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*APPLICATION NUMBER:*  
**BLA 125276/S049**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

<b>Date</b>	October 10, 2012
<b>From</b>	Sally Seymour, MD
<b>Subject</b>	Division Director Summary Review
<b>NDA/BLA #</b>	BLA# 125276
<b>Supplement #</b>	Supplement #49 and #56
<b>Applicant Name</b>	Roche
<b>Date of Submissions</b>	December 12, 2011 and March 6, 2012
<b>PDUFA Goal Date</b>	October 12, 2012
<b>Proprietary Name / Established (USAN) Name</b>	Actemra tocilizumab
<b>Dosage Forms / Strength</b>	injection for intravenous infusion; 20mg/mL
<b>Proposed Indication(s)</b>	1. the treatment of 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)
<b>Action/Recommended Action for NME:</b>	<i>Approval</i>

### 1. Introduction

This is a Division Summary of a supplemental Biologics Licensing Application (BLA) for tocilizumab to broaden the indication from rheumatoid arthritis (RA) patients who have an inadequate response to tumor necrosis factor (TNF) inhibitors to RA patients who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs). No new clinical trials were conducted to support this sBLA as the original BLA application established efficacy in the proposed patient population. However, because tocilizumab was the first IL-6 inhibitor approved for RA patients, the original approval was limited to TNF-inadequate responder population until additional safety data was available. To support the broader indication, Roche provided a comprehensive assessment of the safety of tocilizumab to support a favorable benefit/risk profile in the broader patient population. The safety information includes post-marketing data and data from ongoing long-term extension studies. This summary will provide an overview of the application with the focus on the safety of tocilizumab. This summary also addresses labeling for the prior approval supplement, sBLA 125276/56, to expand information in the product labeling regarding the hypersensitivity Warning.

### 2. Background

Tocilizumab (tradename Actemra) was approved on January 8, 2010, for the treatment of adult patients with moderately to severely active RA who have an inadequate response (IR) to one or more TNF antagonist therapies. Tocilizumab was later also approved for the treatment of systemic juvenile idiopathic arthritis (sJIA) on April 15, 2011.

Tocilizumab is a recombinant humanized anti-human interleukin 6 receptor monoclonal antibody. Tocilizumab is the first IL-6 inhibitor approved for the treatment of patients with RA. While the original BLA included sufficient efficacy data to support the broader indication in RA patients (DMARD IR), because tocilizumab was the first in class of IL-6 inhibitors and the clinical experience with tocilizumab was limited, the FDA limited the indication to patients with RA who have an inadequate response to TNF inhibitors.

In terms of safety, like other immunosuppressive agents approved for patients with RA, tocilizumab increases the risk serious infection. In addition, tocilizumab increases the risk of gastrointestinal perforation, neutropenia, thrombocytopenia, and increased lipid parameters. Because tocilizumab can increase lipid levels, at the time of approval there was concern regarding a potential increased risk of cardiovascular adverse events, therefore, the FDA required a post-marketing randomized, controlled trial to rule out a moderate increase in the risk of serious cardiovascular events. This trial is currently ongoing.

A post-action meeting was held between the sponsor and FDA on June 28, 2010, and part of the discussion was the approach to extend the indication to DMARD-IR patients. The Sponsor proposed to provide safety data on approximately 64,000 patient years of exposure. The FDA agreed and requested analysis of SAEs, serious infection, malignancies and other safety issues identified in the clinical program for tocilizumab. On August 12, 2011, the Sponsor submitted a package to the FDA regarding the format and content of the sBLA, and a pre-sBLA meeting was held on November 14, 2011. FDA generally agreed with the Sponsor's proposed package and requested information on the following additional adverse events: interstitial lung disease, pancreatitis, convulsions, and pancytopenia.

Supplement 56 is a labeling supplement to add information regarding the hypersensitivity and anaphylaxis Warning (described in Section 8) and was submitted during the review period of Supplement 49. The Division combined both supplements and will take action on both at the same time.

### **3. CMC/Device**

The section is not applicable as tocilizumab is an approved product and there is no new CMC information included in this application.

### **4. Nonclinical Pharmacology/Toxicology**

The section is not applicable as tocilizumab is an approved product and there is no new pharmacology/toxicology information included in this application.

### **5. Clinical Pharmacology/Biopharmaceutics**

The section is not applicable as tocilizumab is an approved product and there is no new clinical pharmacology information included in this application.

## 6. Clinical Microbiology

The section is not applicable as tocilizumab is an approved product and there is no clinical microbiology information included in this application.

## 7. Clinical/Statistical-Efficacy

No new clinical trials were submitted in this sBLA as the efficacy of tocilizumab for the proposed indication was established in the original BLA. As described in the package insert for tocilizumab, the original approval of tocilizumab included 5 efficacy trials in patients with RA. The following provides a brief overview of the 5 trials, which are described in the tocilizumab package insert:

- Study 1 (WA17824) - patients who were methotrexate naïve or methotrexate intolerant
- Studies 2-4 (WA17822, WA17823, WA18063) - patients with inadequate response to DMARDs
- Study 5 (WA 18062) - patients with inadequate response to TNF inhibitors (Study 5),

The 3 trials in patients with inadequate response to DMARDs (Studies 2-4) are relevant for the proposed broader patient population. All 3 trials were randomized, double-blinded, placebo controlled add on clinical trials of at least 24 weeks duration comparing tocilizumab 4mg/kg or 8mg/kg + methotrexate/DMARDs to placebo + methotrexate/DMARDs every 4 weeks. Efficacy was based upon the signs and symptoms of RA assessed using the American College of Rheumatology (ACR) response criteria, e.g., ACR 20, 50, and 70 are based upon the proportion of patients achieving 20%, 50%, or 70% improvement, respectively. As shown in the table below taken from the package insert, in Study 2-4, the ACR 20, 50, and 70 response rates were significantly higher in patients treated with tocilizumab compared to patients treated with placebo. Study 2 was a 1 year trial that served as the basis for the efficacy claims for inhibition of structural damage, improvement in physical function, and major clinical response.

**Table 1 Clinical Response at Weeks 24 and 52 in Active and Placebo Controlled Trials  
Actemra (tocilizumab) Package Insert**

		Percent of Patients												
		Study I		Study II			Study III			Study IV		Study V		
		MTX	ACTEMRA 8 mg per kg	Placebo + MTX	ACTEMRA 4 mg per kg + MTX	ACTEMRA 8 mg per kg + MTX	Placebo + MTX	ACTEMRA 4 mg per kg + MTX	ACTEMRA 8 mg per kg + MTX	Placebo + DMARDs	ACTEMRA 8 mg per kg + DMARDs	Placebo + MTX	ACTEMRA 4 mg per kg + MTX	ACTEMRA 8 mg per kg + MTX
Response Rate		N=284	N=286 (95% CI) <sup>a</sup>	N=393	N=399 (95% CI) <sup>a</sup>	N=398 (95% CI) <sup>a</sup>	N=204	N=213 (95% CI) <sup>a</sup>	N=205 (95% CI) <sup>a</sup>	N=413	N=803 (95% CI) <sup>a</sup>	N=158	N=161 (95% CI) <sup>a</sup>	N=170 (95% CI) <sup>a</sup>
<b>ACR20</b>														
Week 24		53%	70% (0.11, 0.27)	27%	51% (0.17, 0.29)	56% (0.23, 0.35)	27%	48% (0.15, 0.32)	59% (0.23, 0.41)	24%	61% (0.30, 0.40)	10%	30% (0.15, 0.36)	50% (0.36, 0.56)
Week 52		N/A	N/A	25% (0.15, 0.28)	47% (0.25, 0.38)	56% (0.25, 0.38)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
<b>ACR50</b>														
Week 24		34%	44% (0.04, 0.20)	10%	25% (0.09, 0.20)	32% (0.16, 0.28)	11%	32% (0.13, 0.29)	44% (0.25, 0.41)	9%	38% (0.23, 0.33)	4%	17% (0.05, 0.25)	29% (0.21, 0.41)
Week 52		N/A	N/A	10% (0.14, 0.25)	29% (0.21, 0.32)	36% (0.21, 0.32)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
<b>ACR70</b>														
Week 24		15%	28% (0.07, 0.22)	2%	11% (0.03, 0.13)	13% (0.05, 0.15)	2%	12% (0.04, 0.18)	22% (0.12, 0.27)	3%	21% (0.13, 0.21)	1%	5% (-0.06, 0.14)	12% (0.03, 0.22)
Week 52		N/A	N/A	4% (0.08, 0.17)	16% (0.12, 0.21)	20% (0.12, 0.21)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
<b>Major Clinical Responses<sup>b</sup></b>														
Week 52		N/A	N/A	1% (0.01, 0.06)	4% (0.01, 0.06)	7% (0.03, 0.09)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

<sup>a</sup> CI: 95% confidence interval of the weighted difference to placebo adjusted for site (and disease duration for Study I only)

<sup>b</sup> Major clinical response is defined as achieving an ACR 70 response for a continuous 24 week period

Drs. Hull and Yim have concluded that the efficacy data submitted and reviewed in the original BLA supports the expanded indication in the broader patient population. I agree with this conclusion. The efficacy data is already adequately described in Section 14 of the tocilizumab package insert; therefore, no changes to Section 14 (Clinical Studies) section are necessary.

## 8. Safety

This sBLA is comprised of safety data for tocilizumab from postmarketing reports, controlled clinical trials, open label long term extension, and epidemiologic data. The controlled clinical trial data included the 5 efficacy trials (4098 patients) and pooled by patient population. The open label extension data has a cut off of April 1, 2011, includes 4009 patients and 14 additional months of long-term safety data since the original BLA with a total of 14,994 patient years. Of the 4009 patients, 700 (17%) were exposed for ≤12 months, 884 (22%) for 13 to 38 months, and 2425 (61%) were exposed for ≥ 4 years. The postmarketing safety data is based upon the Sponsor’s database through July 29, 2011. The Sponsor estimated the patient year exposure for tocilizumab as 65,099 patient years to determine event rates. The Sponsor used MarketScan Healthcare Claims Database, medical literature and other epidemiological data sources such as the US National Vital Statistics Reports and the US Surveillance and Epidemiology End Results (SEER) database to estimate background incidence rates for comparative analyses.

Overall, the Sponsor has provided a comprehensive analysis of available safety data with tocilizumab and has utilized epidemiology data to provide comparison with TNF inhibitors for context. However, it is important to note that there are limitations with some of the data submitted. For example, open label extension data lacks a comparator group and may be subject to selection bias. Given the limitations of post-marketing reports (voluntary reporting), the utility of calculating incidence rates is questionable. Therefore, the primary focus of this

memo is to assess whether there is a new serious safety signal since approval of tocilizumab that would warrant the continued restriction to RA patients with an inadequate response to TNF inhibitors. Drs. Hull and Yim's reviews provide a detailed discussion of the safety data submitted in this sBLA.

Safety signals for tocilizumab known at the time of approval and described in the product label include serious infections, gastrointestinal (GI) perforations, and specific laboratory abnormalities (elevated hepatic transaminases, neutropenia, thrombocytopenia, and elevated lipids). GI perforation, neutropenia, thrombocytopenia, and elevated lipids appeared to be potentially unique to tocilizumab as serious infections are expected with immunosuppressants and seen with other products for RA, such as TNF inhibitors. GI perforations continue to be reported post-approval. Similarly laboratory abnormalities are also noted post-approval, but there does not appear to be a large number of serious adverse events associated with the abnormalities, e.g. hepatic failure, bleeding events due to thrombocytopenia. The effects of elevated lipids on cardiovascular outcomes cannot be assessed adequately using post-marketing and long-term extension data. A post-marketing required safety trial is ongoing with tocilizumab to assess serious cardiovascular events.

At the time of approval, malignancy was not a clear safety signal with tocilizumab. Reports of malignancy were identified during the development program and because tocilizumab is an immunosuppressant, a Warning was included in the product label regarding the potential risk of malignancy. Because of the long latency of malignancy and an increased risk of malignancies in patients with RA, it would be difficult to determine if there was an increased risk of malignancy with tocilizumab. Clusters of unusual malignancies would raise concern and this has not been noted thus far post-approval. Instead the reports are common types of malignancy, e.g. non-melanoma skin cancer, lung, etc.

Demyelinating disorders were noted in the tocilizumab clinical development program. Although there were few reports and the data was not convincing, a Warning was included in the tocilizumab label because other demyelinating events have been reported with other biologic immunosuppressants. There are very few additional reports of demyelinating events with tocilizumab.

Anaphylaxis and hypersensitivity were noted in the tocilizumab clinical development program, albeit infrequently (< 1%). A Warning was included in the product labeling. Following approval, a fatal case of anaphylaxis during infusion of tocilizumab was reported and the labeling was updated to note the fatal case of anaphylaxis. A Contraindication was also added for patients with known history of hypersensitivity to tocilizumab. On March 6, 2012, the Sponsor submitted labeling supplement #56 to add additional information to the product label regarding hypersensitivity. A second fatal case of anaphylaxis during tocilizumab infusion had been reported. The Sponsor was asked to review the hypersensitivity reports to determine if there was a length of time following infusion when patients were at increased risk of hypersensitivity reaction that would warrant monitoring for a certain period of time. The majority of the cases occurred during infusion, including the two fatal cases of anaphylaxis. While the reports of two fatal cases of anaphylaxis are of concern, this should not preclude the expanded indication for tocilizumab. The product labeling has been updated and the

recommendation is for tocilizumab to be administered by a healthcare professional with appropriate medical support to manage anaphylaxis. Drs. Hull and Yim have reviewed the data provided on hypersensitivity and anaphylaxis and have revised the product label to accurately reflect the data. The Sponsor has agreed to the updated language.

The Office of Surveillance and Epidemiology (OSE) monitors the post-marketing reports for tocilizumab and identified four safety issues (pancreatitis, pancytopenia, convulsions, and interstitial lung disease) that we requested the Sponsor address in this submission. Based upon review of the submitted data, the review teams did not believe there was sufficient evidence to support causality and include information in the product label at this time. These events will continue to be monitored.

Drs. Hull and Yim have concluded that the data submitted with this supplement are generally consistent with the original BLA and no new safety signals have been identified that would preclude the broader indication. I agree with this assessment.

## **9. Advisory Committee Meeting**

The section is not applicable as tocilizumab is an approved product and this sBLA was not referred to an AC.

## **10. Pediatrics**

In the January 8, 2010, original BLA approval, pediatric studies were waived in children 0 to 2 years of age and pediatric studies were deferred in children 2 to 17 years of age with polyarticular JIA. This sBLA triggered PREA. Roche referred to the existing pediatric requirement for JIA (waiver in children 0 to < 2 years of age and deferral in children  $\geq 2$  to < 17 years of age), which is acceptable. The pediatric plan was discussed at PeRC and found to be acceptable.

## **11. Other Relevant Regulatory Issues**

There are no other unresolved relevant regulatory issues.

## **12. Labeling**

The product label includes minor modifications to the indicated patient population to remove the limitation of patients who have an inadequate response to tumor necrosis factor (TNF) inhibitors. The indicated population is now patients with RA who have an inadequate response to DMARDs. As discussed above in Section 8, there was also minor modification to the hypersensitivity Warning. Consults from OPDP, DMEPA, and DMPP did not recommend further labeling changes.

## **13. Decision/Action/Risk Benefit Assessment**

- Regulatory Action

The recommended regulatory action is approval. The efficacy of tocilizumab in the broader RA patient population had previously been established in the original BLA. The submitted safety information provides assurance that the safety profile of tocilizumab is adequately established and described in the package insert.

- Risk Benefit Assessment

The submitted safety information supports an acceptable benefit/risk profile for RA patients. Tocilizumab does have risks, but these risks are adequately described in the product label and the risks do not justify keeping tocilizumab as a third line therapy for RA. Broadening the patient population allows prescribers and patients to have another choice of therapies for patients who are inadequate responders to DMARDs. This recommendation is consistent with the clinical team and CDTL recommendations.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

Tocilizumab has a REMS that includes a Communication Plan and Timetable for Assessment. This sBLA included minor modifications to the existing REMS documents, but did not change the elements of the REMS. The Agency and Roche have agreed to the modified REMS.

- Recommendation for other Postmarketing Requirements and Commitments

There are no recommendations for new postmarketing requirements or commitments based upon this sBLA. There are several outstanding PMRs for tocilizumab from previous actions including the following:

- 0-1. Assessment of pharmacokinetic (PK/PD) parameters and dosing, efficacy, safety, tolerance and immunogenicity in the pediatric population ages 2 years to 17 years with polyarticular JIA.
- 0-2. Pregnancy registry to evaluate pregnancy outcomes for women exposed to Actemra during pregnancy. Utilize the established Organization of Teratology Information Specialists (OTIS) pregnancy registry to evaluate pregnancy outcomes.
3. Long-term, observational study of patients who continue to be treated with tocilizumab in the open-label part of the treatment trials WA18695 and WA18696 to evaluate long-term serious risks of Actemra and to accrue safety data on at least 1000-15000 patients treated for 5 years.
4. A randomized, controlled trial to rule out a moderate increase in the risk of serious cardiovascular events with tocilizumab, e.g. stroke, non-fatal MI, cardiovascular death.
5. A randomized trial to study the effects of tocilizumab on therapeutic vaccines. B cell-dependent antigens and T cell dependent antigens will be evaluated.
- 22-1 A pharmacokinetic and safety study of tocilizumab (TCZ) in patients less than 2 years old with active systemic juvenile idiopathic arthritis (sJIA)



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SALLY M SEYMOUR  
10/10/2012