fertility and pre- and postnatal development, including development of the immune response. However, as the tested material does not represent the clinical candidate, exposure margins are not included in the product labeling.

Drs. Mukherjee and Mellon have concluded that the reproductive toxicology studies did not demonstrate any concerning effects of the surrogate antibody on fertility or development. They have also concluded that the sponsor's rationale that carcinogenicity studies cannot be performed using the surrogate antibody due to neutralization of the antibody based on its immunogenicity in the available animal model is acceptable.

I concur with the review team that there are no outstanding toxicology concerns that would preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

There were no outstanding approvability issues related to the clinical pharmacology or biopharmaceutics of the Actemra product. See my review of the original application in Appendix 1 for a summary of the data supporting the BLA.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

Adequate data were submitted with the original application to document that Actemra is effective for the treatment of adult patients with moderately to severely active rheumatoid arthritis alone or in combination with methotrexate or other disease-modifying anti-rheumatic drugs. A summary of that data is included in my review of the original application attached as Appendix 1. As stated in my risk benefit assessment on page 11 of that review:

While the sponsor has clearly demonstrated that Actemra is effective as a treatment for RA, I do not think that they have adequately assessed the risk-benefit ratio for their choice of recommending the 8-mg/kg dose. Overall, this dose does not appear to provide a significant [increased] benefit for most patients compared to the 4-mg/kg dose. While there may be some subpopulations or individual doses that would achieve greater benefit from the higher dose, there also appear to be possible safety concerns that are dose related, in particular the risk of gastrointestinal perforation. In addition, the increased efficacy associated with the higher dose appears to be primarily driven by the product's effect on the CRP levels. The actual clinical components of the ACR20 demonstrate less of an advantage for the higher dose. The sponsor should further evaluate the risk, as well as the overall risk-benefit, of recommending only the 8-mg/kg dose, or consider recommending starting with the lower dose and increasing to the higher dose as needed and as tolerated.

The sponsor has proposed a revised dosing regimen: In patients who have had an inadequate response to one or more DMARDs, a starting dose of 4 mg/kg in combination with DMARDs may be considered, followed by an increase to 8 mg/kg based on clinical response. This new dosing regimen addresses my concern and is acceptable.

8. Safety

In Section 8 of my review of the original application (Appendix 1) I summarized the exposure and safety data submitted in the Actemra BLA. The major serious adverse events of concern were malignancies, serious infections, cerebrovascular events, gastrointestinal perforations, peripheral and central demyelinating events, and laboratory abnormalities, specifically hematologic abnormalities, elevated lipids, and hepatic enzyme and bilirubin elevations. Drs. Okada and Siegel have determined that the rates of these events did not change when the updated safety data was included in their analyses. There were four additional cases submitted with the safety update in which the subjects had liver enzyme and bilirubin levels that were high enough to meet Hy's Law criteria. However, upon close review Drs. Okada and Siegel concur with the sponsor's hepatology experts that these findings are not consistent with Hy's Law criteria based on other features of the cases. Additional evidence from liver biopsies of 16 subjects in the safety database supports the clinical review team's conclusion that Actemra does not result in drug-induced hepatotoxicity, but rather the elevated liver enzymes are likely the result of a pharmacological effect. On page 79 of her review, Dr. Okada notes:

Although the mechanism of action of liver enzyme abnormalities with tocilizumab has not been ascertained, there are plausible mechanisms by which hepatocellular injury could occur with anti-IL6R treatment. First, IL6 appears to have a hepatoprotective effect on various forms of liver injury and promotes hepatocyte regeneration. Therefore inhibition could lead to increased hepatocyte susceptibility to hepatotoxic insults.

Also, hepatocytes express high levels of IL6 receptor; which raises the question of whether, with ubiquitous anti-IL6R monoclonal antibody binding in the liver, even minimal complement-mediated cytotoxicity or antibody-dependent cellular cytotoxicity could result in some hepatic injury.

9. Advisory Committee Meeting

See Appendix 1 for a summary of the Advisory Committee outcomes in my review of the original application.

10. Pediatrics

From page 13 of Dr. Siegel's review of the original application:

The applicant has requested a deferral for patients age 2-17 with polyarticular juvenile idiopathic arthritis (JIA), and a waiver for children 0-2. The applicant has already discussed details of their proposed Phase 3 program in polyarticular JIA with the Agency. This study is planned to commence enrollment in the 4th quarter of 2008, with submission of the final study report planned for 2012. The applicant's proposed plan for studies in children appears adequate.

That study is currently underway. This plan was presented to the Pediatric Review Committee and the members of that committee found it to be acceptable.

11. Other Relevant Regulatory Issues

There are no outstanding additional regulatory issues.

12. Labeling

There are no outstanding labeling issues.

13. Decision/Action/Risk Benefit Assessment

- Recommendation for Regulatory Action
Approval
- Risk Benefit Assessment

The sponsor has responded to all of the concerns outlined in the CR letter (Appendix 2) and has provided sufficient data at this time to demonstrate that the risk-benefit balance for Actemra is reasonable and that the quality of the product is acceptable. However, Actemra has a concerning safety profile, including possible hepatotoxicity, lipid abnormalities which could result in cardiovascular toxicity, neurotoxicity, immunosuppression with high levels of infection and malignancy, and the potential to cause gastrointestinal perforation. For this reason, I am recommending that Actemra be approved as a second-line treatment for RA, as discussed in my review of the original application. This will permit its use for patients who have failed other treatments, while allowing the collection of post-marketing safety data to add to our understanding of the product's safety profile. While we have allowed products with similar safety profiles to be approved as first line therapy for RA in the past, the availability of multiple therapeutic options for this disease that exist at this time changes the risk-benefit balance for Actemra. Having many reasonable options for treatment allows us to be more cautious in introducing a new product with a concerning safety profile, including many unclear signals of potential toxicity, into the treatment armamentarium.

- Recommendation for Postmarketing Risk Management Activities

As noted previously, during the first cycle the review team determined that a REMS was necessary to assure that the risks of Actemra outweighed the benefits, and that the REMS should include an ETASU that would require healthcare professionals prescribing and administering Actemra to be certified as having received training on and to attest that they would follow the approved dosing and administration instructions, including laboratory monitoring regimens, and dose modification and interruption protocols, as well as adverse event reporting. During this review cycle, the division and DRISK staff reassessed this requirement and determined that the adverse events and laboratory abnormalities associated with Actemra treatment are similar to those observed with other products approved to treat RA and do not warrant the ETASU. Therefore the company was notified by teleconference on November 3, 2009, and by letter on November 16, 2009, that a modified REMS proposal should be submitted to the BLA and that the revised REMS need not contain the ETASU. The revised REMS was reviewed by DRISK and found to be acceptable.

- Recommendation for other Postmarketing Study Requirements

Drs. Okada and Siegel have recommended the following PMR studies (reproduced from page 13 of Dr. Siegel's review) and I concur with their recommendation:

- In order to assess whether the lipid abnormalities are associated with an increased risk of cardiovascular thromboembolic events, the Applicant should carry out a cardiovascular outcome study, adequately designed to rule out a moderately increased risk of serious cardiovascular events.
- The applicant should continue the ongoing long-term, open-label treatment studies out to 5 years to further assess long-term safety of tocilizumab.
- They should conduct a study trial of the effects of tocilizumab on therapeutic vaccination. Given the suppressive effects of tocilizumab on the immune system it is uncertain whether individuals receiving therapeutic vaccines will have normal levels of antibody response. It would be preferable for this study to be placebo controlled.
- To fulfill PREA requirements, they should conduct a study in children with polyarticular JIA. They currently have a study in polyarticular JIA ongoing that is adequately designed. The PMR should be to complete that study.
- The Applicant should establish a pregnancy registry to evaluate pregnancy outcomes from women exposed to tocilizumab during pregnancy.

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