CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125276

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Memo

FDA Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II
Division of Anesthesia, Analgesia and Rheumatology Products

Cross-Discipline Team Leader Memorandum

Date	December 14, 2009 Jeffrey N. Siegel 12/14/09
From	Jeffrey Siegel, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	BLA 1252776 Complete Response, 0/64
Applicant	Hoffman-La Roche
Date of Submission	July 9, 2009
PDUFA Goal Date	January 9, 2010
Proprietary Name / **Established (USAN) names**	Actemra Tocilizumab
Dosage forms / Strength	Intravenous, 4 mg/kg or 8 mg/kg every 4 weeks
Proposed Indication(s)	Moderately to severely active rheumatoid arthritis
Recommended:	*Approval, with revisions to the proposed labeling*

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1. Introduction to Review

Tocilizumab is a monoclonal antibody of the IgG1 subclass that binds to the interleukin-6 (IL-6) receptor, thereby inhibiting the biologic activity of IL-6. Interleukin-6 is a cytokine that is an important mediator of inflammation, including the production of acute phase reactants. It also acts as a growth factor for certain cells and regulates cells of the immune system. On November 19, 2007, Hoffman-La Roche submitted a biologic license application (BLA) for tocilizumab (Actemra) for the treatment of patients with moderately to severely active rheumatoid arthritis. The Phase 3 clinical development program included five Phase 3 trials exploring the efficacy and safety of tocilizumab in early and established rheumatoid arthritis (RA) as monotherapy and in combination with methotrexate (MTX) and with other disease-modifying anti-rheumatic drugs (DMARD's). During the review of that original BLA the Agency determined that data from those trials demonstrated efficacy of tocilizumab and that the benefits outweighed the potential risks in patients with moderately to severely active RA. However, several deficiencies precluded approval of the application and the Agency took a Complete Response (CR) action on September 17, 2008. The key deficiencies were 1) the lack of nonclinical perinatal and postnatal developmental toxicology studies; 2) the lack of nonclinical fertility studies and 3) deficiencies noted on inspection of the Chugai Pharmaceuticals manufacturing site. Additional deficiencies were also noted in the CR letter, including changes required to carton and container labeling, the need for a debarment certification and the need for resolution of several issues relating to financial disclosure.

In the current submission the Applicant reported the results of nonclinical studies of perinatal and postnatal development and addressed the deficiencies noted on inspection of the manufacturing site. During review of the submission, there were no major issues concerning pharmacology/toxicology or manufacturing. The deficiencies concerning carton and container labeling, the need for a debarment certification and the need for resolution of the issues related to financial were already adequately addressed. This memo will review the findings relating to the deficiencies noted in the CR letter and review updated safety information included in the application.

2. Background

The Applicant, Hoffman-La Roche, submitted their BLA for tocilizumab with data from five randomized, double-blind, controlled Phase 3 trials. All the Phase 3 trials showed efficacy based on the well-accepted ACR response criteria (Table 1, copied from the review of Dr. Sarah Okada). In studies WA17822, 17823 and 18063 patients with RA with an incomplete response to MTX or other disease modifying anti-rheumatic drugs (DMARDs) continued their DMARD and were randomized to add placebo or tocilizumab. In each study more patients who received tocilizumab had an ACR 20 response than control patients. In study WA18062, among patients with an incomplete response to prior treatment with a TNF blocker more patients randomized to receive tocilizumab had an ACR 20 response than with placebo. Finally, in Study WA17824, patients naïve to MTX were randomized to MTX or tocilizumab. More patients who

received tocilizumab achieved an ACR 20 response than those who received MTX. Of note, prior studies comparing MTX to other DMARD's such as etanercept or adalimumab have not shown significantly higher ACR 20 response rates.

Table 1: Proportion of ACR20/50/70 responders at Week 24 in the 5 Pivotal RA Studies

Percentage of ACR Responders at Week 24 in the 5 Pivotal RA Studies, by Trial Treatment (ITT Populations)						
Study	Pbo + DMARD**	TCZ 4mg/kg + DMARD**	TCZ 8mg/kg + DMARD**	p-value (4 mg/kg)	p-value (8 mg/kg)	
Patients with incomplete response to MTX or other DMARDs						
WA17822	(n=204)	(n=213)	(n=205)			
ACR20	**26**	48	**58**	<0.0001	**<0.0001**	
ACR50	11	32	44	<0.0001	<0.0001	
ACR70	2	12	22	<0.0001	<0.0001	
WA17823	(n=393)	(n=399)	(n=398)			
ACR20	**27**	51	**56**	<0.0001	**<0.0001**	
ACR50	10	25	32	<0.0001	<0.0001	
ACR70	2	11	13	<0.0001	<0.0001	
WA18063	(n=413)		(n=803)			
ACR20	**24**		**61**		**<0.0001**	
ACR50	9		38		<0.0001	
ACR70	3		20		<0.0001	
Patients with incomplete response to prior TNF inhibitor treatment						
WA18062	(n=158)	(n=161)	(n=170)			
ACR20	**10**	30	**50**	<0.0001	**<0.0001**	
ACR50	4	17	29	<0.0001	<0.0001	
ACR70	1	5	12	0.1005	0.0002	
MTX naïve/Early RA patients						
Study	**MTX**		**TCZ 8 mg/kg**	**Tx Diff**	**95% CI**	**p-value**
WA17824	(n=284)		(n=286)			
ACR20	**52**		**70**	**0.19**	**(0.11,0.27)***	<0.0001
ACR50	34		44	0.12	(0.04,0.20)	0.0023
ACR70	15		28	0.14	(0.88,27.59)	0.0002

*Non-inferiority demonstrated if lower limit of 95% CI MRA minus MTX ≥ -0 12 for primary analysis population

**DMARD = MTX for WA17822, 17823 and WA18062; includes MTX and other DMARDs in WA18063

Sources: Tables 17 & 19 of WA17822 CSR, Tables 17 & 18 of WA17823 CSR, Tables 17 & 22 of WA17824 CSR
Tables 21 & 23 of WA18062 CSR, and Tables 17 & 20 of WA18063 CSR

The safety database in the original BLA consisted of 3778 patients with RA treated for any period of time, including 3474 who had received tocilizumab for at least 6 months and 2121 who had received tocilizumab for at least one year. The major safety issues identified with tocilizumab treatment were serious infections, GI perforations, laboratory abnormalities (liver enzyme elevations, hematologic abnormalities and increases in LDL levels) and demyelinating events. Serious infections are an expected adverse event with tocilizumab based on its immunosuppressive mechanism of action. Serious infections were observed at a rate similar to that expected in the RA patient population. These adverse events will be described in more data later in this review along with the additional data accumulated since the original submission.

3. CMC

Non-approval issues were communicated to the Applicant. These concerned 483 observations from a pre-license inspection of the Chugai Pharma Manufacturing Co. plant in April-May, 2008. The Applicant satisfactorily responded to the 483 observations. The BLA is recommended for approval from a CMC perspective.

4. Nonclinical Pharmacology/Toxicology

In order to address the need for nonclinical data to support reproductive safety of tocilizumab, the Applicant conducted studies in mice using the surrogate antibody MR16-1. The studies showed no effect of the surrogate antibody on fertility of male or female mice. In addition, offspring of females treated during pregnancy showed no effects on behavior, learning or reproductive performance. The pharmacology/toxicology reviewer, Dr. Asoke Mukherjee, deemed the studies acceptable to address the pharmacology/toxicology issues in the CR letter. The submission also included a rationale for why carcinogenicity studies cannot be carried out using the surrogate antibody due to neutralization of the antibody based on its immunogenicity in the animal model. Dr. Mukherjee judged the rationale acceptable.

Dr. Mukherjee recommends approval of the BLA with revisions to the proposed labeling. He had no recommendations for any further pharmacology/toxicology studies. At the time of writing of this memo, the pharmacology/toxicology supervisor, Dr. Dan Mellon, was still in the process of writing his secondary review. Dr. Mellon indicated that he concurred with Dr. Mukherjee's conclusions.

5. Clinical Pharmacology/Biopharmaceutics

The submission contained no clinical pharmacology information.

6. Clinical/Statistical

6.1. General Discussion

The original submission contained the results of five randomized, controlled Phase 3 trials that all successfully showed clinical benefit of tocilizumab in patients with moderately to severely active RA. A summary of the results of those studies is provided in section 2.

Safety issues associated with tocilizumab treatment identified in review of the original BLA submission included serious infections, GI perforations, laboratory abnormalities (liver enzyme elevations, hematologic abnormalities and increases in LDL levels) and demyelinating events. A summary of these findings follows in section 6.3 along with additional data accumulated since the original submission.

6.2. Pediatric use/PREA waivers/deferrals

The pediatric condition that corresponds to adult RA is the group with polyarticular juvenile idiopathic arthritis (JIA). The applicant requested a deferral for patients age 2-17 with PJIA, and a waiver for children 0-2, since PJIA is extremely rare in this age group. The Applicant should receive a deferral for JIA patients in pediatric patients 2 years and older and a waiver for children 0-2 years old. They should conduct an efficacy study in JIA patients 4 years and older. If that study shows safety and efficacy then the Applicant should study safety, dosing and pharmacokinetics in the 2 and 3 year old population with JIA.

6.3. Safety

The submission contained information on a total of 4009 patients with 8580 patient-years exposure most of which was to the 8 mg/kg every 4 week dose regimen derived from completed and ongoing trials in patients with RA and from long-term extension studies.

Table 2 (this and all other tables and figures in this section copied from the review of Dr. Sarah Okada) shows the overall rates of death, malignancies, serious adverse events and serious infections (SIEs) in the controlled trials, in the total safety population from the original submission and from the updated safety population. As shown in the table, the rate of death was not increased in tocilizumab-treated patients compared with controls in the controlled trials. Additional accumulated data shows similar mortality rates. Malignancies were observed among tocilizumab-treated patients but at a rate similar to patients in the control group. The exposure-adjusted rate of malignancy was not increased in the updated safety database. Serious infections were more frequent among tocilizumab-treated patients also receiving a DMARD (5.7 events per 100 pt-yrs) compared to patients receiving a DMARD alone (3.9 events per 100 pt-yrs). This rate is similar to what has been observed in patients with RA receiving TNF blockers (5.1 events per 100 pt-yrs). The rate of serious infections did not increase in the updated safety database. Opportunistic infections and serious viral infections were also observed, including 9 cases of TB, 10 cases of herpes zoster exacerbations, 2 cases of atypical mycobacterial infections, a case of Pneumocystis Jiroveci pneumonia, a case of cryptococcal pneumonia, and a case of fungal sinusitis. The serious infections and opportunistic infections observed are consistent with tocilizumab being an immunosuppressive as suggested by its mechanism of action.

Table 2: Exposure-Adjusted Incidence Rates of Deaths, SAE, SIE, and Malignancies

Exposure and Exposure Adjusted Incidence Rates for Deaths, SAEs, SIEs, and Malignancies in the Tocilizumab RA Pivotal Studies and Long-Term Extensions, with Updated Information from All-Exposure Population								
	6-months pooled safety population						Long term safety population	Updated* All-exposure Population
	Placebo + DMARD	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD	TCZ 8mg/kg	All TCZ	Pooled TCZ	
Enrolled	1170	284	774	1582	288	2644	2562	4009
Total patient-years exposure	462	123	321	685	126	1131	3685	8580
Deaths, n (%)	4 (0.3)	1 (0.4)	0	2 (0.1)	3 (1)	5 (0.2)	16 (0.6)	50 (1.2)
Deaths per 100 pt-yrs	0.9	0.8	0	0.3	2.4	0.4	0.4	0.6
Malignancies, n (%)	7 (0.6)	3 (1)	5 (0.6)	10 (0.6)	2 (0.7)	17 (0.6)	60 (2.3)	109 (2.7)
Malignancies per 100 pt-yrs	1.5	2.4	1.6	1.5	1.6	1.5	1.6	1.3
No. with ≥1 SAE, n (%)	62 (5)	8 (3)	46 (6)	95 (6)	11 (4)	152 (6)	393 (15)	nr
Number of SAE	74	15	51	115	12	178	489	1404
SAEs per 100 pt-yrs	16	12	16	17	10	16	13	16
No. with ≥1 SIE, n (%)	17 (1.4)	2 (0.7)	13 (1.7)	38 (2.4)	4 (1.4)	55 (2.1)	133 (5.2)	nr
Number of SIE	18	2	15	39	4	58	141	439
SIEs per 100 pt-yrs	3.9	1.6	4.7	5.7	3.2	5.1	3.8	5.1

*Clinical cut-off date of 6 Feb 09
nr=not reported

Review of the first cycle submission identified elevated liver enzyme associated with tocilizumab. As shown in Table 3, dose-dependent increases in the frequency of AST and ALT elevations were seen with tocilizumab treatment. In the updated safety population just over 50% of patients experienced low level AST and ALT elevations (less than 3x ULN) on one or more occasions. Higher level elevations of AST and ALT (3-8x ULN) occurred less frequently (approximately 4% and 9% for AST and ALT, respectively). The liver enzyme elevations were reversible on dose reduction or discontinuation of tocilizumab and were not associated with clinical hepatotoxicity.

Table 3: Hepatobiliary Laboratory Worst Values

Hepatobiliary Worst Values in the Tocilizumab RA Pivotal Studies and Long-Term Extensions								
		6-months pooled safety population					Long term safety pop	Updated All-Exposure Population
	range	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	Pooled TCZ	
Enrolled		1170	284	774	1582	288	2562	4009
Pts discontinued for abnl		**2 (<1)**	**4 (1)**	**12 (2)**	**28 (2)**	**1 (<1)**	**26 (1)**	**91 (2)**
Dose mod/interrupted		**8 (1)**	**24 (8)**	**19 (2)**	**37 (2)**	**22 (8)**	**151 (6)**	**315 (8)**
AST (U/L)								
>ULN to 3 x ULN	41-120	194 (17)	74 (26)	264 (34)	646 (41)	64 (22)	1176 (46)	1961/3812 (51)
>3 x ULN to 5 x ULN	121-200	3 (0.3)	5 (2)	8 (1)	29 (2)	1 (0.3)	53 (2)	98/3812 (3)
>5 x ULN to 8 x ULN	201-320	-	1 (0.4)	1 (0.1)	1 (0.1)	1 (0.3)	7 (0.3)	22/3812 (0.6)
>8 x ULN	>320	1 (0.1)	-	-	2 (0.1)	1 (0.3)	2 (0.1)	
ALT (U/L)								
>ULN to 3 x ULN	56-165	270 (23)	95 (33)	349 (45)	763 (48)	105 (36)	1370 (53)	2112/3689 (57)
>3 x ULN to 5 x ULN	166-275	15 (1)	11 (4)	36 (5)	80 (5)	4 (1)	170 (7)	267/3689 (7)
>5 x ULN to 8 x ULN	276-440	1 (0.1)	2 (0.7)	10 (1)	21 (1)	1 (0.3)	20 (0.8)	83/3689 (2)
>8 x ULN	>440	2 (0.2)	1 (0.4)	-	2 (0.1)	1 (0.3)	7 (0.3)	
Total Bilirubin (umol/L)								
>ULN to 3 x ULN	18-51	9 (0.8)	2 (0.7)	46 (6)	141 (9)	23 (8)	308 (12)	573 (14)
>3 x ULN to 5 x ULN	52-85	1 (0.1)	-	-	1 (0.1)	-	-	2 (0.04)
>5 x ULN to 8 x ULN	86-136	-	-	-	-	-	-	
>8 x ULN	>136	-	-	1 (0.1)	-	-	-	

*Includes MTX

Source: Tables 40 and 41. STae_rategp_wd_M and STae_rategp_mod_M of Complete Response Safety Update

To distinguish cases of liver enzyme elevations that represent serious drug-induced liver injury from liver enzyme elevations that may not be associated with serious consequences the Agency uses Hy's law criteria, namely cases with elevation of AST and ALT to greater than 3x ULN and an elevated bilirubin above 2x ULN in the absence of other explanations for liver enzyme elevations. The significance of Hy's law criteria is that patients meeting these criteria in association with hepatotoxic drugs have drug-induced liver injury. Furthermore, for every 10 patients experiencing Hy's law criteria approximately one patient will develop liver failure. In the review of the first cycle submission, one patient was identified with elevation of AST and ALT to greater than 3x ULN and an elevated bilirubin above 2x ULN. The event occurred after the patient had been receiving stable doses of tocilizumab when she was begun on relatively high doses of weekly oral MTX. An additional confounder is that the patient had Gilbert's syndrome so was not a Hy's law case. With the additional safety data in the current submission 4 additional cases were observed with liver enzyme elevations with AST and ALT greater than 3x ULN and total bilirubin greater than 2x ULN. The Applicant had these cases adjudicated by hepatology consultants. Brief narratives for these 4 cases are as follows:

- 31 year old woman (Patient 50982/7194) with a history of cholelithiasis received tocilizumab 8 mg/kg + DMARD. While hospitalized for gallstones she had elevated AST 4.6x ULN, and total bilirubin 5.5x ULN. Liver enzymes normalized following cholecystectomy.

- 70 year old woman (Patient 50869/6068) with history of cholecystectomy initially had normal liver enzymes during the controlled portion of Study

WA18696 while receiving placebo + DMARD. In the extension study she began tocilizumab 8 mg/kg + DMARD and had occasional ALT and/or AST elevations not exceeding 3x ULN. She developed thrombocytopenia (70,000/uL) along with epistaxis, joint and back pain and elevated liver enzymes including AST 5.9x ULN, ALT 2.2x ULN, total bili 2.3x ULN and alk phos of 1020 (nl range 35-123 U/L). The elevated liver enzymes normalized after tocilizumab was discontinued. This case was adjudicated as a case of cholestatic liver injury but that tocilizumab cannot be excluded as a cause.

- 29 year old man (Patient 46721/2424) initially received tocilizumab 4 mg/kg + MTX then tocilizumab 8 mg/kg in Study WA 17823. At baseline the patient had mild elevations of total bilirubin (1.7x ULN) that was mostly indirect (1.4x ULN). On Study Day 505 ALT (3x ULN) and total bilirubin (2.4x ULN) were both increased – AST levels were not recorded. MTX dose was decreased to 5 mg/week. Tocilizumab was discontinued and liver enzymes subsequently normalized. This case was adjudicated as Gilbert's syndrome.

- 26 year old woman (Patient 60304/4517) received tocilizumab 8 mg/kg monotherapy in Study WA17824 where she had intermittent ALT elevations of no more than 2.5x ULN with normal bilirubin. In the extension study WA18696 she had MTX added and she had ALT elevations of up to 4x ULN with AST elevations of no more than 1.4x ULN. Subsequently TB was diagnosed and tocilizumab was discontinued. She was begun on INH, pyrazinamide, ethambutol and rifampicin with elevation of AST to 12.5x ULN, elevated ALT up to 4.5x ULN and total bilirubin elevation of 2.7x ULN, which was mostly direct. The liver enzyme elevations resolved after her TB medications were adjusted. Upon adjudication the hepatology consultant determined the most significant liver enzyme elevations were due to antituberculous medications.

In summary, 4 additional cases of liver enzymes were submitted that meet the criteria of ALT and AST elevations of 3x ULN or greater accompanied by bilirubin elevation of 2x ULN or greater. None of these cases meet Hy's law criteria. One case represented cholelithiasis; one case represented Gilbert's syndrome; one case was related to initiation of antituberculous medications that are known to be associated with liver enzyme elevations. One of the cases (Patient 50869/6068) was a case of liver enzyme elevations with a cholestatic picture. The enzyme elevations may have been related to tocilizumab.

Liver biopsy information is available on 16 patients who underwent liver biopsy for persistent AST/ALT elevations. Of these, 12 had steatosis, 1 had a liver abscess and 2 had no abnormalities. Advanced fibrosis was observed in 5 patients, all of whom had potentially confounding conditions, including obesity/diabetes, autoimmune hepatitis and alcohol use.

The Applicant performed a screen for clinical hepatotoxic events that identified 3 cases. One was a case of autoimmune hepatitis where this was a pre-existing condition. The second was a patient with persistent ALT/AST elevations of up to 3x ULN. Liver biopsy showed steatosis. Liver enzymes returned to normal following discontinuation of tocilizumab. The third case was a case of ischemic hepatitis associated with a hypotensive episode related to hypersensitivity to tocilizumab.

Tocilizumab treatment was also associated with cytopenias, presumably due to the role of IL-6 as a hematopoietic growth factor. Up to 20% of patients experience low-level neutropenia (Grade 1 or 2); approximately 4% experience Grade 3 neutropenia (500-1000/mm^3) and less than 1% experience Grade 4 neutropenia (<500/mm^3). Neutropenia is reversible on dose reduction or discontinuation of tocilizumab. A few adverse events were identified that were associated with neutropenia. There was a case of atypical mycobacterial infection that occurred after 2 months of a low lymphocyte count; one patient with a low WBC (400/mm^3) developed sepsis associated with a bile duct stone in the Japanese postmarketing experience. Finally, there was one case of empyema associated with Grade 3 neutropenia. Thrombocytopenia was also observed with tocilizumab treatment. Most cases were mild (more than 75,000/mm^3) with less than 1% Grade 2 or higher. However, 4 patients developed bleeding events associated with Grade 3 or 4 thrombocytopenia (epistaxis-2, hemoptysis-1, hemorrhagic stomatitis-1).

Treatment with tocilizumab was also associated with lipid abnormalities as noted in the original review. TCZ treatment was associated with an increase in all lipid parameters, including mean increases of 30 mg/dl in total cholesterol, 20 mg/dl in LDL, 5 mg/dl in HDL, and 30-40 mg/dl in triglycerides. There was no increase in the rate of cardiovascular adverse events in tocilizumab-treated patients compared to controls in the controlled portions of the clinical trials. Overall, the rate of MI's and strokes was not elevated compared to background rates in the RA patient population. However, the data are not adequate to rule out a modest increase in cardiovascular risk.

Immunogenicity was observed in only 4% of patients receiving tocilizumab. However, antibody formation to tocilizumab was clinically significant. Immunogenicity was associated with a higher rate of anaphylaxis (3% of antibody-positive patients compared to less than 1% of antibody-negative patients). When antibodies to tocilizumab developed that were neutralizing, they were associated with a higher likelihood of withdrawal due to lack of efficacy: of 127 patients who developed neutralizing antibody 52% withdrew due to lack of efficacy compared to 3% overall.

Additional safety concerns noted in the original review included GI perforation and demyelinating disease. As shown in Table 4, a total of 25 GI perforations were observed in the safety database, mostly lower GI events. GI perforations have also been observed in Japanese postmarketing data. The calculated rate of GI perforation with tocilizumab is lower than has been observed with corticosteroids (.39 events/100 pt-yrs) but is higher than that observed in patients receiving TNF blockers (.13 events/100 pt-yrs). With respect to the cases of demyelination, 4 additional cases were reported in the updated safety database bringing the total number of cases to 8. Of these, 3 represent true central demyelination of which one patient had similar symptoms before starting tocilizumab.

Given that the background rate of demyelinating disease in patients with RA is unknown it is uncertain whether these cases of demyelinating disease were caused by tocilizumab treatment. Demyelinating disease has also been observed in patients with RA treated with TNF blockers.

Table 4: Exposure Adjusted Incidence of Gastrointestinal Perforations in RA Patients

Exposure-Adjusted Incidence of GI Perforations in RA Patients						
	TCZ program Events	TCZ program Events/100 pt-yrs	UHC database Events/100 pt-yrs	Marketscan database Events/100 pt-yrs	Japanese Post-Marketing Data Events	Japanese Post-Marketing Data Events/100 pt-yrs
Upper GI	5	0.05	0.03	0.02	2	0.15
Lower GI	20	0.21	0.16	0.14	4	0.15
Total	25	0.27	0.18	0.16	6	0.22

Data cut-off February 6, 2009; 03-25-09 for Japanese post-marketing data
Sources: Tables 14 and 15 of 120 day safety update: section 4.1.13 from Roche 4-9-09, Table 19 of CR safety update

6.3.1. Discussion of primary reviewer's comments and conclusions

The primary clinical reviewer, Dr. Sarah Okada, concluded that the major safety concerns associated with tocilizumab were serious infections, liver enzyme elevations with the potential for serious liver toxicity, cytopenias, GI perforations, demyelinating disease and elevations in lipids. She noted that the serious infections occurred at a rate similar to background rates in the RA patient population and are also seen with other approved immunosuppressive biologics commonly used in the treatment of RA. With respect to the liver enzyme elevations she determined that tocilizumab treatment is associated with liver enzyme abnormalities but does not appear to yet have been directly associated with severe clinical hepatotoxicity. She judged that there was a potential risk for serious liver toxicity but that the risk could be lessened by appropriate monitoring. Similarly, the risks associated with cytopenias could be minimized by appropriate monitoring and dose adjustments or drug discontinuation as needed. Overall she judged the data to indicate that the benefits outweighed the potential risks for patients with moderately to severely active RA.

I concur with Dr. Okada's conclusions.

7. Advisory Committee Meeting

An advisory committee was held for tocilizumab during the previous review cycle. For a detailed description of that committee meeting please see the CDTL review and medical officer review from the previous review cycle. In brief, the committee voted in favor of approval. The committee members expressed concerns about the liver enzyme elevations and about the effect the increased lipid levels might have on cardiovascular risk. They expressed support for studying cardiovascular risk postmarketing.

8. Labeling

8.1. Physician labeling

At the time of completion of this CDTL memo, detailed consideration of the label is ongoing. One concern with respect to labeling is that the Applicant has proposed an indication that would include first-line treatment. Given the serious safety concerns with this product, including serious infections, GI perforations and unknown effects on the rate of cardiovascular thromboembolic events it would be appropriate to initially approve tocilizumab for second line use for patients who have inadequate effect with, or are intolerant of, one or more DMARDs. Then after further experience the indication could be modified to allow first line use if appropriate.

9. Conclusions and recommendations

9.1. Regulatory action

Data from five adequate and controlled Phase 3 trials support the efficacy of tocilizumab in reducing the signs and symptoms of rheumatoid arthritis.

The major safety concerns associated with tocilizumab are serious infections, liver enzyme elevations with the potential for serious liver toxicity, cytopenias, GI perforations, demyelinating disease and elevations in lipids. Given the debilitating nature of the disease, the potential benefits of tocilizumab substantially outweigh the potential risks in the treatment of patients with moderately to severely active RA. So long as the remaining issues concerning the REMS can be worked out and agreement can be reached on labeling, tocilizumab should be approved for the treatment of adult patients with moderately to severely active rheumatoid arthritis.

9.2. Safety concerns to be followed postmarketing

The major safety concerns that should be followed postmarketing are serious infections, including opportunistic infections, liver failure, GI perforation and demyelinating disease. While the increase in lipids may potentially indicate an increased risk for cardiovascular thromboembolic events the clinical trial data do not indicate a risk of cardiovascular events higher than background rates in the RA population. Therefore, it is unclear that routine pharmacovigilance will provide new information about the cardiac safety of tocilizumab.

9.3. Risk Evaluation and Mitigation Strategy (REMS)

9.3.1. General considerations on the need for, and goals of, any REMS beyond standard labeling and pharmacovigilance

In the first cycle it was determined that tocilizumab should have a REMS to include a Medication Guide, Communication Plan and Elements to Assure Safe Use (ETASU) to mitigate the risks of serious infections, GI perforation, changes in liver function, cytopenias, elevations in lipids, malignancies and demyelinating disease. The ETASU

was to consist of a restricted distribution program where healthcare professionals prescribing and administering tocilizumab would be certified as having received training on and would attest to follow approved product dosing and administration instructions, including laboratory monitoring regimens and dose modification/interruption protocols, and adverse event reporting. However, during review of this submission it was determined that the risks with tocilizumab were not markedly different form those associated with other approved biologics and small-molecule drugs prescribed by rheumatologists for the treatment of RA and that rheumatologists are able to adequately manage those risks as part of their usual practice.

Based on these considerations, the review division, DAARP, and the Office of Surveillance and Epidemiology (OSE) determined that ETASU were not warranted and should not be required. Therefore the Applicant was notified 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 Applicant has submitted a revised REMS containing a Medication Guide, Communication Plan, and Timetable for Assessment of the REMS. The revised REMS is still undergoing review by the Office of Surveillance and Epidemiology (OSE), Division of Risk Management (DRISK).

9.4. Postmarketing studies

9.4.1. Required studies

Several postmarketing studies should be required for tocilizumab:

- 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.

9.4.2. Commitments (PMCs)

No additional clinical PMC's are necessary.

9.4.3. Other agreements with Sponsor

None.