Side effects: Do reports to the FDA reflect drug label warnings?

STAT examined reports on serious side effects for leading drugs for rheumatoid arthritis from 2010 through 2016. We expected market leaders Humira and Remicade to have many more cases relative to Actemra for two reasons: Humira and Remicade have been used by vastly larger numbers of patients, and unlike with Actemra, those other drugs' labels warn patients and doctors that they might cause most of these side effects. The difference between expected and actual numbers of cases were most pronounced with interstitial lung disease, but substatial for other serious adverse events. The data raise questions about Actemra's safety, experts said.

	Side effect				
Drug	Heart attack	Stroke	Heart Failure	Interstitial Lung disease	Pancreatitis
Actemra					
Labeled?	No	No	No	No	No
Cases	410	359	224	222	132
Remicade					
Labeled?	Yes	No	Yes	Yes	No
Cases	664	651	367	135	362
Humira					
Labeled?	Yes	Yes	Yes	Yes	No
Cases	2134	1895	1434	234	549

Sources: FDA approved warning labels, FDA adverse events reports
Reporting by STAT

FDA - mandated trials after Actemra's 2010 approval

Concerned about possible cardiovascular side effects, the FDA required longer-term trials after approval. Here are some results.

Title	Date results reported	Notable serious adverse events not on Actemra warning label	Drug used	# cases	# patients	%	Mean age	Study duration	ClinicalTrials.gov ID
^A Long-term Extension Study of Tocilizumab (Myeloma Receptor Antibody [MRA]) in Patients With Rheumatoid Arthritis	11/5/13	Cardiac disorders overall	Actemra	24	538	4.5%	50.8	up to 261 weeks	NCT00721123
		Cardiac disorders overall + stroke	Actemra	27	538	5.0%			
		Fatal + nonfatal myocardial infarction + stroke	Actemra	8	538	1.5%			
^An Extension Study of Tocilizumab (Myeloma Receptor Antibody [MRA]) in Patients Completing Treatment in Tocilizumab Core Studies	9/26/14	Cardiac disorders overall	Actemra + others	94	2067	4.5%	52.2	up to 371 weeks	NCT00720798
		Cardiac disorders overall + stroke	Actemra + others	123	2067	6.0%			
		Fatal + nonfatal myocardial infarction + stroke	Actemra + others	54	2067	2.6%			
	10/19/16	Cardiovascular death	Actemra	36	1538	2.3%	61.0	166 weeks average	NCT01331837
		Cardiovascular death	Enbrel	35	1542	2.3%			
		Nonfatal myocardial infarction	Actemra	28	1538	1.8%			
		Nonfatal myocardial infarction	Enbrel	31	1542	2.0%			
		Nonfatal stroke	Actemra	24	1538	1.6%			
		Nonfatal stroke	Enbrel	15	1542	1.0%			
		All-cause mortality	Actemra	64	1538	4.2%			
		All-cause mortality	Enbrel	64	1542	4.2%			
		Heart failure	Actemra	12	1538	0.8%			
		Heart failure	Enbrel	8	1542	0.5%			
		Major adverse cardiovasular event + hospitalized for heart failure	Actemra	90	1538	5.9%			
		Major adverse cardiovasular event + hospitalized for heart failure	Enbrel	85	1542	5.5%			
		Fatal + nonfatal myocardial infarction	Actemra	29	1538	1.9%			
		Fatal + nonfatal myocardial infarction	Enbrel	32	1542	2.1%			
		Fatal + nonfatal stroke	Actemra	26	1538	1.7%			
		Fatal + nonfatal stroke	Enbrel	16	1542	1.0%			
		Fatal + nonfatal myocardial infarction + stroke	Actemra	55	1538	3.6%			
		Fatal + nonfatal myocardial infarction + stroke	Enbrel	48	1542	3.1%			
*Comparative Cardiovascular Safety of Tocilizumab Vs Etanercept in Rheumatoid Arthritis: Results of a 1.4% Randomized, Parallel-Group, Multicenter, Noninferiority, Phase 4 Clinical Trial		Major adverse cardiovasular event + nonelective coronary revascularization and hospitalization for unstable angina	Actemra	84	1538	5.5%			
		Major adverse cardiovasular event + nonelective coronary revascularization and hospitalization for unstable angina	Enbrel	84	1542	5.4%			

Sources: ClinicalTrials.gov; Arthritis Rheumatology

^No inclusion critieria.

*History of or risk factor for cardiovascular disease or extra-articular rheumatoid arthritis manifestation, but no current/recent serious cardiovascular disease.

Reporting by STAT

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

FDAAA Section 915 New Molecular Entity (NME) Postmarket Safety Summary

Date: March 28, 2013

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Product Name: Actemra (tocilizumab) Solution for Intravenous Infusion

Application Type/Number: BLA 125276

Applicant/Sponsor: Genentech, Inc.

US Approval Date: January 8, 2010

Tracked Safety Issues (TSIs):

TSI #	Safety Issue	Status	Status Date	Signal Source
TSI #1009	Anaphylaxis	CLOSED	04/19/11	Regulatory Submission
TSI #1086	Infections, GI Perforations. Liver Functions Changes, Demyelinating Orders, Neutropenia, Thrombocytopenia. and malignancies	CLOSED	11/14/12	Regulatory Submission
TSI #1120	Fetal Complications	CLOSED	06/22/12	Regulatory Submission
TSI #1121	Immune System Disorder	CLOSED	06/22/12	Regulatory Submission
TSI #1122	Myocardial Infarction	CLOSED	11/09/12	Regulatory Submission

OSE RCM #: 2010-601

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

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1 INTRODUCTION

This document summarizes the postmarket safety experience 18 months after approval of a product or after use of the product by at least 10,000 patients, whichever is later, in accordance with Title IX, section 915 of the Food and Drug Administration Amendments Act of 2007 (FDAAA). New serious adverse events, known adverse events reported in an unusual number, or other new potential safety concerns are described in this document.

This evaluation by the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE) is a systematic, collaborative process, which involves a review of potential safety concerns identified for the new molecular entity (NME), Actemra (BLA 125276, tocilizumab) since approval by the FDA on January 8, 2010. This document includes a summary of general safety information, an overview of adverse events in the FDA Adverse Event Reporting System (FAERS) database, drug usage data, a literature review, a medication error analysis, and a discussion of postmarket clinical trial findings (see respective sections).

Section 10 of this document contains a summary of the relevant safety findings.

2 GENERAL SAFETY INFORMATION

OND Point of Contact: Nikolay Nikolov, MD, Medical Officer, DPARP, ODE II, OND, CDER

2.1 Product Pharmacologic Class

ACTEMRA (tocilizumab) is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1κ (gamma 1, kappa) subclass with a typical H_2L_2 polypeptide structure. Each light chain and heavy chain consists of 214 and 448 amino acids, respectively. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds. ACTEMRA has a molecular weight of approximately 148 kDa.

2.2 Mechanism of action

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 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. 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.

2.3 Indication(s)

2.3.1 US Indication(s)

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor inhibitor indicated for treatment of:

Rheumatoid Arthritis (RA)

- 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).

Systemic Juvenile Idiopathic Arthritis (SJIA)

- Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.

2.3.2 Non-US Indication(s), if applicable

Roche's co-development partner, Chugai Pharmaceutical Co. Ltd., has received approval in Japan in April 2005 for the use of tocilizumab in the treatment of multi-centric 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).

2.4 Labeling

2.4.1 List of significant safety-related labeling

- Boxed Warning
  - Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections have occurred in patients receiving ACTEMRA.
  - If a serious infection develops, interrupt ACTEMRA until the infection is controlled.
  - Perform test for latent TB; if positive, start treatment for TB prior to starting ACTEMRA.
  - Monitor all patients for active TB during treatment, even if initial latent TB test is negative.
- Contraindications
  - ACTEMRA should not be administered to patients with known hypersensitivity to ACTEMRA.
- Warnings and Precautions
  - Serious Infections – do not administer ACTEMRA during an active infection, including localized infections. If a serious infection develops, interrupt ACTEMRA until the infection is controlled.
  - Gastrointestinal (GI) perforation – use with caution in patients who may be at increased risk.
  - Laboratory monitoring – recommended due to potential consequences of treatment-related changes in neutrophils, platelets, lipids, and liver function tests.
  - Hypersensitivity reactions, including anaphylaxis and death have occurred.
  - Live vaccines – should not be given with ACTEMRA.

2.4.2 List of safety-related labeling revisions since US Approval and the date of each revision

- Fatal anaphylaxis, Safety labeling supplement #23, approved on April 15, 2011:
  - Revisions to sections 4. Contraindications, 5. Warnings and Precautions, 6. Adverse Reactions.
- Safety/efficacy supplement #49 served as the basis for expanding the indication to adult patients with RA who have had inadequate response to one or more DMARDs, approved on October 11, 2012

2.4.3 List of any safety concerns among products in the same pharmacologic class as the NME under evaluation that are not currently labeled

ACTEMRA is the only IL-6R targeting therapeutic approved on the market. Others products, targeting IL-6 signaling, are in development. The safety data from those

development programs appear to have a safety profile, consistent with the safety profile of ACTEMRA and no new safety signals have been identified for this pharmacologic class of drugs.

2.5 Clinical trials and studies

2.5.1 List of proposed or ongoing Postmarket Requirements (PMRs) and the status of the study

- Study WA19977 under PREA (requirement date January 8, 2010): 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.
    - Protocol submission October 16, 2009
    - Enrollment complete: N=188
    - Part I and II complete and submitted as an efficacy supplement 64, Part III, open-label extension is ongoing
    - Data from Part I and Part II are under review in efficacy supplement #64 in house.
    - Final study report submission: March 31, 2014
- Study NP25737 under PREA (requirement date April 15, 2011): A pharmacokinetic and safety study of tocilizumab (TCZ) in patients less than 2 years old with active systemic juvenile idiopathic arthritis (sJIA)
    - Final Protocol Submission: June 30, 2011
    - Study Completion Date: March, 2014
    - Final Report Submission: October, 2014
    - The study is ongoing.
- Pregnancy registry to evaluate pregnancy outcomes for women exposed to Actemra (tocilizumab) during pregnancy. Utilize the established Organization of Teratology Information Specialists (OTIS) pregnancy registry to evaluate pregnancy outcomes. The timetable to conduct this study is as follows:
    - Final Protocol Submission: July 30, 2010
    - Study Completion Date: December 31, 2016
    - Final Report Submission: December 31, 2017
    - The study enrollment is ongoing.
- 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 1000-1500 patients treated for 5 years (study is ongoing). The timeline to conduct this study is as follows:
    - Final Protocol Submission: December 17, 2009
    - Study Completion Date: June 30, 2013
    - Final Report Submission: June 30, 2014
    - The study is ongoing, enrollment is complete (n=2584)
- Study WA25204, 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 (study is ongoing). The timeline to conduct this study is as follows:

- Final Protocol Submission: July 30, 2010
- Study Completion Date: February 28, 2018
- Final Report Submission: February 28, 2019
- The study enrollment is ongoing (n=100 as of December 13, 2011)

- Study NA25256, A randomized trial to study the effects of tocilizumab on therapeutic vaccines. B cell-dependent antigens (e.g., pneumococcal polysaccharide vaccine) and T cell-dependent antigens (e.g., tetanus toxoid) will be evaluated (study is complete). The timeline to conduct this study is as follows:
  - Final Protocol Submission: April 30, 2010
  - The study is complete.
  - Final Report Submission: November 30, 2012
  - The final clinical study report is under review by the Division.

2.5.2 List of new studies and/or postmarket US clinical trials other than those listed in 2.5.1

The following planned, initiated or continuing safety studies are reported by sponsor in the most recent Periodic Safety Update Report (as of October 10, 2012):

- (b) (4)
-
-
-
-
-

The sponsor is also monitoring tocilizumab safety using the following registries:

- British Society of Rheumatology Biologics Register (BSRBR)
- Swedish Registry (ARTIS)

- German Registry (RABBIT)

2.5.3 List of new safety concerns identified from ongoing IND studies

Subcutaneous (SC) formulation-signal of increased infection-related mortality, under review in BLA 125,472 in house, also discussed in section 2.8.1 below.

2.6 List of FDA Safety Communications (e.g., Drug Safety Communications, FDA Dear Healthcare Professional (DHCP) letters, Public Health Advisories (PHA), Recalls, and/or MedWatch Safety Alerts) with dates and appropriate links

No FDA Safety Communications have been issued since the approval of the original tocilizumab BLA.

2.7 List of any unique reporting requirements or enhanced pharmacovigilance plans requested by FDA

During drug development, GI perforations were identified as a potential safety signal associated with the use of tocilizumab and the sponsor was required to submit quarterly updates for GI perforations and cumulative incidence. In June 2010 the Division granted the sponsor's request to discontinue the quarterly updates and to continue providing these data as part of the periodic adverse drug experience reports.

2.8 Pending or potential regulatory activities

2.8.1 List of potential safety issues from review of periodic safety update reports and/or periodic adverse drug experience reports (PSURs/PADERs)

No new safety issues have been identified from the periodic safety update reports or periodic adverse drug experience reports as potential safety signals. The overall safety of tocilizumab remains consistent with the safety data previously reviewed under the original BLA and subsequent supplements. These observations are consistent with the review and conclusions of safety supplement #49 (entered in DARRTS 09/10/2012). The safety analyses in this supplement were derived from the accumulated clinical safety data from placebo-controlled studies, long-term extension studies and post-marketing global safety database. The overall exposure-adjusted incidence rates of mortality, SAEs, serious infections, including opportunistic infections and tuberculosis, gastrointestinal disorders, nervous system disorders, neoplasms and cardiac disorders, have remained stable or decreased numerically over time. Post-marketing safety review of tocilizumab revealed several cases of pancreatitis, pancytopenia, convulsions, and interstitial lung disease However, these were infrequent and spontaneously observed in the RA patient population making it difficult to draw conclusions on the relative risk attributable to TCZ administration.

The major safety issues previously identified and already addressed via labeling and REMS remain:

- Serious infections, including opportunistic infections and tuberculosis, consistent with TCZ mechanism of action as an immunosuppressant. The

overall incidence of these events has remained stable over time with prolonged exposure.

- Gastro-intestinal perforations. GI perforations continue to accrue in TCZ development but the exposure-adjusted incidence rates remain stable and generally below the expected rates associated with the use of systemic corticosteroids and non-steroidal anti-inflammatory drugs.
- Laboratory abnormalities, such as decreased blood cell counts, elevated liver test and lipids remain consistent with the findings in the original BLA.
- Anaphylaxis: Since the approval of BLA 125276, two cases of fatal anaphylaxis were reported in the post-marketing experience which prompted the sponsor to propose the safety labeling supplement #23 (discussed above).
- Demyelinating disorders were reported in a small number of cases and do not appear to increase over time.

The sponsor has developed a subcutaneous (SC) formulation of TCZ. Signal of increased infection-related mortality in the tocilizumab SC development program identified by the sponsor and DSMB. Sponsor has distributed a Dear Investigator letter to alert investigators of this signal and to strengthen the vigilance in the SC development studies. Sponsor's response to the related IR is under review in BLA 125,472.

2.8.2 List of pending regulatory actions in the US (new indications, labeling updates, regulatory briefings, advisory committees, etc.)

- BLA 125,472 for the SC formulation is currently under review with PDUFA goal action date of October 21, 2013.
- pJIA efficacy supplement (64) under review, PDUFA due data, April 29, 2013
- Pediatric Advisory Committee for sJIA approval, March 14, 2013, Sheraton Silver Spring

2.8.3 List of pending regulatory actions <u>in other countries</u> (if known)

OND is not aware of pending regulatory actions in other countries. Tocilizumab has not been withdrawn from any market nor had a licensing application suspended in any country as of this review.

2.8.4 List of any pending Pharmacology-Toxicology; Chemistry, Manufacturing and Control (CMC); or other related safety issues not previously mentioned

There are no PharmTox or CMC issues.

2.9 List of <u>potential or ongoing</u> safety issues for discussion

- Fatal anaphylaxis: labeling was recently updated
- Subcutaneous (SC) formulation: signal of increased infection-related mortality, currently under review
- Risk of serious cardiovascular events: a randomized, controlled trial currently ongoing

- Serious infections, including opportunistic infections and tuberculosis: adequately addressed through labeling and REMS
- Gastrointestinal perforations: adequately addressed through labeling and REMS
- Laboratory abnormalities, such as decreased blood cell counts, elevated liver test and lipids: adequately addressed through labeling and REMS
- Demyelinating disorders: theoretical risk addressed in labeling and REMS

3 OFFICE OF CLINICAL PHARMACOLOGY (OCP)

OCP Point of Contact: Liang Zhao, PhD, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 2

3.1 List of potential safety issues for discussion, if applicable

None

3.2 Summary of results for potential safety issue(s)

None

4 FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) OVERVIEW

OSE Point of Contact: Sara Camilli, PharmD, Safety Evaluator, Division of Pharmacovigilance I

4.1 List of potential safety issues for discussion

- **Pancreatitis**: The established association of tocilizumab with increased lipid parameters provides biologic plausibility for pancreatitis. There were 39 reports of pancreatitis in this summary, including some that described concurrence with hyperlipidemia. Overall, there is a large amount of confounding by underlying disease and not enough information in the remaining reports to warrant further review at this time. Recommend continued monitoring.
- **Hepatotoxicity**: Given the established association with increased transaminases, there is theoretical potential for severe hepatotoxicity. Although this reviewer notes a few reports of hepatotoxicity temporally associated with tocilizumab exposure, confounding factors and missing information limit our ability to assess for a causal association. Recommend continued monitoring.
- **Cytopenias (Anemia, Pancytopenia, Agranulocytosis):** The events are biologically plausible given that IL-6 is an essential hematopoietic growth factor. Tocilizumab is currently labeled for thrombocytopenia, neutropenia, and leukopenia. These reports demonstrate a possible temporal association between administration of tocilizumab and anemia, pancytopenia, and agranulocytosis. However, most reports were confounded by underlying disease and concomitant medications or did not provide laboratory values. Recommend continued monitoring.

These events are presented in the tables that follow and are discussed in more detail in Section 4.11.

4.2 FAERS Search Strategy

For the FAERS overview, please note that these are total counts of FAERS reports. Report counts may include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse, etc.), miscoded reports, or unrelated reports. Reported outcomes for this section are the coded outcomes submitted to FDA; causality and the role of the product in the coded outcome have not been determined for this evaluation.

The FAERS database was searched with the strategy described in Table 4.2.1.

Table 4.2.1. FAERS Search Strategy*	
Date of search	November 16, 2012
Time period of search	January 8, 2010 (US Approval) – August 31, 2012
Product Terms	Actemra, tocilizumab
BLA number	125276

* See Appendix A for a description of the FAERS database.

The FAERS search on November 16, 2012 yielded 3502 reports.

4.3 FAERS Search Results

Table 4.3.1. Descriptive characteristics of FAERS Reports for tocilizumab received by FDA from January 8, 2010 to August 31, 2012 (N=3502)*		
Sex	Male	924
	Female	2443
	Unknown	135
Country of reporter	United States	472
	Foreign	3027#
	Unknown	3
Report type	Expedited	3390
	Direct	78
	Periodic	34
Serious Outcomes^	Death	498
	Life-threatening	305
	Hospitalized	1785
	Disability	97
	Congenital anomaly	4
	Other serious	1658

* May include duplicates

\# One third of the foreign reports were reported from Japan.

^ Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. A report may have one or more outcome.

4.4 Breakdown of FAERS Reports by Age

Table 4.4.1. Breakdown of FAERS Reports by age for tocilizumab received by FDA from January 8, 2010 to August 31, 2012 (N=3502)*	
Age Group	**Number of Reports* (US)**
< 2 yrs	7 (1)
2 yrs – 5 yrs	28 (2)
6 yrs – 11 yrs	58 (2)
12 yrs – 16 yrs	39 (2)
17 yrs – 20 yrs	34 (3)
21 yrs – 30 yrs	104 (9)
31 yrs – 40 yrs	169 (20)
41 yrs – 50 yrs	376 (42)
51 yrs – 60 yrs	672 (93)

Table 4.4.1. Breakdown of FAERS Reports by age for tocilizumab received by FDA from January 8, 2010 to August 31, 2012 (N=3502)*	
Age Group	**Number of Reports* (US)**
61 yrs – 70 yrs	759 (89)
71 yrs +	540 (60)
Unknown	716 (149)

* May include duplicates

4.5 Most Frequently Reported MedDRA Preferred Terms (PTs) for FAERS Reports with Serious and Non-Serious Outcomes

Table 4.5.1. Most Frequently Reported MedDRA PTs with N ≥ 40 for tocilizumab, received by FDA from January 8, 2010 to August 31, 2012 sorted by decreasing number of FAERS reports per PT

Total Number of Reports* = 3502

MedDRA PT	Number of FAERS Reports	Labeled^ (Yes/No), Location or Other Category
Pneumonia	152	Yes, W/P, AR
Arthralgia	140	Yes, AR
Death	118	U
Drug Ineffective	101	U
Pyrexia	98	Yes, MG
Diarrhoea	95	Yes, AR
Headache	92	Yes, AR, MG
Sepsis	91	Yes, W/P, AR
Rheumatoid Arthritis	89	No, IR
Dyspnoea	87	Yes, AR
Malaise	84	No, IR, DR
Interstitial Lung Disease	81	No
Nausea	77	No
Pain	73	No, IR, DR
Vomiting	73	Yes, MG
Hypertension	70	Yes, AR, MG
Anaemia	69	No
Myocardial Infarction	69	No
Rash	69	Yes, AR, MG
Oedema Peripheral	68	Yes, AR
Cellulitis	67	Yes, W/P, AR
Dizziness	66	Yes, AR
Urinary Tract Infection	66	Yes, W/P, AR
Fall	65	No

Table 4.5.1. Most Frequently Reported MedDRA PTs with N ≥ 40 for tocilizumab, received by FDA from January 8, 2010 to August 31, 2012 sorted by decreasing number of FAERS reports per PT

Total Number of Reports* = 3502

MedDRA PT	Number of FAERS Reports	Labeled^ (Yes/No), Location or Other Category
Abdominal Pain	62	Yes, AR
Chest Pain	61	No, DR
Fatigue	57	No, IR, DR
Pain In Extremity	57	No, IR
Pruritus	56	Yes, AR
Infection	55	Yes, BW, W/P, AR, MG
Disseminated Intravascular Coagulation	53	No
Septic Shock	52	Yes, W/P, AR
Hepatic Function Abnormal	49	Yes, W/P, AR
Histiocytosis Haematophagic	49	Yes, AR
Pulmonary Embolism	49	No
White Blood Cell Count Decreased	49	Yes, AR
Nasopharyngitis	48	Yes, AR
Skin Ulcer	47	No, labeled for infections
Arthritis	46	No, IR
Cerebrovascular Accident	41	No
Deep Vein Thrombosis	41	No

* A report may contain more than one preferred term

^ Definitions: BW = Box Warning, C = Contraindications, W/P = Warnings/Precautions, AR = Adverse - Reactions, DI = Drug Interactions, OD = Overdosage, SP= Use in Specific Populations, PCI = Patient Counseling Information, MG = Medication Guide or Other Categories: DR = Disease-related, IR = Indication-related, PR= Procedure-related, U = Uninformative

4.6 MedDRA PTs from FAERS Reports with Serious Outcomes

Table 4.6.1. MedDRA PTs with N ≥ 40 from FAERS Reports with Serious Outcomes‡ for tocilizumab, received by FDA from January 8, 2010 to August 31, 2012 sorted by decreasing number of FAERS reports per PT

Total Number of Reports* = 3423

MedDRA PT	Number of FAERS Reports	Labeled^ (Yes/No), Location or Other Category
Pneumonia	150	Yes, W/P, AR
Arthralgia	138	Yes, AR
Death	118	U
Drug Ineffective	100	U

Table 4.6.1. MedDRA PTs with N ≥ 40 from FAERS Reports with Serious Outcomes[‡] for tocilizumab, received by FDA from January 8, 2010 to August 31, 2012 sorted by decreasing number of FAERS reports per PT Total Number of Reports* = 3423		
MedDRA PT	**Number of FAERS Reports**	**Labeled[^] (Yes/No), Location or Other Category**
Pyrexia	97	Yes, MG
Diarrhoea	91	Yes, AR
Sepsis	91	Yes, W/P, AR
Headache	90	Yes, AR, MG
Rheumatoid Arthritis	88	No, IR
Dyspnoea	86	Yes, AR
Interstitial Lung Disease	81	No
Malaise	81	No, IR, DR
Nausea	72	No
Vomiting	72	Yes, MG
Pain	71	No, IR, DR
Hypertension	69	Yes, AR, MG
Myocardial Infarction	69	No
Anaemia	68	No
Oedema Peripheral	68	Yes, AR
Cellulitis	67	Yes, W/P, AR
Rash	66	Yes, AR, MG
Urinary Tract Infection	66	Yes, W/P, AR
Fall	64	No
Chest Pain	61	No, DR
Dizziness	59	Yes, AR
Abdominal Pain	58	Yes, AR
Pain In Extremity	57	No, IR
Infection	55	Yes, BW, W/P, AR, MG
Fatigue	54	No, IR, DR
Pruritus	54	Yes, AR
Disseminated Intravascular Coagulation	53	No
Septic Shock	52	Yes, W/P, AR
Histiocytosis Haematophagic	49	Yes, AR
Pulmonary Embolism	49	No
Nasopharyngitis	48	Yes, AR
White Blood Cell Count Decreased	48	Yes, AR
Skin Ulcer	47	No, labeled for infections
Hepatic Function Abnormal	46	Yes, W/P, AR
Arthritis	45	No, IR

Table 4.6.1. MedDRA PTs with N ≥ 40 from FAERS Reports with Serious Outcomes‡ for tocilizumab, received by FDA from January 8, 2010 to August 31, 2012 sorted by decreasing number of FAERS reports per PT Total Number of Reports* = 3423		
MedDRA PT	**Number of FAERS Reports**	**Labeled^ (Yes/No), Location or Other Category**
Deep Vein Thrombosis	41	No
Cerebrovascular Accident	40	No

‡ Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. A report may have one or more outcomes.

* A report may contain more than one preferred term

^ Definitions: BW = Box Warning, C = Contraindications, W/P = Warnings/Precautions, AR = Adverse Reactions, DI = Drug Interactions, OD = Overdosage, SP = Use in Specific Populations, PCI = Patient Counseling Information, MG = Medication Guide or Other Categories: DR = Disease-related, IR = Indication-related, PR = Procedure-related, U = Uninformative

4.7 MedDRA PTs from FAERS Reports with Fatal Outcomes

Table 4.7.1. MedDRA PTs with N>10 from FAERS Reports with Fatal Outcomes for tocilizumab, received by FDA from January 8, 2010 to August 31, 2012 sorted by decreasing number of FAERS reports per PT Total Number of Reports* = 498		
MedDRA PT	**Number of FAERS Reports**	**Labeled^ (Yes/No) Location**
Death	118	U
Pneumonia	47	Yes, W/P, AR
Sepsis	45	Yes, W/P, AR
Interstitial Lung Disease	27	No
Cardiac Arrest	26	No, DR
Multi-Organ Failure	26	No, DR
Disseminated Intravascular Coagulation	25	No
Respiratory Failure	21	No
Septic Shock	21	Yes, W/P, AR
Cardiac Failure	19	No
Myocardial Infarction	16	No
Histiocytosis Haematophagic	15	Yes, AR
Infection	15	Yes, BW, W/P, AR, MG
Pyrexia	14	Yes, MG
Renal Failure Acute	14	No
Urinary Tract Infection	14	Yes, W/P, AR
Pleural Effusion	13	No
Acute Respiratory Distress	12	No

Table 4.7.1. MedDRA PTs with N>10 from FAERS Reports with Fatal Outcomes for tocilizumab, received by FDA from January 8, 2010 to August 31, 2012 sorted by decreasing number of FAERS reports per PT Total Number of Reports* = 498		
MedDRA PT	**Number of FAERS Reports**	**Labeled^ (Yes/No) Location**
Syndrome		
Arthralgia	12	Yes, AR
Renal Failure	12	No
Sudden Death	12	No
Cerebral Infarction	11	No
Pneumocystis Jiroveci Pneumonia	11	Yes, BW, W/P

* A report may contain more than one preferred term

^ Definitions: BW = Box Warning, C = Contraindications, W/P = Warnings/Precautions, AR = Adverse Reactions, DI = Drug Interactions, OD = Overdosage, SP = Use in Specific Populations, PCI = Patient Counseling Information, MG = Medication Guide, U = Uninformative

4.8 Designated Medical Events

Designated Medical Events (DMEs) are events that are inherently serious, severe, and often product-related. OSE created the DME list for working purposes; it has no regulatory significance. See Appendix B for a list of OSE's Designated Medical Events.

Table 4.8.1. MedDRA DME-related PTs from FAERS Reports for tocilizumab, received by FDA from January 8, 2010 to August 31, 2012, sorted by decreasing number of FAERS reports per PT Total Number of Reports* = 437		
MedDRA DME-related PT	**Number of FAERS Reports**	**Labeled^ (Yes/No) Location**
Renal failure *Renal failure = 28* *Renal failure acute = 25* *Renal impairment = 21*	74	No
Acute respiratory failure *Respiratory failure = 29* *Acute respiratory distress syndrome = 21* *Acute respiratory failure = 10*	57	No
Disseminated intravascular coagulation	53	No
Septic shock	52	Yes, W/P, AR
Acute pancreatitis *Pancreatitis acute = 21* *Pancreatitis = 16* *Pancreatitis necrotising = 3*	39	No
Agranulocytosis *Neutropenia = 28*	38	Yes, W/P, AR

Table 4.8.1. MedDRA DME-related PTs from FAERS Reports for tocilizumab, received by FDA from January 8, 2010 to August 31, 2012, sorted by decreasing number of FAERS reports per PT Total Number of Reports* = 437		
MedDRA DME-related PT	**Number of FAERS Reports**	**Labeled^ (Yes/No) Location**
Agranulocytosis = 9 *Febrile neutropenia = 1*		(neutropenia only)
Pancytopenia	35	No
Seizure *Convulsion = 22* *Epilepsy = 8* *Grand mal convulsion = 4*	34	No
Anaphylaxis *Anaphylactic reaction = 15* *Anaphylactic shock = 10* *Anaphylactoid reaction = 3*	28	Yes, W/P, AR
Colitis ischaemic	15	No
Sudden death *Sudden death = 12* *Sudden cardiac death = 2*	14	Yes, BW, W/P for serious infections, hypersensitivity reactions
Pulmonary fibrosis	11	No
Liver failure *Acute hepatic failure = 5* *Hepatic failure = 4* *Hepatic encephalopathy = 2*	10	No
Aplastic Anaemia *Bone marrow failure = 7* *Aplastic anaemia = 1* *Aplasia pure red cell = 1*	9	No
Deaf *Sudden hearing loss = 3* *Deafness = 2* *Deafness unilateral = 2* *Deafness bilateral = 1*	8	No
Liver necrosis *Hepatitis acute = 5* *Hepatitis fulminant = 2*	7	No
Blind *Blindness = 3* *Blindness transient = 1*	4	No
Erythema multiforme	5	No
Haemolysis	4	No
Pulmonary hypertension	4	No
Ventricular fibrillation	4	No
Completed suicide	3	No
Dermatitis exfoliative	3	No

Table 4.8.1. MedDRA DME-related PTs from FAERS Reports for tocilizumab, received by FDA from January 8, 2010 to August 31, 2012, sorted by decreasing number of FAERS reports per PT Total Number of Reports* = 437		
MedDRA DME-related PT	**Number of FAERS Reports**	**Labeled^ (Yes/No) Location**
Haemolytic anaemia	2	No
Thrombotic thrombocytopenic purpura	2	No
Transmission of an infectious agent via product	1	No
Rhabdomyolysis	1	No

* A report may contain more than one preferred term

^ Definitions: BW = Box Warning, C = Contraindications, W/P = Warnings/Precautions, AR = Adverse Reactions, DI = Drug Interactions, OD = Overdosage, SP= Use in Specific Populations, PCI = Patient Counseling Information, MG = Medication Guide

4.9 Data Mining Search Strategy

The Empirica Signal database was searched with the strategy described in Table 8.

Table 4.9.1. Data Mining Search Strategy*	
Data Refresh Date	8/27/2012
Product Terms	tocilizumab
Empirica Signal Run Name	Generic By Year (S)
MedDRA Search Strategy	All adverse events, retrieved at the MedDRA PT level

* See Appendix A for description of Data Mining of FAERS using Empirica Signal.

4.10 Data Mining Results

Data mining scores **do not**, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation.

Table 4.10.1. Data Mining Results with EB05 ≥ 2 for tocilizumab by MedDRA Preferred Terms (sorted by Descending EB05 Scores)

MedDRA PT	SOC	N	EB05	EBGM	EB95
Rheumatoid vasculitis	Vasc	13	58.7	95.4	148.4
Upper respiratory tract inflammation	Resp	32	52.9	71.5	95.0
Histiocytosis haematophagic	Neopl	48	26.9	34.3	43.3
Juvenile arthritis	Musc	16	20.3	31.4	46.8
Infective spondylitis	Infec	5	20.3	52.5	112.8
Arthritis bacterial	Infec	19	13.6	20.5	29.8
Rheumatoid nodule	Musc	11	9.8	21.0	35.6
Disseminated intravascular coagulation	Blood	47	6.7	8.8	11.7

Table 4.10.1. Data Mining Results with EB05 ≥ 2 for tocilizumab by MedDRA Preferred Terms (sorted by Descending EB05 Scores)

MedDRA PT	SOC	N	EB05	EBGM	EB95
Diverticular perforation	Gastr	12	6.6	16.0	28.3
Gastrointestinal perforation	Gastr	15	6.6	13.7	23.2
Interstitial lung disease	Resp	83	6.3	7.7	9.2
Vasculitis	Vasc	30	6.1	8.9	13.0
Enterocolitis	Gastr	15	5.6	11.3	20.3
Skin ulcer	Skin	46	5.6	7.2	9.3
Pleurisy	Resp	20	4.8	7.5	12.2
Erysipelas	Infec	15	4.8	8.7	16.6
Pneumocystis jiroveci pneumonia	Infec	23	4.7	6.9	10.3
Subarachnoid haemorrhage	Nerv	20	4.5	6.8	10.6
Arthritis infective	Infec	12	4.2	8.4	18.1
Panniculitis	Skin	8	4.2	13.7	32.7
Septic shock	Infec	52	4.2	5.3	6.6
Diverticulum intestinal haemorrhagic	Gastr	7	4.1	15.8	39.3
Hepatic function abnormal	Hepat	45	3.9	5.1	6.4
Cellulitis	Infec	62	3.7	4.5	5.6
Subcutaneous abscess	Infec	13	3.7	6.1	10.9
Infectious peritonitis	Infec	26	3.6	5.0	6.9
C-reactive protein increased	Inv	33	3.4	4.5	6.0
Rheumatoid arthritis	Musc	86	3.4	4.0	4.8
Colitis ischaemic	Gastr	15	3.3	5.2	8.0
Extremity necrosis	Vasc	8	3.3	8.1	23.0
Immunodeficiency	Immun	11	3.2	5.5	9.9
Diverticulitis	Infec	29	3.2	4.4	5.8
Gastroenteritis	Infec	21	3.2	4.6	6.5
Hypercholesterolaemia	Metab	19	3.1	4.6	6.7
Necrotising fasciitis	Infec	9	3.1	6.0	14.3
Synovitis	Musc	10	3.0	5.3	9.8
Retinal vasculitis	Eye	4	3.0	28.8	97.5
Abscess limb	Infec	9	2.9	5.5	11.5
Cerebral infarction	Nerv	27	2.9	4.1	5.5
Organising pneumonia	Resp	10	2.9	5.0	8.6
Large intestine perforation	Gastr	13	2.9	4.6	7.1
Sepsis	Infec	86	2.8	3.3	3.9
Pyelonephritis	Infec	13	2.8	4.4	6.8
Enteritis infectious	Infec	7	2.8	6.4	20.0
Cutaneous vasculitis	Skin	6	2.7	8.2	30.3
Infectious pleural effusion	Infec	6	2.7	8.1	29.8
Ulcerative keratitis	Eye	8	2.7	5.1	10.7
Large intestine carcinoma	Neopl	6	2.6	7.5	27.9
Peritonitis	Infec	8	2.6	4.9	9.6
Cerebral haemorrhage	Nerv	27	2.5	3.5	4.8
Psoas abscess	Infec	5	2.5	10.5	43.4
Demyelination	Nerv	9	2.5	4.4	7.5

Table 4.10.1. Data Mining Results with EB05 ≥ 2 for tocilizumab by MedDRA Preferred Terms (sorted by Descending EB05 Scores)

MedDRA PT	SOC	N	EB05	EBGM	EB95
Peripheral arterial occlusive disease	Vasc	10	2.5	4.3	7.0
Castleman's disease	Neopl	4	2.5	19.9	81.0
Pneumonia pneumococcal	Infec	6	2.4	6.0	21.7
Acute respiratory distress syndrome	Resp	18	2.4	3.6	5.2
Hyperlipidaemia	Metab	25	2.4	3.3	4.6
Gastric cancer	Neopl	10	2.3	4.0	6.5
Phlebitis	Vasc	10	2.2	3.8	6.2
Leukopenia	Blood	33	2.2	3.0	3.9
Leukocytoclastic vasculitis	Skin	9	2.2	3.9	6.5
White blood cell count decreased	Inv	50	2.2	2.7	3.4
Infected skin ulcer	Infec	6	2.2	4.6	11.5
Abscess	Infec	16	2.2	3.3	4.9
Lymphocyte count decreased	Inv	12	2.2	3.5	5.5
Large intestinal ulcer	Gastr	7	2.1	4.1	7.4
Pyoderma gangrenosum	Skin	6	2.1	4.5	10.3
Abdominal abscess	Infec	8	2.1	3.8	6.6
Pancytopenia	Blood	36	2.1	2.7	3.5
Arthritis	Musc	46	2.0	2.6	3.3
Skin infection	Infec	9	2.0	3.6	5.9
Lymphadenitis	Blood	6	2.0	4.1	8.2
Pneumonia bacterial	Infec	8	2.0	3.7	6.3
Bronchopneumonia	Infec	11	2.0	3.3	5.3

4.11 Reviewer Comments on Severity and Frequency of Adverse Events

The events reported in Sections 4.5 – 4.10 of this document were generally consistent with the product labeling (i.e., serious infections, hypersensitivity reactions, gastrointestinal perforations) or underlying rheumatologic disease. The unlabeled events disseminated intravascular coagulation, renal failure, and respiratory failure were reported in the setting of sepsis.

The remainder of this section focuses on select serious, unlabeled adverse events.

Pancreatitis: There were 39 reports of pancreatitis, which is an unlabeled event. Six reports had a fatal outcome; pancreatitis was listed as the cause of death in five. Considering all 39 reports, approximately 75% of patients were treated for RA. Some reports described concurrence of hyperlipidemia, a labeled adverse event for tocilizumab and a risk factor for pancreatitis. Many reports, including 3 of the deaths, were confounded by underlying disease (e.g., cholecystitis, chronic pancreatitis, alcohol use, unspecified pancreatic or gall bladder disease, vasculitis, hyperlipidemia, pancreatic vein thrombosis, etc.). Most of the remaining non-fatal reports and the remaining 3 fatal reports did not contain enough information, such past medical history or laboratory values, for a full assessment. This reviewer notes one unconfounded report

of a positive rechallenge (ISR 8315591). However, tocilizumab therapy was continued after the second pancreatitis episode, which questions the role of tocilizumab.

The established association of tocilizumab with hyperlipidemia provides biologic plausibility for pancreatitis. Overall, there is a large amount of confounding by underlying disease and not enough information in the remaining reports to warrant further review at this time. Recommend continued monitoring.

Hepatotoxicity: There were 16 reports of severe hepatic events. Although tocilizumab is labeled for transaminase elevations, clinically significant hepatic injury did not occur in the clinical trials and is not included in the current product labeling. Events reported in this summary include hepatic failure, acute hepatic failure, hepatic encephalopathy, hepatitis fulminant, and hepatitis acute. Of note, there was one report of acute hepatic failure that appeared to be autoimmune-related (ISR 8720731) and one report of a liver transplant in a patient with JIA (ISR 8406749). Ten patients were treated for RA, 4 patients for JIA, 1 patient for Castleman's disease, and the indication for use was unknown in the remaining report. There were 19 additional reports of jaundice and hyperbilirubinemia. Most reports were confounded by underlying disease (e.g., malignancy, multi-organ failure, macrophage activation syndrome, hepatic disease, etc.) or did not provide enough information for a full assessment.

Although, there were reports of hepatotoxicity temporally associated with tocilizumab exposure, multiple confounding factors and missing information in the reports do not support causal association. Given the established association with increased transaminases and theoretical potential for future reports of severe hepatotoxicity, recommend continued monitoring.

Cytopenias: Considering all cytopenias, tocilizumab is specifically labeled for neutropenia, thrombocytopenia, and leukopenia. Cytopenias are biologically plausible given that IL-6 is an essential hematopoietic growth factor. There were multiple reports of pancytopenia, agranulocytosis, and anemia in this summary. However, confounding factors and lack of laboratory information in the reports reviewed do not support further review of these reports at this time. Recommend continued postmarket monitoring.

> **Pancytopenia/ Bone Marrow Failure**: There were 34 reports of pancytopenia and 7 reports of bone marrow failure. Many reports were confounded by concomitant methotrexate (labeled for pancytopenia), were confounded by underlying disease (e.g., MAS, lymphoma), or the reports did not include enough information for assessment. Laboratory values for hemoglobin, white blood cell count, and platelets were rarely provided. Some events occurred after tocilizumab discontinuation.
>
> **Agranulocytosis:** There were 9 reports of agranulocytosis. One report described severe neutrophil granulocytopenia 4 days after starting tocilizumab for arteritis temporalis. Diagnosis was confirmed via bone marrow biopsy. Treatment included granulocyte colony stimulating factor (G-CSF). Relevant concomitant medications included ramipril, which is labeled for agranulocytosis. The remaining reports were confounded by concomitant medications (most commonly methotrexate), confounded by underlying

disease (e.g., disseminated intravascular coagulation), lacked key details for a full assessment, or were miscoded for the adverse event.

Anemia: There were 90 reports of anemia, including 2 reports of hemolytic anemia, and 1 report each of aplastic anemia and pure red cell aplasia. The reports were generally confounded by underlying disease (e.g., chronic renal failure, bleeding, malignancy, pre-existing anemia) or concomitant medications, such as methotrexate. Anemia is a labeled adverse event for methotrexate.

Myocardial Infarction: There were 91 reports of myocardial infarction (MI) or acute MI, including 21 deaths. Many also reported the event chest pain. Myocardial infarction is an unlabeled event. Some reports show a close temporal association, such as MI occurring during the infusion or shortly thereafter. However, the reports were generally confounded by underlying risk factors (e.g., advanced age, history of MI, hypertension, smoking, obesity, family history, diabetes, etc.) or there was not enough information to assess for risk factors. In addition, tocilizumab is labeled for increased lipid parameters, which may contribute to the risk of cardiac events.

All reports were confounded by underlying RA, a possible independent risk factor for MI and cardiovascular death.[1,2] An increase in lipid parameters, which is a labeled event, may also contribute to the risk of cardiac events. Rates of cardiovascular events and cerebrovascular events in the pre-approval clinical trials were similar to background rates. The sponsor has a Post Marketing Requirement (PMR) for a randomized control trial to rule out a moderate increase in risk of serious cardiovascular events (i.e., stroke, non fatal MI, cardiovascular death); final report submission is due to FDA in 2019.[3] Compared to spontaneous reports, the randomized clinical trial data will better inform about a possible increased risk of cardiac events with tocilizumab use. Due to the confounding of the reports, including confounding by RA indication, recommend continued monitoring and analysis of the PMR study, when available.

Venous Thromboembolic Events: There were 82 reports of pulmonary embolism or deep vein thrombosis, including 9 reports with an outcome of death. Tocilizumab is not labeled for venous thromboembolic events (VTEs). At least 64 patients were treated for RA, which has been suggested by some as a potential risk factor for VTE.[4,5] The reports were generally confounded by other underlying risk factors (e.g., immobility, smoking, etc.) or did not provide enough information to perform an assessment. The sponsor assessed for VTE in tocilizumab-treated patients in the clinical trial and postmarket setting, but did not identify a safety signal; DPARP

[1] Avina-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum 2008;59(12):1690-7.
[2] Mellana WM, Aronow WS, Palaniswamy C, Khera S. Rheumatoid arthritis: cardiovascular manifestations, pathogenesis, and therapy. Curr Pharm Des. 2012;18(11):1450-6.
[3] Actemra BLA 125276 FDA Approval Letter. January 8, 2010. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/125276s000ltr.pdf. Accessed on January 30, 2013.
[4] Holmqvist ME, Neovius M, Eriksson J, et al. Risk of venous thromboembolism in patients with rheumatoid arthritis and association with disease duration and hospitalization. JAMA 2012;308(13): 1350-6.
[5] Kang JH, Keller JJ, Lin YK, Lin HC. A population-based case-control study on the association between rheumatoid arthritis and deep vein thrombosis. J Vasc Surg 2012;56(6):1642-8.

later concurred with the sponsor's assessment.[6] Due to confounding and limited information, recommend continued monitoring.

Convulsion, Interstitial Lung Disease: Due to a potential signal from the FAERS reports, at a pre-sBLA meeting on November 14, 2011, FDA asked the sponsor to include a safety analysis of convulsion and interstitial lung disease with their sBLA submission for an expanded indication. The sponsor's comprehensive analysis of the clinical trial and postmarketing data concluded that rates of these events in the postmarket setting and clinical trials were consistent with that expected in patients with RA.[7] Although reports of these events in the FAERS database continue, the reports remain confounded, and do not warrant further investigation at this time.

[6] Nikolov NP. Review of response to IR regarding a safety report of fatal portal and hepatic vein thrombosis. IND 11972 (1707), IND (b) (4) ((b) (4)), IND (b) (4) ((b) (4)). (b) (4)

[7] Actemra BLA (b) (4)/49.0 (Supplement). Section 2.7.4 Summary of Clinical Safety. Roche. Submitted 12 Dec 2011.

5 DRUG USAGE DATA

OSE Point of Contact: Travis Ready, PharmD, Drug Use Analyst, Division of Epidemiology II

5.1 List of potential safety issues for discussion

- Drug utilization data indicate there may be some use in the pediatric population aged 0-1. Actemra® is indicated for use in patients aged 2 years and older.

5.2 Data Sources Used

The IMS Health, IMS National Sales Perspective™ data was used to determine the settings to which Actemra® vials were sold. From Jan 2010 through Aug 2012, sales data for Actemra® by number of vials sold from the manufacturer to various channels of distribution indicated that approximately (b) (4)% of Actemra® was distributed to non-retail settings (non-federal hospitals, clinics, long-te care, home health care, federal facilities, prisons, etc.) (b) (4)% were sold to mail-order/specialty pharmacies, and (b) (4)% were sold to outpatient retail pharmacies. Among the non-retail settings, approximately (b) (4)% of Actemra vials were sold to clinics.[8]

Based on these sales distribution, Source Healthcare Analytics' ProMetis Lx® database was used to provide the number of unique patients with a procedure and/or pharmacy prescription claim for Actemra®, stratified by patient age (0-1, 2-5, 6-11, 12-16, 17-20, 21-30, 31-40, 41-50, 51-60, 61-70, and 71 years and older) from Jan 2010 through Aug 2012, inclusive. These data are not projected nationally and only represent this sample.

Patient selection was based on the presence of pharmacy claims using National Drug Codes (NDC) for Actemra® (NDC codes: 50242-0136-01, 50242-0135-01, and 50242-0137-01) or the presence of medical claims data using the Health Care Common Procedure Coding System for Actemra® administration (J-code 3262). Approximately (b) (4)% of the total number of Actemra® patients in the sample were captured using the procedure code and (b) (4)% of patients were captured using prescriptions claims data. For this review, both prescription and procedure claims data were analyzed to capture the administration of Actemra® by a trained healthcare provider during a clinic or office visit. The prescriber's specialty was captured for prescription claims as well as for medical claims using the provider ID number. Diagnoses were captured using claims data if the claim was made anytime within 180 days prior to or 180 days subsequent to any Actemra® claim.

[8] IMS Health, IMS National Sales Perspectives™. Data extracted Dec 2012. File: 2010-601 NSP Actemra sales by channel by month Dec2012.xlsx

5.3 Results

Figure 5.3.1 shows the sales data for Actemra® by the number of vials sold from the manufacturer to all channels of distribution by month from January 2010 through August 2012. During the time period examined, approximately (b) (4) vials of Actemra® were sold to all channels of distribution. Overall, there was an increase in the total number of Actemra® vials distributed from approximately (b) (4) sold in January 2010 to approximately (b) (4) vials sold in August 2012. However, there were fluctuations in the number of vials sold every few months or so.

Figure 5.3.1

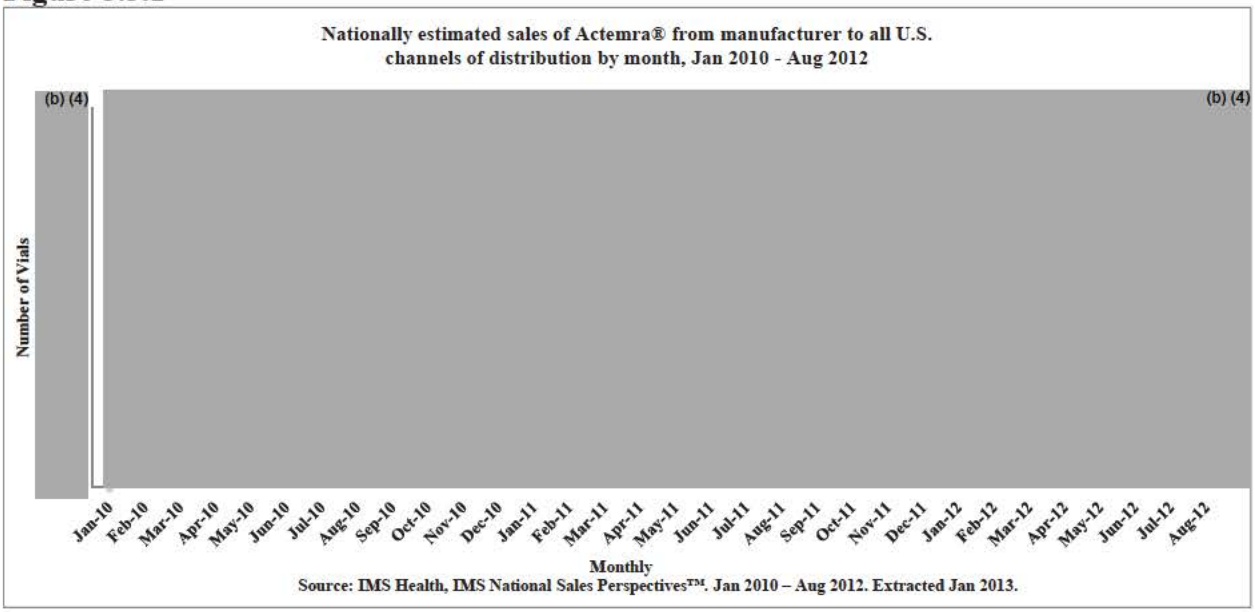

Table 5.3.1 provides the total number of unique patients stratified by age (0-1, 2-5, 6-11, 12-16, 17-20, 21-30, 31-40, 41-50, 51-60, 61-70, and 71 years and older) with a procedure and/or pharmacy prescription claim for Actemra® from Jan 2010 to Aug 2012, aggregated. During the study period, (b) (4) patients had a claim for Actemra®. The majority of the patients were 17 years of age and older. Patients aged 51 to 60 years accounted for the largest proportion of patients, accounting for approximately (b) (4)% of adult patients ((b) (4) patients). Patients aged 61-70 years and 41-50 years followed, accounting for approximately (b) (4)% ((b) (4) patients) and (b) (4)% ((b) (4) patients) of adult patients, respectively. The pediatric population aged 0 to 16 years accounted for approximately (b) (4)% ((b) (4) patients) of the total number of patients.

Table 5.3.1

Total number of patients with a procedure and/or pharmacy claim for Actemra stratified by patient age, Jan 2010 - Aug 2012		
	Jan 2010 - Aug 2012	
Patient Age	Patient Count (N)	*Share (%)*
Actemra®	(b) (4)	*100.0%*
0-16 years	(b) (4)	(b) (4)
0-1 years		
2-5 years		
6-11 years		
12-16 years		
17 years and older		
17-20 years		
21-30 years		
31-40 years		
41-50 years		
51-60 years		
61-70 years		
71+ years		
‡Claims are from U.S. commercial, Medicare Part D, Cash and Medicaid Part D, Cash and Medicaid Plans: Data includes patients with prescription and/or procedure claims.		
*Age is at first claim during calendar year		
Source: Source Healthcare Analytics CPA®. Jan 2010 - Aug 2012. Extracted Jan 2013. File 2010-601, Actemra® NME, by age and gender, Jan 2013.xls		

(*Table 5.3.2*) We also examined the total number of patients stratified by patient age and sex with a procedure and/or pharmacy prescription claim for Actemra® for the review period. Of the (b) (4) patients with a procedure and/or pharmacy prescription claim for Actemra®, the majority of patients were female ((b) (4)% or (b) (4) patients) compared to males ((b) (4)% or (b) (4) patients).

Table 5.3.2

Total number of patients with a procedure and/or pharmacy claim for Actemra stratified by patient age and sex, Jan 2010-Aug 2012

	Jan 2010 through Aug 2012								
	Total		Males			Females			
	Patients (N)	*Share (%)*	Patients (N)	*Share* %	*Horiz Share* %	Patients (N)	*Share* %	*Horiz Share* %
Actemra® Total Market	(b) (4)	*100.0%*	(b) (4)	*100.0%*	(b) (4) %	(b) (4)	*100.0%*	(b) (4) %
0-1 year	(b) (4)	(b) (4) %	(b) (4)	(b) (4) %	(b) (4) %	(b) (4)	(b) (4) %	(b) (4) %
2-5 year		%		%	%			%
6-11 year		%		%	%			%
12-16 year		%		%	%			%
17-20 year		%		(b) (4)	%			(b) (4) %
21-30 year		%			%		(b) (4)	%
31-40 year		%			(b) (4) %			%
41-50 year		(b) (4) %		%	%			%
51-60 year		%		%	%			%
61-70 year		%		%	%			%
71 years and older		%		%	%			%

Source:Source Health Care ProMetis Lx ®, Extracted Jan 2013. File: SHA 2010-601 Actemra total age 1_30_12.x

(*Table 5.3.3*) During the study period from Jan 2010 through Aug 2012, the majority of patients were prescribed Actemra® by Rheumatologists, accounting for approximately (b) (4)% of the total number of patients. Internal medicine specialists accounted for approximately (b) (4)% of the total number of procedures and/or pharmacy prescription claims for Actemra®.

Table 5.3.3

Total number of patients with a procedure and/or pharmacy prescription claim for Actemra stratified by prescribing specialty, Jan 2010 – Aug 2012		
	Jan 2010 - Aug 2012	
	Patient Count (N)	***Share (%)***
Actemra®	(b) (4)	***100.0%***
Rheumatology	(b) (4)	(b) (4) %
Internal Medicine		
Other		
Primary Care		
Pediatrics		
Allergy		
Unspecified		%
‡ Claims are from U.S. commercial, Medicare Part D, Cash and Medicaid Part D, Cash and Medicaid Plans: Data includes patients with prescription and/or procedure claims.		
***Age is at first claim during calendar year**		
Source: Source Healthcare Analytics CPA®. Jan 2010 - Aug 2012. Extracted Jan 2013. File 2010-601, Actemra® NME, by age and gender, Jan 2013.xls		

(*Table 5.3.4*) During the study period from Jan 2010 through Aug 2012, approximately (b) (4) % (b) (4) patients) of patients with a claim for Actemra® had a concurrent diagnosis relating to rheumatoid or osteoarthritis. Of these, approximately (b) (4) % ((b) (4)) patients had a concurrent diagnosis of "Rheumatoid Arthritis" (ICD-9 code 714.0). Approximately (b) (4) % (b) (4) patients) of patients with diagnosis data had a concurrent diagnosis of "Juvenile Rheu atoid Arthritis NOS" (ICD-9 code 714.30).

Table 5.3.4

Total number of patients with a prescription or medical claim for Actemra® and a concurrent diagnosis relating to rheumatoid arthritis and osteoarthrosis from a sample of outpatient retail and mail-order/specialty pharmacies, clinics, hospitals, and physician offices, cumulative January 2010 through Aug 2012.

	Cumulative Jan 2010 - Aug 2012	
	Patients*	%
Total Actemra Patients	(b) (4)	*100.00%*
Total Actemra® patients with a concurrent diagnosis relating to rheumatoid arthritis and osteoarthrosis**	(b) (4)	(b) (4) %
714.0 Rheumatoid Arthritis		%
714.30 Juv Rheum Arthritis NOS		
714.31 Polyart Juv Rheum Arthr, acute		
714.32 Pauc Juv Rheum Arthr, acute		
715.90 Osteoarthrosis		
714.33 Monoart Juv Rheum Arthr		

***Patient count can sum to greater than the total unique patient count for the time period if patients had multiple diagnoses during the time period examined.**

****Total patient count with a concurrent diagnosis relating to rheumatoid arthritis and osteoarthrosis did not equate to the total unique patient count in table 1 due to the unreported data for patients with a concurrent diagnosis other than rheumatoid arthritis and osteoarthrosis or patients without a concurrent diagnosis.**

Source: Source Healthcare Analytics ProMetis Lx. Jan 2010 through Aug 2012. Data extracted Jan 2013.

5.4 Discussion

The majority of Actemra® use was in the female population over 17 years of age while patients aged 51 to 60 years accounted for the largest proportion of use. We estimated that Actemra® is distributed primarily to the non-retail and outpatient retail pharmacy settings based on sales distribution analysis from the IMS Health, IMS National Sales Perspectives™. Therefore, Actemra® utilization data were obtained from a sample of non-retail pharmacy settings such as clinics, hospitals, and physicians' offices, as well as outpatient retail pharmacies including mail order/specialty pharmacies. Less than (b) (4) patients were captured in the sample, yet (b) (4) vials were sold to all channels of distribution. Based on these product sales data, we estimated that over (b) (4) patient exposures have occurred for Actemra® over the cumulative time period. The amount of product purchased by these distribution channels may be a possible surrogate for use. These data do not provide a direct estimate of use, but they do provide a national estimate of units sold from the manufacturer into the various channels of distribution.

Data from Source Healthcare Analytics' ProMetis Lx® provides patient counts with a procedure and/or pharmacy prescription claim for Actemra® from a sample of pharmacies and data providers. The administration of Actemra® by a trained healthcare provider during a clinic or office visit was included in this review using analysis of both prescription and procedure claims data. Approximately (b) (4)% of the total number of Actemra® patients in the sample was captured using the procedure code, and (b) (4)% was captured using prescription claims data. The procedure code J3262 captures the administration of Actemra® injection.

While the sample data in this analysis includes data from non-retail, outpatient pharmacy, and mail-order/specialty pharmacies, the proportion of sales to the settings of care captured in the sample data are unknown; therefore, nationwide projections are not available at this time. It is unknown whether these Source Healthcare Analytics data are representative of Actemra® use in the entire U.S.

6 LITERATURE REVIEW

OSE Point of Contact: Jane L. Gilbert, MD, PhD, Medical Officer, Division of Pharmacovigilance I

6.1 List of potential safety issues for discussion

- **Psoriasis.** Three cases are reported in the literature. Two (Laurent) are confounded by a prior history of psoriasis, the third (Wendling) describes a new eruption of psoriasis, after the third infusion of tocilizumab (TCZ), in a patient with rheumatoid arthritis. These cases are unexpected as psoriasis is associated with increased IL-6 production. Nevertheless, new onset or reactivated psoriasis has been identified with other biologics, including TNF blockers.

- **Necrotizing Fasciitis.** Two cases of necrotizing fasciitis are reported in the literature (Yoshida; van de Sande). One case resulted in death. Authors of both articles mention that TCZ's suppression of acute-phase reactants such as C-reactive protein (CRP) may mask the presentation of necrotizing fasciitis.

- **Skin related issues.** In addition to the reports of psoriasis and necrotizing fasciitis, the literature includes a report of acute generalized exanthematous pustulosis (Izquierdo), malignant melanoma (Bonny) and two reports of cellulitis (Hirao), (already labeled).

- **Inflammatory Eye Disease.** Two cases of inflammatory eye disease are described in the literature (Wendling). One involved new onset uveitis in a B27+ patient with AS. The second involved keratitis in a patient with RA. The second case describes a positive de-challenge and re-challenge.

6.2 Publication Search & Retrieval (Systematic Search Strategies)

6.2.1 Literature Search Strategy

The medical literature was searched with the strategy described in **Table 6.2.1**. The focus of the literature was identification of new (unlabeled), clinically serious or otherwise compelling new safety concern for tocilizumab.

Table 6.2.1. Literature Search Strategy	
Date of search	February 13, 2013.
Database	PubMed@FDA
Search Terms	Actemra, Tocilizumab, Safety, Adverse, Pancreatitis, Hepatotoxicity, Cytopenia
Years included in search	January 8, 2010 through August 31, 2012

This search yielded 161 publications. Titles were reviewed for relevance, and abstracts of 48 of those most relevant articles were retrieved. After reviewing the abstracts and excluding those that focused primarily on [for example] efficacy, pharmacokinetics, pharmacodynamics and non-clinical studies, 13 articles were selected for more detailed review. Of these, psoriasis, inflammatory eye disease, and necrotizing fasciitis were identified as the most compelling safety issue advanced in the literature to date.

6.2.2 Citations of Selected Publications

Bonny, M. et al. Rapidly progressive malignant melanoma in a patient treated with tocilizumab. Letter to editor. J Am Acad Dermatol 2012; 67: e78-e79.

Hirao, M. et al. Diagnostic features of mild cellulitis phlegmon I patients with rheumatoid arthritis treated with tocilizumab: a report of two cases. Mod Rheumatol 2011; 21: 673-677.

Izquierdo, J.H. et al. Acute generalized exanthematous pustulosis due to tocilizumab in a rheumatoid arthritis patient. Case Report Rheumatol 2012: 517424.

Laurent, S. et al. Onset of psoriasis following treatment with tocilizumab. Letter to editor. Br J Dermatol 2010; 136:1364-5.

van de Sande, M and van Slobbe-Bijlsma, E. Necrotizing fasciitis in a rheumatoid arthritis patient treated with tocilizumab. Rheumatology 2012;51:577-78.

Wendling, D. et al. Psoriasis onset with tocilizumab treatment for rheumatoid arthritis. Letter to editor. J Rheumatol 2012 Mar; 39(3): 657.

Wendling, D. et al. Onset of inflammatory eye disease under tocilizumab treatment for rheumatologic conditions: a paradoxical effect? Letter to editor. J Rheumatol 2011; Oct; 38(10): 2284.

Yoshida, A. et al. Necrotizing fasciitis in a patient with rheumatoid arthritis treated with tocilizumab. Mod Rheumatol 2012;22: 317-18.

6.3 Results

6.3.1 Adverse Events - Unlabeled

- Psoriasis
- Inflammatory Eye Disease

6.3.2 Adverse Events - Labeled, but with Specific Concerns

- Necrotizing Fasciitis. Though the risk of infection is prominently labeled (Boxed Warning), necrotizing fasciitis is a serious manifestation that may be masked by inhibition of acute phase reactants.

6.3.3 Off-label Use

None

6.3.4 Other Relevant Safety Findings

None

7 MEDICATION ERRORS OVERVIEW

OSE Point of Contact: Teresa McMillan, PharmD, Safety Evaluator, Division of Medication Error Prevention and Analysis

7.1 List of potential safety issues for discussion

- There were no safety issues identified for discussion
- There were no product quality issues identified for discussion

7.2 Have any DMEPA postmarket safety reviews regarding medication errors been completed or are pending for this NME? (If yes, describe briefly.)

Although there have been no postmarket safety reviews completed for this product as of January 17, 2013, a label and labeling review (OSE Review #2010-2255) which provided for a new indication of Systemic Juvenile Idiopathic Arthritis was completed on January 10, 2011. An AERS search was conducted for this review and three cases were identified. All three cases were excluded from further evaluation because they described adverse events unrelated to medication errors. In addition, there is no pending post marketing safety review for this NME.

7.3 Is this NME on a safety watch-list in DMEPA?

This NME was not on a safety watch-list in DMEPA as of January 2013.

7.4 Results

7.4.1 FAERS Counts (may include duplicate reports) for medication error cases as of August 31, 2012

The FDA Adverse Event Reporting System (FAERS) database was searched on January 17, 2013 using the MedDRA High Level Group Term (HLGT) "Medication Errors" and the MedDRA High Level Terms (HLT) "Product Label Issues", "Product Packaging Issues", and "Product Quality Issues NEC" along with the product name "*ACTEMRA*" and active ingredient "*TOCILIZUMAB*". The time frame for this review was determined to be December 15, 2010 (date of the last AERS search for Actemra in OSE Review #2010-2255 dated January 10, 2011) to August 31, 2012 (lock date for this review). The search strategy retrieved 3 cases.

Two of the three cases were not considered relevant to our medication error review since they reported adverse events that were not related to a medication error. Therefore one foreign case was evaluated.

The case involved a patient receiving an overdose of Actemra for 5 consecutive infusions. The patient received 1000 mg per infusion. No root cause or outcome was reported. It was also noted

by the reporter that the Actemra prescribing information states that Actemra doses exceeding 800 mg per infusion are not recommended and doses above 1.2 grams have not been evaluated in clinical studies.

We reviewed the Prescribing Information and found it adequate to help mitigate the medication error observed.

7.4.2 List of Medication Error Reports from other source(s) as of date(s) (e.g., MedMARX, DQRS, etc.)

The Division of Medication Error Prevention and Analysis obtains additional medication error data from sources other than FAERS due to the limited reporting of medication errors to MedWatch. Other sources of data include the Periodic Adverse Drug Event Reports (PADERs) submitted by the Applicant, FDA's Drug Quality Reporting System (DQRS) database, and the Institute for Safe Medication Practices (ISMP)[1]. In addition, DMEPA searches public and private list serves and websites (e.g. National Patient Safety Foundation), reviewing public discussions of how medications are actually used to learn about real or potential medication errors involving Actemra. The results of the queries are reflected below in **Table 7.4.2**.

Table 7.4.2: Database Sources Searched for Medication Errors

Source	Date Searched	Number of Cases
Institute for Safe Medication Practices (ISMP)[9]		
• Quantros MedMARX (n=0)	12/4/2012	0
• MERP (n=0)	12/4/2012	0
• ISMP Newsletters (n=0)	12/4/2012	0
FDA Drug Quality Reporting System (DQRS) (n=0)	1/24/2013	0
Periodic Adverse Drug Event Reports (PADERs)	4/12/2012-10/10/2012	14
www.healthboards.com (discussion board)	1/24/2013	0
www.prescriptiondrug-info.com (discussion board)	1/24/2013	0
www.rheumatology.org	1/24/2013	0
www.ncbi.nlm.gov/pubmed	12/4/2012	0
American Society of Health System Pharmacists (ASHP) (www.ashp.org)	12/7/2012	0
National Patient Safety Foundation (www.npsf.org)	12/4/2012	0
American Pharmacists Association (APhA) (www.pharmacist.com)	12/4/2012	0

A review of the April 12, 2012- October 10, 2012 Periodic Adverse Drug Event Report using the search term "medication errors" identified 14 cases. One of the fourteen cases was an adverse event unrelated to a medication error. Thus a total of 13 cases were further evaluated.

[1] This document contains proprietary data from the Institute for Safe Medication Practices (ISMP) and Quantros, which cannot be shared outside of the FDA. Users wanting this information must contact the Division of Medication Error Prevention and Analysis.

- Wrong dose [overdose] (n=6) In all 6 cases, all patient's received a higher dose than prescribed. No root cause or outcome was noted in any of the cases.
- Incorrect administration time (n=2) In both cases, Actemra was administered over 1.5 hours instead of over 1 hour and no root cause or outcome was noted.
- Wrong route (n=2) Actemra was administered paravenously in one case and intramuscular in the other. No root cause or outcome was noted in any of the cases.
- Incorrect preparation of drug (n=2) The patient was prescribed a dose of 760 mg. Four vials of Actemra (400 mg, 200 mg, 80 mgX2) were diluted individually in 100 mL bags instead of together in one 100 mL bag. In the second case, a patient received Actemra that was prepared "48 days" prior to infusion instead of 24 hours prior to infusion. In both cases no root cause or outcome was noted.
- Missed dose (n=1). A patient missed a dose. No root cause or outcome was noted.

We reviewed the Prescribing Information and noted that it clearly states the dosing and administration time, route of administration as well as the dilution preparation steps. Also, the labels and labeling prominently display the route of administration. We also note that the total drug content and the amount of drug per milliliter are prominently displayed on the carton labeling and the container label. Thus, we find the Prescribing Information, carton labeling, and the container labels adequate to help mitigate the medication errors observed. We will also continue our routine surveillance monitoring for any additional medication errors.

8 RISK EVALUATION MITIGATION STRATEGY (REMS) OVERVIEW

OSE Point of Contact: Carolyn L. Yancey, MD, Senior Medical Officer, Division of Risk Management (DRISK)

8.1 Does the product have an approved REMS?

Yes

8.2 REMS approval date:

- ***Initial REMS approval:*** *January 8, 2010*
- ***Approval of most recent REMS modification:*** *October 11, 2012*
- ***Approval of previous REMS Modifications:*** *See Section 8.3.3 below*

8.3 Brief Description of REMS program

8.3.1 REMS goals

The goal of the ACTEMRA REMS is:

- To inform healthcare providers about the serious risks associated with ACTEMRA

8.3.2 Current REMS Elements

A. Communication Plan

Genentech targets adult and pediatric healthcare providers, specifically, rheumatologists, rheumatology healthcare providers, infectious disease specialists, gastroenterologists and hematologists, family practitioners, general practitioners, osteopaths, internists and internal medicine specialists, emergency medicine specialists, neurologists, oncologists, and infusion specialists.

Elements of the communication plan include the following:

1. A **Dear Healthcare Provider Letter** is distributed to adult and pediatric prescribers (as cited above). This letter will be distributed within 60 days of approval of a new indication.
2. **Prescriber Education Slide Deck** provides information on specific safety risks (demyelination, malignancy, lipid elevations and monitoring advice and hypersensitivity reactions, including anaphylaxis). The Prescriber Education Slide Deck will be available for 3 years following approval of the REMS Modification. The Prescriber Education Slide Deck will be available within 60 days of the REMS modification approval through the following distribution methods:

- The www.ACTEMRAREMS.com website
- Genentech Rheumatology Medical Science Liaisons (MSL)
- Hard copy mailing, upon request, through Genentech's toll-free medical information line

3. Journal information pieces target healthcare providers through professional societies
   - For quarterly presentation as a printed information piece in *Arthritis and Rheumatism*, *The Rheumatologist*, *Clinical Infectious Diseases*, *Clinical Gastroenterology and Hepatology*, *American Family Physician*, *Annals of Internal Medicine*, *Annals of Emergency Medicine, Neurology, Pediatrics, AAP (American Academy of Pediatrics) News, and Infectious Diseases in Children* for 3 years following product approval
   - For quarterly presentation as a printed information piece in the *Journal of Clinical Oncology* for 5 years following product approval
4. Actemra REMS program website is available at www.ACTEMRAREMS.com
   - Genentech will ensure that all materials listed in or appended to the ACTEMRA REMS program will be available through the ACTEMRA REMS program website www.ACTEMRAREMS.com or by calling 1-800-228-3672. The ACTEMRA REMS program website will exist for 3 years following approval of the REMS Modification.

B. Timetable for Submission of Assessments

REMS assessments are submitted to FDA at 18 months, 3 years and 7 years after approval of the original REMS (January 8, 2010). *See Section 8.4.2 below.*

8.3.3 Any significant modifications since initial REMS approval

REMS Modifications (prior to the most recent REMS Modification on October 11, 2012) include:

- June 20, 2012: Added Prescriber Education Slide Deck to enhance training on specific serious safety risks (demyelination, malignancy, lipid elevations and monitoring advice, and hypersensitivity reactions, including anaphylaxis) associated with use of Actemra
- April 15, 2011: Two revisions: 1) a new indication for the treatment of systemic juvenile idiopathic arthritis (S-JIA) was added to the REMS, 2) the Medication Guide was removed as an element in the REMS; the Medication Guide is part of approved labeling.

  The original REMS included two goals:

  - The first goal to inform healthcare providers about the serious risks with Actemra listed all the serious adverse events associated with Actemra* and was condensed to more simply state "serious risks" to be more consistent with current REMS goals and to leave open the potential to modify the safety issues, as necessary.
  - The second goal, informing patients about the serious risks with Actmera, was removed as the Medication Guide was removed as a REMS element.

* *Serious infections, gastrointestinal perforations, changes in liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, elevations in lipid parameters in peripheral blood, demyelinating disorders, and malignancies.*

8.4 REMS Assessments

8.4.1 What is the timetable for submission of assessments

REMS assessments are submitted to FDA at 18 months, 3 years and 7 years after approval of the original REMS (January 8, 2010).

8.4.2 Date of most recent REMS assessment submission

The 3-Year REMS Assessment Report submitted on January 3, 2013 includes a 60-Day Review Date on March 5, 2013.

8.4.3 Major findings and recommendations (from most recent assessment)

The Division of Risk Management and the DPARP concluded that the 18-Month REMS assessment report (submitted on July 7, 2011) is complete.** Survey of patient and prescriber knowledge about the serious risks associated with Actemra were conducted in the 18-Month REMS Assessment. Review of the patient knowledge survey focused on questions related to risk-specific information contained in the "What is the most important information I should know about Actemra?" section of the Medication Guide. Review of the prescriber knowledge survey focused on questions related to risk-specific information contained in the REMS Communication Plan.

Patients did not understand that Actemra can cause perforation of the stomach or intestines, and cancer. Prescribers demonstrated high awareness of the risks of infection and gastrointestinal perforation. Prescribers did not have high awareness of the risk of demyelination, malignancy, and lipid monitoring advice for patients treated with Actemra. Adverse event reports were consistent with approved labeling.

Though the Medication Guide has been removed as an element of the REMS (April 15, 2011), the Medication Guide was revised as a Safety Labeling Change based on the 18 month REMS assessment report. A Prescriber Education Slide Deck was added to the Communication Plan materials to improve prescriber education about key serious risks with Actemra.

** *DRISK REMS Assessment Review (dated August 30, 2011), written by Jodi M. Duckhorn, M.A., Senior Social Science Analyst, DRISK*

9 OVERVIEW OF INSPECTIONS OR AUDITS

OC Point of Contact: Haley Seymour, Consumer Safety Officer, DSC

9.1 Summary of results or audits conducted, if applicable

There have been no Risk Evaluation and Mitigation Strategies (REMS) or Postmarketing Adverse Drug Experience (PADE) audits conducted for Actemra (tocilizumab) BLA 125276, since the approval of the drug on January 8, 2010.

9.2 Summary of inspection findings, if applicable

There have been no Risk Evaluation and Mitigation Strategies (REMS) or Postmarketing Adverse Drug Experience (PADE) inspections conducted for Actemra (tocilizumab) BLA 125276, since the approval of the drug on January 8, 2010.

10 DISCUSSION AND ACTION ITEMS

10.1 Summary of Discussion from February 15, 2013 meeting

On February 15, 2013 reviewers from OND and OSE discussed the 915 background assessment for the NME Actemra (BLA 125276, tocilizumab).

Review of the sections of this document suggests the following new potential safety issues:

- **Safety issue 1 - Inflammatory eye disease:** Review of the published medical literature identified 2 cases of inflammatory eye disease: uveitis and keratitis. One case was a positive re-challenge. Several reports of various inflammatory eye diseases (i.e., uveitis, keratitis, and scleritis) were also identified in FAERS. These events are not included in the current product labeling. Due to the small number of cases, more information is needed to determine whether this event is a potential safety signal.
- **Safety issue 2 – Serious infections (include necrotizing fasciitis):** Serious infections were a major safety concern at the time of approval and continue to be reported in postmarket reports. Review of the published medical literature identified 2 reports of necrotizing fasciitis associated with tocilizumab exposure. These literature reports suggested that tocilizumab suppression of acute-phase reactants may have masked the presentation of necrotizing fasciitis. Several additional reports of necrotizing fasciitis were identified in FAERS. Although necrotizing fasciitis is not specifically identified in current product labeling, serious infections are well described and are included in a Boxed Warning. Masking of acute signs and symptoms of infection is described in the Warning and Precaution. In addition, the risk of serious infections is addressed through REMS elements.
- **Safety issue 3 - Pancreatitis:** Review of FAERS identified 39 reports of pancreatitis temporally associated with tocilizumab exposure. Some reports described concurrent hyperlipidemia; however, since laboratory values were absent, a clear association between hyperlipidemia and pancreatitis was not apparent. Increases in all types of lipid parameters were observed in clinical trials and are labeled in Warnings and Precautions. Overall, there is a large amount of confounding by underlying disease and not enough information in the remaining reports to warrant further review at this time.
- **Safety issue 4 – Hepatotoxicity:** Increased transaminases are labeled in Warnings and Precautions and are addressed through REMS elements. Clinically relevant hepatotoxicity was not observed in clinical trials. Review of FAERS identified 16 reports of severe hepatic events, including hepatic failure, temporally associated with tocilizumab exposure. Confounding factors and limited information limit assessment for causal association.
- **Safety issue 5 – Cytopenias:** Neutropenia, leukopenia, and thrombocytopenia occurred in clinical trials and these events are labeled in Warnings and Precautions or Adverse Reactions. Reports of other cytopenias were identified in this summary. Review of FAERS identified over 100 reports of anemia, pancytopenia, and agranulocytosis temporally associated with tocilizumab exposure. Most reports were

confounded by underlying disease and concomitant medications or did not provide laboratory values.

- **Safety issue 6 – Psoriasis:** Review of the published medical literature identified 3 cases of new or worsening psoriasis in tocilizumab-treated patients. There were additional reports in FAERS, but these were generally poorly documented. This event is unexpected as psoriasis is associated with increased IL-6 production. Although the mechanism is not understood, similar reports have been received for other biologics, such as the Tumor Necrosis Factor Alpha (TNF) blockers.

There were no active Tracked Safety Issues known prior to the initiation of this 915 background assessment.

10.2 Action Items

In addition to routine postmarket pharmacovigilance activities, FDA will address the following safety issues:

- **Safety issue 1 - Inflammatory eye disease:** DPARP and DPV will consider sending an Information Request to the sponsor to examine postmarketing and clinical trial data for inflammatory eye disease.
- **Safety issue 2 – Serious infections (include necrotizing fasciitis):** The current product labeling adequately addresses serious infections and the masking of acute inflammation. No further action recommended.
- **Safety issue 3 - Pancreatitis:** Recommend continued monitoring due to confounding and limited information in the cases reviewed.
- **Safety issue 4 - Hepatotoxicity:** Recommend continued monitoring due to confounding and limited information in the cases reviewed.
- **Safety issue 5 – Cytopenias:** Recommend continued monitoring due to confounding and limited information in the cases reviewed.
- **Safety issue 6 – Psoriasis:** Recommend continued monitoring due to confounding and limited information in the cases reviewed.

10.3 Summary for Web Posting

Table 10.3.1 Summary of Evaluation Findings and FDA Actions Taken and Active Ongoing Surveillance Activities

Product Name: Trade (Active Ingredient) BLA Number Approval Date	**Major Indication(s)**	**Summary of Evaluation Findings**	**Actions Taken and Ongoing Surveillance Activities**
Actemra (tocilizumab) BLA 125276 January 8, 2010	For 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). For the treatment of patients 2 years of age and older with active systemic juvenile idiopathic arthritis.	No new safety concerns were identified.	No regulatory actions required at this time.

10.4 Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid trade names or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012 and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Data Mining of FAERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. "Data mining" refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

Drug Utilization Database Descriptions

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Source Healthcare Analytics' ProMetis Lx®

The Source Healthcare Analytics' ProMetis Lx® database is a longitudinal patient data source which captures adjudicated prescription claims across the United States across all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. The database contains approximately 4.8 billion prescriptions claims linked to over 190 million unique prescription patients, of which approximately 70 million patients have 2 or more years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9 diagnosis history of which nearly 91 million prescription drug patients are linked to a diagnosis. The overall sample represents nearly 30,000 pharmacies, 1,000 hospitals, 800 outpatient facilities, and 80,000 physician practices.

10.5 Appendix B. List of OSE Designated Medical Events and associated MedDRA Preferred Terms (MedDRA version 15.1)

Designated Medical Event	MedDRA Preferred Terms
Acute pancreatitis	Pancreatic necrosis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising, Pancreatitis
Acute respiratory failure	Acute respiratory distress syndrome, Acute respiratory failure, Respiratory failure
Agranulocytosis	Agranulocytosis, Febrile neutropenia, Neutropenia
Amyotrophic lateral sclerosis	Amyotrophic lateral sclerosis
Anaphylaxis and anaphylactoid reactions	Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Anaphylactoid shock
Aplastic anemia	Aplasia pure red cell, Aplastic anemia, Bone marrow failure
Blind	Blindness, Blindness transient, Blindness unilateral, Optic ischaemic neuropathy, Sudden visual loss
Colitis ischaemic	Colitis ischaemic, Intestinal infarction
Congenital anomalies	Congenital anomaly
Deaf	Deafness bilateral, Deafness neurosensory, Deafness permanent, Deafness transitory, Deafness unilateral, Deafness, Sudden hearing loss
Diss. intravascular coagulation	Disseminated intravascular coagulation
Endotoxic shock, confirmed or suspected	Endotoxic shock, Septic shock
Haemolysis	Haemoglobinaemia, Haemoglobinuria, Haemolysis, Haptoglobin decreased, Intravascular haemolysis
Hemolytic anemia	Coombs negative haemolytic anaemia, Coombs positive haemolytic anaemia, Haemolytic anaemia
Liver failure	Acute hepatic failure, Hepatic encephalopathy, Hepatic failure, Subacute hepatic failure
Liver necrosis	Hepatitis acute, Hepatitis fulminant, Hepatic necrosis
Liver transplant	Liver transplant
Neuroleptic malignant syndrome	Neuroleptic malignant syndrome
Pancytopenia	Pancytopenia
Progressive multifocal leukoencephalopathy	Progressive multifocal leukoencephalopathy
Product infectious disease transmission	Product contamination microbial Transfusion-transmitted infectious disease Transmission of an infectious agent via product
Pulmonary fibrosis	Pulmonary fibrosis
Pulmonary hypertension	Cor pulmonale, Pulmonary hypertension
Renal failure	Renal failure, Renal failure acute, Renal impairment
Rhabdomyolyisis	Rhabdomyolysis
Seizure	Convulsion, Epilepsy, Grand mal convulsion
Serotonin syndrome	Serotonin syndrome
Stevens-Johnson syndrome	Erythema multiforme, Stevens-Johnson syndrome
Sudden death	Sudden cardiac death, Sudden death
Suicide	Completed suicide
Torsade de Pointes	Torsade de pointes
Toxic epidermal necrolysis	Dermatitis exfoliative, Toxic epidermal necrolysis
TTP	Thrombotic thrombocytopenic purpura
Ventricular fibrillation	Ventricular fibrillation

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/s/

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