CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125472Orig1s000

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	October 21, 2013
From:	Banu A. Karimi-Shah, M.D. Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA Sarah Yim, M.D. Associate Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
BLA Number:	125472
Applicant Name:	Genentech
Date of Submission:	December 21, 2012
PDUFA Goal Date:	October 21, 2013
Proprietary Name:	Actemra®
Established Name:	Tocilizumab
Dosage form:	Pre-filled syringe-162 mg/0.9 mL
Proposed Indications:	Moderately to Severely Active Rheumatoid Arthritis in Adults with an Inadequate Response to one or more DMARD therapies (b) (4)
Action:	Approval

1. Introduction

Genentech submitted Biologic Licensing Application (BLA) 125472 on December 21, 2012, in support of subcutaneous (SC) administration of tocilizumab (TCZ) in adult rheumatoid arthritis (RA) patients. Tocilizumab for intravenous (IV) infusion was first approved in the United States on January 8, 2010 (BLA 125276) for the treatment of moderately to severely active RA patients who have had an inadequate response to one or more TNF antagonists, and received subsequent approval for the broader group of RA patients who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Subsequently, tocilizumab IV was also approved for systemic juvenile idiopathic arthritis (sJIA) and polyarticular juvenile idiopathic arthritis (pJIA) on April 15, 2011 and April 29, 2013, respectively. It was the first in class (IL-6 receptor antagonist) biologic agent for the treatment of adult patients with RA, and pediatric patients with sJIA and pJIA, approved in the United States.

Tocilizumab is currently marketed as a solution for intravenous infusion, to be administered over 60 minutes. For RA, the current IV dosing is 4 mg/kg every 4 weeks followed by an increase to 8 mg/kg every 4 weeks based on clinical response. For pJIA, the currently approved IV dosing is 10 mg/kg given once every 4 weeks for patients weighing < 30 kg, and 8 mg/kg for patients weighing ≥30 kg. For sJIA, the currently approved IV doing is 12 mg/kg given once every 2 weeks for patients < 30 kg, and 8 mg/kg for patients ≥ 30 kg.

This BLA consists of data to support the Applicant's proposed marketing of tocilizumab as a fixed dose (162 mg) subcutaneous injection in pre-filled syringes to be given once weekly in adult RA patients weighing ≥100 kg, and once every other week in patients weighing <100 kg, increasing to once per week based on clinical response. The proposed indication for the fixed dose subcutaneous formulation is the same as the currently approved RA indication for intravenous tocilizumab.

This summary review provides an overview of the application with emphasis on the clinical section. The efficacy and safety data provided support the approval of this BLA.

2. Background

The classes of drugs used for the treatment of RA include: non-steroidal anti-inflammatory drugs (NSAIDs), selective COX-2 inhibitors, corticosteroids, and disease modifying anti-rheumatic drugs (DMARDs). NSAIDs and COX-2 inhibitors are utilized primarily for symptomatic relief of pain and are useful co-therapies because of their anti-inflammatory and analgesic effects. Corticosteroids are versatile agents with potent anti-inflammatory effects, but their use is limited by long-term toxicity. DMARDs are a diverse group of therapeutic agents that reduce signs and symptoms of RA as well as slow disease progression (i.e., produce a disease-modifying effect) as evidenced by retarding radiographic progression of joint damage. Approved DMARDs and some of their features are listed in Table 1 and Table 2. Methotrexate is the most commonly used DMARD because of its proven efficacy, and well-understood long-term effects. Large molecule biologic products are considered to be disease-modifying when they have been shown to inhibit progression of joint damage, which is true for the majority (Table 2). In the treatment of RA, methotrexate is often the initial DMARD used, and then it is combined with other DMARDs, commonly biologics, to enhance clinical effect.

Table 1. Approved Non-Biologic Disease Modifying Anti-Rheumatic Drugs (DMARDs)

	Product	NDA	Sponsor	Year of Approval[1]
1	Sulfasalazine (AZULFIDINE)	7-073	Pfizer	1950
2	Methotrexate sodium (METHOTREXATE SODIUM)	8-085 (PO) 11-719 (IV) 204824 (SC)	Multiple	1953
3	Hydroxychloroquine (PLAQUENIL)	9-768	Sanofi-Aventis	1955
5	Azathioprine (IMURAN)	16-324	Prometheus Labs	1968
6	Penicillamine (CUPRIMINE)	19-853	Aton	1970
7	Auranofin (RIDAURA)	18-689	Prometheus Labs	1985
8	Cyclosporine (NEORAL) Cyclosporine (SANDIMMUNE)	50-715 50-625	Novartis	1995 1990
9	Leflunomide (ARAVA)	20-905	Sanofi-Aventis	1998
10	Tofacitinib (XELJANZ)	203214	Pfizer	2012

Other formulations (e.g., solutions) are not included in this table.
[1]The initial approval of these small molecules may have not been for RA.

Table 2. Approved Biologic Products for the Treatment of RA in the United States

	Product	BLA (sponsor)	Year Approved for RA[1]	Characteristics	ROA
1	Etanercept (ENBREL®)	103795 (Immunex)	1998	Fusion protein (TNF inhibitor)	SC
2	Infliximab (REMICADE®)	103772 (COBI)	1999	Monoclonal antibody (TNF inhibitor)	IV
3	Anakinra (KINERET®)	103950 (Amgen)	2001	Human IL-1 receptor antagonist (IL-1 inhibitor)	SC
4	Adalimumab (HUMIRA®)	125057 (Abbott)	2002	Monoclonal antibody (TNF inhibitor)	SC
5	Abatacept (ORENCIA®)	125118 (BMS)	2005	Fusion protein (costimulation modulator – inhibits T-cell activation)	IV SC
6	Rituximab (RITUXAN®)	103705 (Genentech & Biogen Idec)	2006	Monoclonal antibody [anti-CD20 (B-cell depleter)]	IV
7	Golimumab (SIMPONI®) (SIMPONI ARIA®)	125289 (COBI) 125433	2009 2013	Monoclonal antibody (TNF inhibitor)	SC IV
8	Certolizumab Pegol (CIMZIA®)	125160 (UCB)	2009	Fab fragment conjugated to PEG (TNF inhibitor)	SC
9	Tocilizumab (ACTEMRA®)	125276 (Roche)	2010	Monoclonal antibody (Il-6 receptor inhibitor)	IV

[1]Infliximab was originally approved in 1998 for Crohn's Disease and rituximab was originally approved for non-Hodgkin's Lymphoma in 1997. Certolizumab Pegol was originally approved for Crohn's disease in 2008.

The clinical efficacy and safety data that supported the original approval of tocilizumab for the claim of reducing signs and symptoms (clinical response), inhibiting progression of structural damage (radiographic response), and improving physical function and health-related outcomes in RA were from five controlled clinical studies in patients 18 years of age and older with active RA. These studies are described in the currently approved tocilizumab product label. The current submission to support approval of subcutaneous administration of tocilizumab is based on one non-inferiority study comparing the efficacy and safety of tocilizumab subcutaneous and intravenous dosing (WA22762 or SC-I), one placebo-controlled superiority study (NA25220 or SC-II), as well as long-term open label extensions of these studies. New pharmacokinetic studies were also conducted to assess the clinical pharmacokinetics of tocilizumab following subcutaneous administration.

3. Chemistry, Manufacturing, and Controls

Tocilizumab is a recombinant human monoclonal antibody targeting the interleukin 6 receptor (IL-6R). Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit IL-6-mediated signaling through these receptors. IL-6 is a pleiotropic pro-inflammatory cytokine

produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes and fibroblasts. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis.

Tocilizumab solution for subcutaneous administration is supplied as a sterile, colorless to yellowish, preservative-free liquid solution with an approximate pH of 6.0. It is supplied in a 1 mL ready-to-use, single-use prefilled syringe (PFS) with a needle safety device. Each device delivers 0.9 mL (162 mg) of tocilizumab, in a histidine buffered solution composed of tocilizumab (180 mg/mL), polysorbate 80, L-histidine and L-histidine monohydrochloride, L-arginine and L-arginine hydrochloride, L-methionine, and water for injection. The subcutaneous tocilizumab drug substance manufacturing process (b) (4) this does not impact quality attributes such as potency, aggregates other size or charge variants, or the levels of process-related impurities. Adequate data were provided to support the requested shelf life of 30 months for (b) (4) storage of the tocilizumab PFS when stored at 2-8° C.

The drug product will be supplied in a pre-filled syringe sealed with a rigid needle shield (RNS) and a needle safety device (NSD). It is manufactured by (b) (4) Labeling, assembly with the NSD, and secondary packaging are performed by F. Hoffman-La Roche Ltd in Kaiseraugst, Switzerland. An inspection waiver was issued for (b) (4) An inspection was conducted for F. Hoffmann-La Roche Ltd. by CIN-DO on July 22-25, 2013. The Office of Compliance at CDRH recommends that the inspection be classified as a Voluntary Action Indicated (VAI). The violations identified during the inspection appear to have minimal probability of producing non-conforming combination products.

CDRH also reviewed the human factors data which were acceptable. During the clinical trials there was a very low frequency (< 0.01%) of needle clogging, noted in the CDRH review. Since the presence of a potential clog is of very low frequency, the impact to patient harm with a repeated no-dose would be considered extremely low. This issue does not require further action at this time.

4. Nonclinical Pharmacology and Toxicology

Information regarding the toxicology profile of tocilizumab was submitted and reviewed with the original application to support chronic intravenous administration for the approved adult RA indications. This submission includes two nonclinical studies that provide support for the change in route of administration from intravenous to subcutaneous. These nonclinical studies provide adequate support for the safety of the new subcutaneous route of administration in RA patients.

5. Clinical Pharmacology and Biopharmaceutics

The pharmacokinetic (PK) data in this submission are derived primarily from the two pivotal phase 3 clinical trials in patients with RA (WA22762 and NA25220) as well as

six clinical pharmacology studies that were designed to characterize the PK and pharmacodynamic (PD) profiles of tocilizumab following IV and SC administration, and to evaluate the immunogenicity of tocilizumab when administered SC.

Based on the population PK analysis, the bioavailability of tocilizumab following SC administration for a typical patient was estimated to be 79.5% (95%CI: 77.9 – 81.1%). Following SC dosing in RA patients, the absorption half-life was around 3-5 days. The $t_{1/2}$ of tocilizumab is concentration dependent. For IV administration, the concentration-dependent apparent $t_{1/2}$ is up to 11 days for 4 mg per kg every 4 weeks (q4w) and up to 13 days for 8 mg per kg q4w in patients with RA at steady-state. For SC administration, the concentration-dependent apparent $t_{1/2}$ is up to 13 days for 162 mg every week (qw) and 5 days for 162 mg every other week (q2w) in patients with RA at steady-state.

The SC dose regimens for the two phase 3 studies (WA22762 and NA25220) were determined based on PK, PD, and safety data from two phase 1/2 studies (MRA227JP and NP22623) in patients with RA. Based on these two study results, it was found that the PD profiles (CRP, ESR, and sIL-6R) corresponding to the tocilizumab 162 mg SC qw regimen were most comparable to those following the tocilizumab 8 mg/kg IV Q4W regimen. In comparison, the162 mg SC q2w regimen led to slower and less pronounced PD responses than 8 mg/kg IV q4w and 162 mg SC qw regimens. However, the PD responses following the 162 mg SC q2w regimen were superior to the 81 mg SC q2w and qw regimens.

6. Clinical Microbiology

Both the drug substance and drug product sections of this BLA submission were reviewed from a microbial control, CMC sterility assurance, and microbiology quality perspective, and were found to be acceptable. As a part of a post-marketing commitment, the Applicant has agreed to determine the (b) (4) volume necessary for (b) (4) and will provide their report by October 30, 2013.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Characteristics of the relevant clinical studies that form the basis of the review and regulatory decision for this application are shown in Table 3. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

Table 3: Summary of Clinical Program for Tocilizumab SC

Study [Sites]	Design	Study duration	Treatment[†]	N	Study Population	Endpoints
Pivotal efficacy and safety studies						
WA22762 [25 countries] **(SC-I)**	R, DB, AC	24 weeks	TCZ 162 mg SC qw TCZ 8 mg/kg IV q4w	631 631	Moderate to Severely Active RA Age: 18-86 (53)	ACR20 response (non-inferiority)
NA25220 [21 countries] **(SC-II)**	R, DB, PC	24 weeks	TCZ 162 mg SC q2w Placebo SC q2w Escape at > 12 weeks TCZ 162 mg SC q2w	437 219 162	Moderate to Severely Active RA Age: 18-82 (52)	ACR20 response
Long-Term Extensions[1]						
WA22762-LTE	OL, R	72 weeks	TCZ 162 mg SC qw TCZ 8 mg/kg IV q4w IV-SC switch SC-IV switch	524 377 186 48	Moderate to Severely Active RA Age: 18-86 (53)	Safety
NA25220-LTE	OL, R	72 weeks	TCZ 162 mg SC q2w TCZ 162 mg SC q2w to AI PBO to TCZ 162 mg SC q2w PBO to TCZ 162 mg SC q2w AI Escape Therapy: TCZ 162 mg SC qw PFS/AI	167 168 61 59 7	Moderate to Severely Active RA Age: 18-82 (52)	Safety

TCZ: tocilizumab; R: randomized; DB: double-blind; AC: active control; PC: placebo control; OL: open label; PFS: pre-filled syringe; AI: autoinjector (not being proposed in this application); PBO: placebo
[1]All long-term extensions were ongoing at the time of submission. Clinical data cut-off was January 2012.
All SC treatments were via PFS unless otherwise specified.
All patients had inadequate response to DMARDs and were being treated with concomitant non-biological DMARD background therapy.

b. Design and conduct of the studies

Study WA22762 was a randomized, double-blind, double-dummy, active-controlled, parallel group, global study (209 sites in 25 countries) conducted in patients with active RA having an inadequate response to DMARDs. After meeting eligibility criteria, 1262 patients were randomized in 1:1 ratio to receive either tocilizumab 162 mg SC weekly or tocilizumab IV 8 mg/kg every 4 weeks. Patients were stratified by weight (<60 kg, 60-100kg, >100 kg) region, and remained on background DMARD therapy. The primary efficacy endpoint was the proportion of patients achieving ACR20 response at week 24, with the primary analysis being a comparison between subcutaneous and intravenous tocilizumab in the per protocol population. Study WA22762 was designed to determine the non-inferiority of the SC regimen with a non-inferiority margin (NIM) of 12% using the ACR20 at 24 weeks as the primary endpoint. Non-inferiority of tocilizumab SC was claimed if the lower bound of the adjusted 95% CI for the difference between the

response rates, tocilizumab SC minus tocilizumab IV, was not less than 12 percentage points. If this was met the 95% CI would then be tested against a 10% NIM. The non-inferiority limits were defined to ensure maintenance of at least 65% (12% NIM) and 70% (10% NIM) of the ACR20 response seen with tocilizumab 8 mg/kg IV q4w versus placebo in the previous IV trials. The effect size of IV tocilizumab in previous placebo-controlled studies using the proportion of patients achieving ACR20 responses at 6 months was 48-60%. The NIM was selected in agreement with previous Agency advice to the applicant. Other efficacy endpoints included ACR50 and ACR70 responses, physical function characterized by HAQ-DI, and changes in DAS28. Safety assessments included recording of adverse events, vital signs, clinical laboratory measures, physical examination, and immunogenicity. PK assessments were also conducted in a sub-study.

Study NA25220 was a randomized, double-blind, placebo-controlled, parallel group, global study (124 centers in 21 countries) conducted in patients with active RA having an inadequate response to DMARDs. After meeting eligibility criteria, 656 patients were randomized to receive either tocilizumab 162 mg SC or placebo every other week. From weeks 12 to 48, patients initially randomized to receive either tocilizumab or placebo could move to open label escape therapy with tocilizumab 162 mg SC once weekly if there was < 20% improvement in swollen joint count (SJC) and tender joint count (TJC) from baseline. The primary efficacy endpoint was the percentage of patients with ACR20 response at week 24. Other efficacy endpoints included ACR50 and ACR70 responses, physical function characterized by HAQ-DI, and change from baseline in the van de Heijde modified Sharp radiographic score at Week 24. Safety assessments were similar to Study WA22762.

c. Efficacy findings and conclusions

The submitted clinical program showed that fixed dose subcutaneous administration of tocilizumab every week was not inferior to the currently approved high dose of tocilizumab given via intravenous administration and that tocilizumab SC every other week was superior to placebo in patients with RA. The primary efficacy endpoint was ACR20 response at week 24, with the primary analysis being a comparison between the IV and SC tocilizumab per protocol populations in Study WA22762 (SC-I), with the NIM as described above; and IV tocilizumab versus placebo (ITT population) in Study NA25220 (SC-II). The primary efficacy results as well as some additional secondary endpoints are summarized in Table 4.

Various subgroup analyses were performed. At week 24, the ACR20/50/70 responses in Study WA22762 were comparable for the SC qw and IV 8 mg/kg arms across the three body weight categories, with responses in both arms decreasing with increasing body weight. In Study NA25220, ACR responses with TCZ SC q2w also decreased with increasing body weight. Per Dr. Hoberman's analysis, logistic regression analysis showed that the overall response rate is slightly lower in those who weighed at least 100 kg compared to those who weighed between 60 and 100 kg. However, there was no evidence of any interaction between treatment and weight category.

Based on phase 3 study results, tocilizumab 162 mg SC qw and 8 mg/kg IV q4w treatment regimens demonstrated comparable efficacy. The tocilizumab 162 SC q2w dosing regimen also showed clinically superior efficacy improvements to placebo. However, the treatment effect was less pronounced in patients weighing > 100 kg weight group treated with tocilizumab 162 kg SC q2w treatment compared to the same body weight groups for tocilizumab 162 kg SC qw and 8 mg/kg IV q4w treatments (50.0%, 50.8%, 38.5%, and 27.3% for 162 mg SC qw, 162 mg SC q2w, 8 mg/kg IV q4w, and placebo in terms of ACR20 responses, respectively, at week 24 in ITT population). By directly comparing the ACR20 responses of patients weighting > 100 kg between SC qw and SC q2w treatments (i.e., 50.0 % vs. 38.5%), the decreased ACR responses for 162 mg SC q2w treatment is likely to be associated with less drug exposure. In addition, it was reported that a substantial % of escape patients who escalated from the q2w SC regimen to the qw SC regimen showed an improvement in efficacy. Therefore, dose escalation from SC q2w to SC qw for patients weighing > 100 kg to gain therapeutic advantage is reasonable. Similarly, there is adequate clinical data to support the starting dosing regimen of 162 mg SC q2w for patients weighing <100 kg. The ACR20 response was similar for both dosing regimens in patients weighing < 100 kg (>60%).

Subgroup analysis by region revealed that the overall response rate in North America was statistically significantly less than Europe, South America, and the Rest of the World. A possible explanation, per the Division's statistical reviewer, may be different regional administration of the trial regarding criteria for dropout, as more patients withdrew from the trial in North America due to lack of consent, adverse events, lost to follow up, and switching to escape therapy.

Table 4: Clinical Response in Studies SC-I and SC-II at Week 24				
	SC-I[a]		SC-II[b]	
	TCZ SC 162 mg every week + DMARD N=558	TCZ IV 8 mg/kg + DMARD N=537	TCZ SC 162 mg every other week + DMARD N=437	Placebo + DMARD N=219
ACR20				
No. Responders (%) [95% CI]	387 (69%) [66%, 73%]	394 (73%) [70%, 77%]	266 (61%) [56%, 65%]	69 (32%) [25%, 38%]
Weighted difference (95% CI)	-4% (-9.2, 1.2)		30% (22.0, 37.0)	
ACR50				
No. Responders (%) [95% CI]	262 (47%) [43%, 51%]	261 (49%) [44%, 53%]	174 (40%) [35%, 44%]	27 (12%) [8%,17%]
Weighted difference (95% CI)	-2% (-7.5, 4.0)		28% (21.5, 34.4)	
ACR70				
No. Responders (%) [95% CI]	134 (24%) [21%, 28%]	150 (28%) [24%, 32%]	86 (20%) [16%, 23%]	11(5%) [2%, 8%]
Weighted difference (95% CI)	-4% (-9.0, 1.3)		15% (9.8, 19.9)	
Change in DAS28 [Adjusted mean]				
	-3.5	-3.5	-3.1	-1.7
Adjusted mean difference (95% CI)	0 (-0.2, 0.1)		-1.4 (-1.7; -1.1)	
DAS28 < 2.6				
No. Responders (%) [95% CI]	198 (38%) [34%, 43%]	184 (37%) [33%, 41%]	111 (32%) [27%, 37%]	5 (4%) [1%, 7.5%]
Weighted difference (95% CI)	0.9 %(-5.0, 6.8)		28.6 (22.0, 35.2)	
HAQ-DI Response ≥ 0.3				
No. Responders (%) [95% CI]	336 (65%) [61%, 69%]	337 (67%) [63%, 71%]	202 (58%) [53%, 63%]	58 (47%) [38%, 56%]
Weighted difference (95% CI)	-2.3% (-8.1, 3.4)		12.1 (2.2, 22)	
a: Per Protocol Population; b: Intent to Treat Population				

8. Safety

a. Safety database

New safety data submitted with this application come primarily from the two pivotal studies, WA22762 (SC-1) and NA25220 (SC-II). The data reviewed come from the 24-week controlled clinical trial periods as well as the open-label long-term extension periods for both studies. Overall, 1465 patients received subcutaneous tocilizumab, with 908 patients exposed to qw, and 557 exposed to and q2w dosing regimen. The safety database was adequate for review.

b. Safety findings and conclusion

The safety data submitted for subcutaneous administration do not raise any new safety concerns for subcutaneous tocilizumab. The safety findings were generally similar to that of intravenous tocilizumab, both in this program, and historical intravenous controls. As this application seeks approval for two subcutaneous dosing regimens, 162 mg qw and 162 mg q2w, it is important to note that serious adverse events, adverse events,

infections, injection site reactions, and Grade 1/2 neutropenia occurred more frequently in the qw group as compared with the q2wgroup. While limited by cross-study comparison, the assessment of safety profiles of each dosing regimen supports the initiation of SC tocilizumab therapy with q2w dosing in patients weighing < 100 kg.

Taking into account that the clinical studies demonstrated a higher safety risk for the SC qw versus the SC q2w dosing regimen, starting with the lower (more infrequent) dosing regimen, as is done with the IV dosing, is reasonable.

c. REMS/RiskMAP

The data in this application do not suggest any new or unexpected safety signals. Tocilizumab IV has a REMS which has been updated with the information regarding the SC formulation and route of administration. A REMS modification will be requested of the Applicant for the tocilizumab IV BLA (125276).

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application. Efficacy and safety findings in the clinical program for the fixed dose subcutaneous formulation of tocilizumab were consistent with findings from the intravenous tocilizumab experience and did not warrant discussion at an advisory committee meeting.

10. Pediatric

Tocilizumab administered by the intravenous route is already approved for sJIA (since April 2011) and pJIA (since April 2013) in patients 2 years of age and older. The Applicant has requested a deferral of PREA-required studies in pJIA patients 2-17 years old, and a waiver for the 0-2 year old age group, given that pJIA is extremely rare in very young children. In response to a written request, the Applicant submitted the protocol for a 52-week pJIA study in 48 children 1-17 years of age, assessing PK endpoints at Week 14. The deferral and waiver requests were discussed at a Pediatric Review Committee (PeRC) meeting held on August 28, 2013. PeRC and the Division were in agreement that the pediatric proposal was acceptable.

11. Other Relevant Regulatory Issues

a. DSI Audits

A DSI audit of study sites was conducted as part of the intravenous tocilizumab BLA review. No further audit was conducted for this application. During review of this BLA no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. No potentially conflicting financial interests were identified.

c. Others

There are no outstanding issues with consults received from DDMAC, DMEPA, or from other groups within CDER or CDRH.

12. Labeling

a. Proprietary Name

There is no issue with the proposed proprietary name as the name Actemra was previously reviewed and found to be acceptable. The product is currently marketed under the trade name Actemra.

b. Physician Labeling

The labeling of Actemra was reviewed previously with the original approval of the intravenous product in 2010 for RA, and later in 2011 and 2013, with approval of the sJIA and pJIA indications, respectively. With this application, the existing label will be updated to include the new information regarding the tocilizumab subcutaneous formulation and relevant data from the new studies. The main changes are in the following sections of the label – Dosage and Administration, Dosage Forms and Strengths, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Description, Clinical Pharmacology, and Clinical Studies. The Division and Genentech have agreed on the final labeling language.

c. Carton and Immediate Container Labels

New carton and container labels were submitted for the single-dose prefilled syringe proposed for marketing. These were reviewed by various disciplines of this Division, OBP, and DMEPA, and were found to be acceptable.

d. Patient Labeling and Medication Guide

The current patient labeling and medication guide will be updated to include information on the new subcutaneous route of administration.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The Applicant has submitted adequate data to support approval of tocilizumab 162 mg solution for fixed dose subcutaneous administration once every other week and/or once weekly. The action for this application will be an Approval.

b. Risk Benefit Assessment

The overall risk-benefit assessment supports approval of tocilizumab for fixed dose subcutaneous administration in patients with RA. The submitted data show that the benefit of tocilizumab administered by the subcutaneous route is not inferior to that of the intravenous route, and is superior to placebo in the treatment of patients with RA. The safety of tocilizumab administered via the subcutaneous route does not show any new or unique safety findings.

c. Post-marketing Risk Management Activities

This application triggers PREA. The applicant will be required to conduct a study of SC tocilizumab in pJIA patients ages 2 to 17 years. This study has also been included as part of written request for tocilizumab, as listed in Section 10 above. The Applicant proposed timelines to submit the study reports by May 2018 are acceptable.

The data in this application do not suggest any new or unexpected safety signals. Tocilizumab IV has a REMS which will be updated with the information regarding the SC formulation and route of administration. The revised REMS will then be submitted to the BLAs for both the IV (125276) and SC (125472) formulations.

d. Post-marketing Study Commitments

One microbiology PMC has already been agreed to by the Applicant. The Applicant has agreed that they will determine the flush volume necessary for a stable bubble point after sterile filtration and will provide the report by October 30, 2013.

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

/s/

BANU A KARIMI SHAH
10/21/2013

SARAH K YIM
10/21/2013