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

Pediatric Postmarket Adverse Event Review

Date:	December 4, 2012
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Product Name:	Actemra (tocilizumab)
Pediatric Exclusivity Approval Date:	N/A
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Applicant/Sponsor:	Roche
OSE RCM #:	2012-1680

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EXECUTIVE SUMMARY

In accordance with the Pediatric Research Equity Act (PREA), the Division of Pharmacovigilance (DPV) was asked to summarize post-marketing reports of adverse events associated with the use of Actemra® (tocilizumab) in pediatric patients (0-17 years of age). The main focus of this review is pediatric deaths and pediatric reports of serious unlabeled adverse events with tocilizumab.

Actemra® (tocilizumab) injection is an interleukin-6 (IL-6) receptor inhibitor indicated for the treatment of systemic juvenile idiopathic arthritis (SJIA) in patients ages 2 years and older.

The Adverse Event Reporting System (AERS) database was searched for all reports of adverse events (serious and non-serious) from the US approval date of January 8, 2010 up to the "data lock" date of June 30, 2012. AERS contained 3088 reports for tocilizumab. Pediatric reports represent approximately 4% of the total (118/3088).

After removing duplicate and non-pediatric reports from the case series, we reviewed 112 pediatric cases reported with tocilizumab use, including five fatal reports where the age was not reported but where case narratives suggested a pediatric patient.

There were 12 deaths in the pediatric case series. The reported causes of death in the 12 fatal pediatric cases were macrophage activation syndrome (MAS) (n=3), acute respiratory obstruction (n=1), cardiac arrest (n=1), respiratory failure/hemorrhagic shock (n=1), multi-organ failure (n=1), pulmonary hemorrhage (n=1), sepsis (n=1), or unknown (n=3).

Additionally, we identified 100 non-fatal pediatric cases. Approximately 25% of the cases involved serious infections and approximately 20% of the cases involved MAS, both of which are labeled events. Approximately 10% of cases involved gastrointestinal (GI) events that are labeled terms, closely related to labeled terms, or may be related to underlying comorbidities including perforations (labeled), and enterocolitis, GI hemorrhages, pancreatitis, intussusception, ileus and diarrhea (all unlabeled). The GI hemorrhage cases reported concomitant use of glucocorticoids and/or methotrexate, which confounds assessment. About 10% of pediatric cases involved hypersensitivity reactions, which are labeled in Warnings and Precautions.

There were 16 cases primarily describing hepatic or neurologic events, including increased transaminases (n=5), hepatitis (n=2), and one case each of unspecified liver disorder, cerebral hemorrhage, convulsion, demyelination, encephalitis, Guillain-Barre syndrome, pachymeningitis, pseudotumor cerebral, and reflex sympathetic dystrophy. Increased transaminases are labeled events, and the hepatitis cases were confounded by concomitant medications and medical conditions. The single cases are not considered safety signals at this time; however these events will be encompassed in ongoing pharmacovigilance monitoring.

The remaining pediatric cases involved events related to the underlying rheumatologic condition, nephrolithiasis (labeled based on studies in adult rheumatoid arthritis patients), or single case reports of adverse events. No new potential safety signals were identified in the remaining reports.

Based on the data summarized in this review, DPV recommends no labeling changes at this time.

DPV will continue to monitor adverse events associated with the use of tocilizumab.

1 INTRODUCTION

1.1 PRODUCT FORMULATIONS AND INDICATIONS

Actemra® (tocilizumab) injection, an interleukin-6 (IL-6) receptor inhibitor, received FDA approval on April 15, 2011 for the treatment of systemic juvenile idiopathic arthritis (SJIA) in patients ages 2 years and older. FDA initially approved Actemra® on 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 tumor necrosis factor (TNF) antagonist therapies.

1.2 PEDIATRIC FILING HISTORY

This PREA review was triggered by Study WA18221, a pivotal Phase III double-blind, placebo controlled, parallel group multi-center 2-arm study, conducted in three parts that assessed the safety and efficacy of tocilizumab in patients with active SJIA.[1] This pivotal study enrolled 112 subjects and was conducted across 43 centers in 17 countries, including the US. Part I of the study assessed the primary endpoint: a comparison of the American College of Rheumatology (ACR30) response with the absence of fever at week 12. Part II was a 92-week single-arm, open-label extension. Part III was a three-year single-arm, open-label extension.

The following studies were also reviewed as supportive data:

- Study LRO320 – an open-label, single-ascending-dose study in 18 children with SJIA to assess the safety and pharmacokinetic (PK) aspect of tocilizumab
- Study MRA011JP – an open-label study of 11 pediatric patients with SJIA with inadequate response to corticosteroids
- Study MRA316JP – a phase III, dual-phase (open-label and blind period) study in 56 pediatric patients with SJIA with inadequate response to corticosteroids
- Study MRA317JP – a phase III, open-label, long-term treatment study of 37 pediatric patients enrolled in studies MRA011JP or MRA316JP to assess efficacy, safety, and PK
- Study MRA324JP – a long-term, open-label study initiated to provide expanded access to tocilizumab for patient with SJIA in Japan who were showing resistance to existing treatments

1.3 PEDIATRIC LABELING

The following sections of the tocilizumab product labeling[2] pertain to the pediatric population and this review:

- Warnings and Precautions (e.g., liver enzyme elevation, low neutrophil count, low platelet count and lipid)
- Adverse Reactions (e.g., infections, MAS, anaphylaxis, immunogenicity)
- Use in Specific Populations (i.e., use in other conditions not established)

See Appendix A for a complete listing of the relevant pediatric labeling.

2 METHODS AND MATERIALS

2.1 AERS SEARCH STRATEGY

The Adverse Event Reporting System (AERS) was searched with the strategy described in Table 1 (see Appendix B).

Table 1. AERS Search Strategy*	
Date of search	July 19, 2012
Time period of search	January 8, 2010^ - June 30, 2012
Product Terms	Actemra, tocilizumab
Additional criteria	Refer to Appendix B

* See Appendix C for description of the AERS database.
^ US Approval date

3 RESULTS

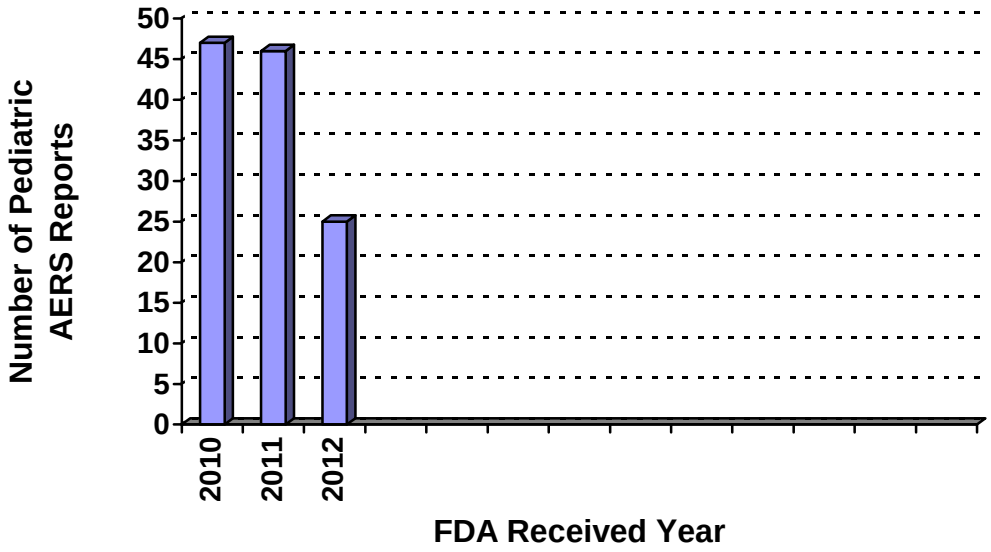
3.1 AERS REPORTS

Table 2. Total number of AERS reports* (January 8, 2010 to June 30, 2012)			
	All reports (US) ^	**Serious‡ (US)**	**Death (US)**
Adults (≥18 years)	2376 (292)	2323 (268)	321 (34)
Pediatrics (0-17 years)	118 (7)	115 (7)†	7 (0)
Age unknown (null values)	594 (112)	577 (107)†	94 (35)#,†
Total	3088 (411)	3015 (382)	422 (69)

* May include duplicates and have not been assessed for causality
^ US counts in parentheses
‡ 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.
#Includes 5 deaths
† See Figure 2

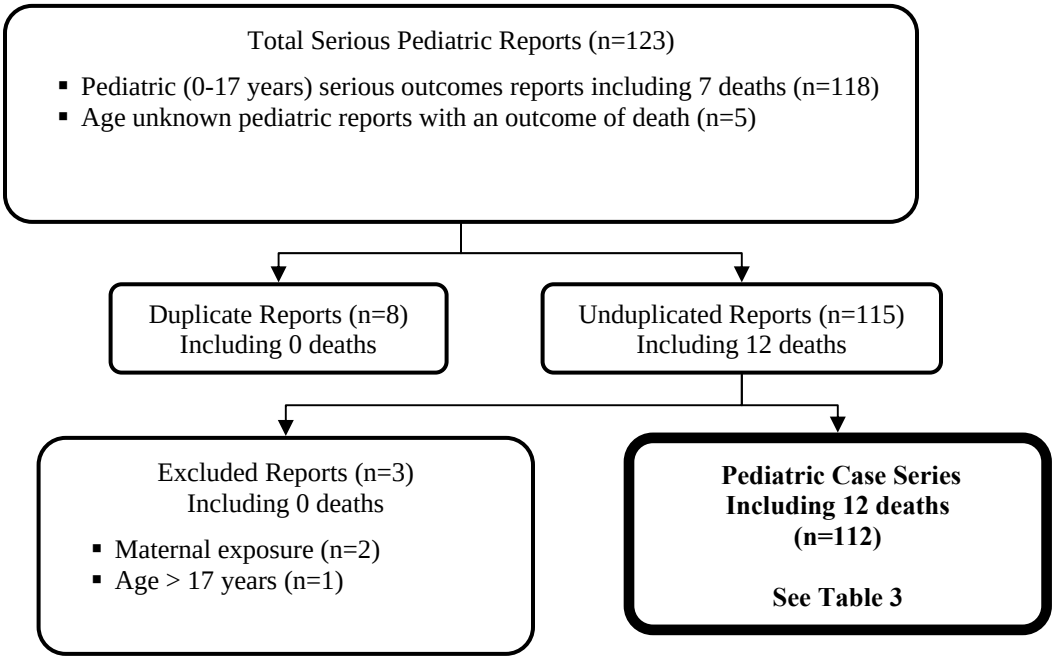
Figure 1. Total Number of Pediatric Reports (including serious and non-serious) for tocilizumab, by year of FDA receipt (January 8, 2010 to June 30, 2012) (n=118)

These numbers include data where age (0-17 years) is known and may contain duplicate reports.



In addition to reviewing pediatric reports with serious outcomes, we also reviewed all reports with the age unknown reporting an outcome of death to determine if the report concerned a pediatric patient. Five additional death reports in pediatric patients were identified. **Figure 2** below summarizes the specific selection of cases to be reviewed in **Section 4**.

3.2 FIGURE 2. SELECTION OF SERIOUS PEDIATRIC AERS CASES



3.3 DESCRIPTIVE CHARACTERISTICS FROM PEDIATRIC CASE SERIES

Table 3 summarizes the 112 AERS cases for 109 unique patients from the Pediatric Case Series with tocilizumab. The pediatric case series includes reports from randomized controlled trials and surveillance studies conducted in Japan that were submitted to the AERS database.

Appendix D lists all the AERS case numbers, AERS Individual Safety Report (ISR) numbers and Manufacturer Control Numbers (MCN) for the Pediatric Case Series.

Table 3. Descriptive characteristics of Pediatric Case Series January 8, 2010 through June 30, 2012 (N=112)[@]				
Age	0 - 1 month	0	6-11 years	46
	1 month - <2 years	3	12-17 years	36
	2-5 years	22	Unknown	5
Sex	Male	41	Unknown	7
	Female	64		
Country of reporter	United States	7	Foreign	105
Report type	Expedited	110	Direct	2
Event date	2008	15	2011	33
	2009	16	2012	4
	2010	27	Unknown	17
Daily dose (n=64)	Average dose	8 mg/kg	Range	3.5 – 15 mg/kg
Duration of therapy (n=95)	Mean	7 months	Range	Same day to 40 months
	Median	4 months		
Indications	SJIA	79	Castleman's disease	3
	JIA/JRA	9	RAP	1
	PJIA	9	Takayasu arteritis	1
	RA	7	Unknown	3
Primary Serious Outcomes* (n=109)	Death	12	Disability	1
	Life-threatening	8	Other serious	31
	Hospitalized	57		

[@] 112 unique reports for 109 unique patients

* 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.

Definitions: JIA = juvenile idiopathic arthritis; JRA = juvenile rheumatoid arthritis; PJIA = polyarticular juvenile idiopathic arthritis; RA = rheumatoid arthritis; RAP = relapsing polychondritis; SJIA = systemic juvenile idiopathic arthritis

4 DISCUSSION OF SERIOUS PEDIATRIC CASE SERIES

4.1 SUMMARY OF PEDIATRIC DEATHS (N=12)

The AERS database contained 12 fatal pediatric cases associated with the use of tocilizumab through June 30, 2012. All were foreign reports; the age and gender were not reported in 5 cases. The remaining 7 cases described males (n=3) and females (n=4) with a median age of 7 years, ranging from 1 to 16 years (n=7). The indications were SJIA (n=10), Still's disease (n=1), or RA (n=1). The median dose of tocilizumab was 8 mg/kg, ranging from 7 to 8 mg/kg (n=3). The median time to death after initiating tocilizumab was 23 months, ranging from 3 to 34 months (n=5). Reported causes of death were macrophage activation syndrome (n=3), acute

respiratory obstruction (n=1), cardiac arrest (n=1), multi-organ failure (n=1), pulmonary hemorrhage (n=1), respiratory failure/hemorrhagic shock (n=1), sepsis (n=1), or unknown (n=3).

A comprehensive assessment of all death cases suggests that patients died from complications of labeled drug safety issues (MAS, sepsis) or reasonably expected outcomes of primary disease processes (acute respiratory obstruction, cardiac arrest) . Six patients died of complications of MAS, and one patient died of sepsis, which are labeled adverse events. One patient with a tracheostomy and history of recurrent respiratory infections and chronic bronchitis died of an acute respiratory obstruction. One patient with pulmonary hypertension died of cardiac arrest one year after tocilizumab was discontinued.

Three patients died of unknown causes. One patient with multiple congenital anomalies developed interstitial pneumonia and acute respiratory distress syndrome, but the cause of death was unclear. In the remaining two reports, there was insufficient information to assess the cause of death.

Narrative Summaries of Pediatric Deaths (n=12)

Macrophage Activation Syndrome (n=3)

ISRs 7540742, 7531811, 7531812, Indonesia, Rcv'd by FDA June 2011. Three patients (between ages 2 and 17 years) enrolled in a clinical trial for tocilizumab treatment of SJIA developed MAS and died. Further information was not reported.

Fatal cases confounded by MAS (n=3)

ISR 7757521, Japan, Rcv'd by FDA September 2011. A 2-year-old male died of multi-organ failure 3 months after initiating tocilizumab for SJIA. He started tocilizumab in November 2010. After the 4th dose, he became unconscious after a blood draw, and was diagnosed with MAS. He was treated with dexamethasone, plasma exchange, and cyclosporine, which was later discontinued for encephalopathy. Later that month, blood tests were positive for Escherichia coli, Streptococcus constellatus, cytomegalovirus, and he was treated with IV antibiotics and ganciclovir. Dialysis was initiated for renal failure and his condition rapidly worsened. He died of suspected vasculitis, respiratory failure, and renal failure.

ISR 8309018, Japan, Rcv'd by FDA April 2012. A 7-year-old male died of pulmonary hemorrhage after tocilizumab was initiated for SJIA. He had a history of MAS, DIC, and hepatic failure. One year after initiation of tocilizumab, he developed a mumps virus infection and "hepatic function disorder," which resolved. On an unspecified date, he developed MAS, DIC, and hepatic failure. He was treated with steroid pulse therapy, plasma exchange. On unspecified dates, tocilizumab was discontinued and he died of pulmonary hemorrhage. Autopsy results were not provided.

ISR 8473099, Japan, Rcv'd by FDA June 2012. A 9-year-old female died of respiratory failure/hemorrhagic shock approximately 3 years after tocilizumab was initiated for SJIA. In April 2009, she started tocilizumab. In January 2012, she developed herpes labialis infection and

in February 2012, PCP and MAS. She was treated with TMP/sulfa, pulse steroids, cyclosporine, and plasmapheresis. Subsequently she developed a gastrointestinal hemorrhage. Blood culture was positive for MRSE, suggesting sepsis via catheter infection. CV catheter was removed. A chest CT showed right pneumothorax, presumably secondary to PCP. The following day, the pneumothorax progressed to hemopneumothorax; she died of respiratory failure and hemorrhagic shock.

Other cause of death (n=3)

ISR 7587244, Australia, Rcv'd by FDA July 2011. A 6-year-old male died of sepsis after receiving tocilizumab for SJIA as part of a randomized controlled trial. He started tocilizumab in April 2009. Concomitant medications included methotrexate and ibuprofen. Two weeks later, he experienced "gastroenteritis-type symptoms," and his grandparents took him to the hospital when he became lethargic. En route to the hospital, he fell unconscious. CPR at the hospital was unsuccessful and he was pronounced dead. Per autopsy, cause of death was sepsis. Blood cultures were reported as "positive," but an organism was not identified.

ISR 7244148, Italy, Rcv'd by FDA January 2011. A 16-year-old female died of cardiac arrest 2 years after tocilizumab was initiated for SJIA as part of a clinical trial. Approximately 1 year after tocilizumab was initiated, she was hospitalized with right heart failure, pulmonary hypertension, and pulmonary edema. Tocilizumab was held, and she improved after treatment with steroids, antibiotics, diuretics, and oseltamivir (H1N1 infection was subsequently excluded). She then experienced macrophage activation syndrome and was treated with cyclosporine. Heart failure resolved, she started bostentan for pulmonary hypertension, and tocilizumab was permanently discontinued. Approximately 1 year later she died of cardiac arrest (described as atrioventricular block). Concomitant medications included flurbiprofen. Relevant cardiac medical history was not reported.

ISR 7287262, Brazil, Rcv'd by FDA February 2011. A 13-year-old female died of acute respiratory obstruction while receiving tocilizumab for rheumatoid arthritis. Relevant medical history included a tracheostomy, recurrent respiratory infections, and chronic bronchitis. She was confined to a wheelchair. She started monthly treatment with tocilizumab in May 2010. In November 2010, one week after the most recent tocilizumab dose she presented to the ER with acute respiratory obstruction, worsening of bronchospasm, worsening of tracheobronchitis, and urinary tract infection. She died the same day.

Cause of death unknown (n=3)

ISR 6634921, Japan, Rcv'd by FDA March 2010: A 1-year-old female died after tocilizumab treatment for SJIA. She was a neonate born at 31 weeks at low birth weight with congenital abnormalities including cleft palate and hypoplastic kidneys. She started tocilizumab in September 2008 at 1 year. After the first dose, she developed bronchial pneumonia and was treated with IV antibiotics. After the second dose, she developed an allergic exanthema on the face/trunk. She then developed acute renal failure and metabolic acidosis due to dehydration. After the 13th tocilizumab dose, she developed bronchitis and was treated with an antifungal and antibiotic. She then fell into a "shock state" and was ventilated. She was diagnosed with

interstitial pneumonia and acute respiratory distress syndrome. She was later extubated and pneumonia improved. Cause and timing of death is unclear from the report.

ISR 7519083, Australia, Rcv'd by FDA June 2011. A patient (demographics not reported) with SJIA was enrolled in a clinical trial for tocilizumab. Medical history and concomitant medications were not reported. On an unspecified date, the patient died.

ISR 8146544, Brazil, Rcv'd by FDA February 2012. A patient experienced diarrhea and died of an unknown cause after tocilizumab treatment for Still's disease. Medical history and concomitant medications were not reported.

4.2 SUMMARY OF NON-FATAL SERIOUS PEDIATRIC ADVERSE EVENTS (N=100)

4.2.1 Serious Infections (n=20)

We identified 20 non-fatal cases of serious infection as the primary event. All cases, except one, were foreign reports of males (n=9) and females (n=11), with a median age of 8 years, ranging from 2 to 16 years. The indications were SJIA (n=15), PJIA (n=4), and RA (n=1). Most patients (n=18) were treated with concomitant immunosuppressants, such as methotrexate or corticosteroids. Three cases reported sepsis or septic shock. Eight cases reported multiple types of infections. Types of infections included gastroenteritis (n=5), pneumonia (n=4), bronchitis (n=2), herpes (n=3), abscess (n=2), infectious enterocolitis (n=2), cellulitis (n=1), mumps (n=1), otitis media (n=1), osteonecrosis (n=1), parovirus (n=1), upper respiratory tract infection (n=1), pharyngitis (n=1), appendicitis (n=1), unspecified infections (n=2).

We did not identify any cases of active tuberculosis (TB). However, we considered one case (ISR 8471370) to be a possible case of latent tuberculosis. This 6-year-old male developed pneumonia 3 months after initiation of tocilizumab. On an unspecified date an abnormal chest tomography showed a "calcified Ghon's focus;" however, a Diaskin tuberculosis test was negative.

As a biologic product which suppresses the immune system, infections are anticipated and the product label includes a description of a variety of serious infections including sepsis, tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections in a Box Warning and in the Warnings and Precautions section of the product label. Unlabeled infectious adverse events included appendicitis, infectious enterocolitis, mumps, osteonecrosis, and parvovirus.

4.2.2 Macrophage Activation Syndrome (n=13)

We identified 13 non-fatal cases of macrophage activation syndrome as the primary event. All cases were foreign reports. Demographics included 3 males and 10 females, with a median age of 7 years, ranging from 4 to 16 years. All patients were treated for SJIA. The median time to event after initiation of tocilizumab was 6 months, ranging from 4 days to 33 months.

MAS is a serious life-threatening condition associated with SJIA with mortality rates up to 20% [3]. MAS is to be expected in patients with the most severe manifestations of juvenile rheumatoid disease. Given that tocilizumab is a relatively new biologic agent, the biologic is most likely given patients with severe rheumatoid disease. Thus, all MAS cases were confounded by indication.

MAS is labeled in the Adverse Reactions section of the tocilizumab label.

4.2.3 Gastrointestinal Events (n=10)

We identified 10 cases of gastrointestinal events. All were Japanese reports of males (n=5) and females (n=5) with a median age of 9 years, ranging from 2 to 15 years. Patients were treated for SJIA (n=8) or PJIA (n=2). The median time to onset after initiation of tocilizumab was 4 months, ranging from 1 to 15 months.

Gastrointestinal events included enterocolitis (n=3), three bleeding events including small intestinal hemorrhage (n=1), gastrointestinal hemorrhage (n=1), anal hemorrhage (n=1), pancreatitis acute (n=1), intussusception and pneumatosis cytoides intestinalis (n=1), ileus (n=1), and gastric perforation (n=1). The cases reporting gastrointestinal bleeding events all reported use of corticosteroids and 1 case reported use of methotrexate. Gastrointestinal bleeding is a labeled adverse event of both corticosteroids and methotrexate. The single case of pancreatitis occurred in a 5-year-old female patient who had been receiving tocilizumab for 4 months; the patient was also receiving prednisone and cyclosporine, which are both labeled for pancreatitis.

The current product labeling describes low platelets without bleeding in the Warnings and Precautions section of labeling. Unlabeled events include anal hemorrhage, enterocolitis, gastrointestinal hemorrhage, ileus, intussusception, pancreatitis, and small intestinal hemorrhage.

4.2.4 Hypersensitivity (n=11)

We identified 11 cases of hypersensitivity as the primary event. The cases included 2 domestic reports and 9 foreign reports of males (n=2), females (n=8) and unknown gender (n=1), with a median age of 12 years, ranging from 1 to 17 years. Patients were treated for SJIA (n=6), JRA/JIA (n=3), RA (n=1), or Castleman's disease (n=1). Ten cases were considered serious; no patients died. The hypersensitivity reaction occurred after the first dose (n=4), the second dose (n=3), the third dose (n=3), or was unspecified (n=1).

Two cases (ISRs 7288373 and 7269978) reported anaphylaxis after the third tocilizumab dose despite pre-medicating the patient. An additional three cases (ISRs 6942823, 7953265, 8174020) were considered "possible" anaphylaxis based on the symptoms described in the reports. Various symptoms of hypersensitivity were reported in the remaining 6 cases, including, fever (n=3), angioedema (n=2), pruritus (n=2), rash (n=2), chest pain (n=1), cough (n=1), dizziness (n=1), hypotension (n=1), nausea (n=1), peripheral edema (n=1), shivering (n=1), and urticaria (n=1).

Labeled events include anaphylaxis, angioedema, fever, peripheral edema, pruritus, rash, chest pain, cough, dizziness, and urticaria. Unlabeled events include hypotension, nausea, and shivering.

4.2.5 Hepatic Events (n=8)

We identified 8 cases of hepatic events as the primary event. All were foreign reports of males (n=5) and females (n=3), with a median age of 9 years, ranging from 6 to 16 years. Patients were treated for SJIA (n=5), JIA (n=1), PJIA (n=1), or relapsing polychondritis (n=1). Six cases were considered serious, and 2 cases were non-serious; there were no deaths. The median time to onset after initiation of tocilizumab was 1 month, ranging from 2 weeks to 20 months (n=6).

Events included increased transaminases (n=5), hepatitis (n=2), or unspecified liver disorder (n=1). In one hepatitis case (ISR 7647777), a 16-year-old female patient with SJIA developed hepatitis 20 months after initiating tocilizumab. She was also receiving methotrexate and possibly had macrophage activation syndrome. Methotrexate and tocilizumab were discontinued and the hepatitis resolved; tocilizumab was restarted. In the second hepatitis case (ISR 7603964), an 8-year-old female with SJIA developed hepatitis 2 weeks after the first tocilizumab dose; methotrexate, acyclovir, famotidine, alendronate, methylprednisolone and prednisolone were used concomitantly. The patient had a history of increased liver function tests prior to use of tocilizumab. Liver biopsy revealed steatosis, hepatocellular disturbances and bile duct disorder; drug-induced hepatitis was the most likely diagnosis. The reporter commented that it was difficult to determine the point of onset of the liver disorder. These two hepatitis cases are considered confounded by concomitant medications and medical conditions.

Labeled events include increased transaminases; increases in frequency and magnitude of these elevations occurred when potentially hepatotoxic drugs (e.g., MTX) were used in combination with tocilizumab. Hepatitis is an unlabeled event.

4.2.6 Neurologic Events (n=8)

We identified 8 cases of neurologic events as the primary event. All cases were foreign reports of males (n=3) and females (n=5) with a median age of 9 years, ranging from 4 to 17 years. Patients were treated for SJIA (n=4), PJIA (n=1), RA (n=1), Castleman's disease (n=1), or unspecified (n=1). There were zero deaths. The median time to onset after initiation of tocilizumab was 4 months, ranging from < 1 day to 2 years (n=7).

Events included a single case each of cerebral hemorrhage, convulsion, demyelination, encephalitis, Guillain-Barre syndrome, pachymeningitis, pseudotumor cerebral, and reflex sympathetic dystrophy. All cases were considered serious; there were no deaths.

The current product labeling describes a theoretical risk of demyelinating disorders and low platelets without bleeding in the Warnings and Precautions section. All other reported neurologic adverse events were considered unlabeled.

4.2.7 Malignancy (n=1)

We identified one case of malignancy in a pediatric patient treated with tocilizumab. This case (ISR 8425866) described a 16-year-old female diagnosed with Stage II Hodgkin's lymphoma (HL) after receiving 3 doses of tocilizumab for SJIA (approximately 2 months after initiating tocilizumab). The diagnosis was biopsy confirmed. Concomitant immunosuppressant included methotrexate, and she was treated with rilonacept for 18 months prior to initiation of tocilizumab. She had a "strong" family history of malignancy, including breast cancer, melanoma, and neuroblastoma. Treatment and outcome for the HL were not provided.

The current product labeling describes a theoretical risk of malignancy in the Warnings and Precautions section.

4.2.8 Remaining Non-Fatal Pediatric Adverse Events (n=29)

The remaining 29 cases not categorized in the above sections are summarized in Appendix E. The most common events in this category included worsening or flares of rheumatologic disease (n=5) and nephrolithiasis (n=3). The rheumatologic events were considered related to the underlying indication for use. Nephrolithiasis is a labeled event for tocilizumab based on studies of adult rheumatoid arthritis patients.

The 21 remaining pediatric cases describe events that occurred only once. No safety signals were identified in these single cases.

5 CONCLUSION

One hundred and twelve pediatric cases reported with tocilizumab use from U.S. approval to June 30, 2012 were reviewed. There were 12 fatal cases; the most commonly reported cause of death was MAS, infection, or an unknown cause of death.

We identified 100 non-fatal pediatric cases for this review. Approximately a quarter of the pediatric cases involved serious infections, which are well described in the Actemra labeling. About 20% of the pediatric cases involved MAS, which is also a labeled event.

Approximately 10% of pediatric cases involved GI events, such as the labeled events of GI perforations and unlabeled events of enterocolitis, GI hemorrhages, pancreatitis, intussusception, ileus and diarrhea. About 10% of pediatric cases involved hypersensitivity reactions, which are described in the Warning and Precaution section of the Actemra label.

There were 16 cases that described hepatic or neurologic events. Increased transaminases are labeled events for tocilizumab. The 2 hepatitis cases reviewed were confounded by concomitant medications and medical conditions. No potential safety signals were identified in the remaining reports.

Overall, based on the reports in this pediatric case series, it was generally difficult to ascertain if the reported adverse event was due to tocilizumab as many patients were taking other

immunosuppressant agents concurrently, such as prednisone, methotrexate or cyclosporine. Also, patients had underlying autoimmune conditions which affect their risk of infections and other events described in this review. Thus, a review of these pediatric cases did not identify any new potential safety signals which warrant a change in the tocilizumab labeling.

6 RECOMMENDATIONS

Based on the data summarized in this review, DPV recommends no labeling changes at this time. DPV will continue to monitor adverse events associated with the use of tocilizumab.

7 REFERENCES

1. Coyle K. Clinical review: tocilizumab for systemic juvenile idiopathic arthritis. sBLA12576/22. March 22, 2011.
2. Tocilizumab (Actemra) Product Labeling. Roche. April 2011.
3. Grom A. Macrophage activation syndrome: a review of diagnosis, treatment, and prognosis. The Rheumatologist. December 2010. Available at: http://www.the-rheumatologist.org/details/article/973181/Macrophage_Activation_Syndrome.html.

8 APPENDICES

8.1 APPENDIX A. PEDIATRIC PRODUCT LABELING

5 WARNINGS AND PRECAUTIONS
5.3 Laboratory Parameters
Systemic Juvenile Idiopathic Arthritis
A similar pattern of liver enzyme elevation, low neutrophil count, low platelet count and lipid elevations is noted with ACTEMRA treatment in the SJIA population. Neutrophils, Platelets, ALT and AST should be monitored at the time of the second infusion and thereafter every 2 to 4 weeks. Lipids should be monitored as above for RA *[see Dosage and Administration (2.3)]*.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Systemic Juvenile Idiopathic Arthritis
The data described below reflect exposure to ACTEMRA in one randomized, double-blind, placebo-controlled trial of 112 pediatric patients with SJIA 2 to 17 years of age who had an inadequate clinical response to nonsteroidal anti inflammatory drugs (NSAIDs) or corticosteroids due to toxicity or lack of efficacy. At baseline, approximately half of the patients were taking 0.3 mg/kg/day corticosteroids or more, and almost 70% were taking methotrexate. The trial included a 12 week controlled phase followed by an open-label extension. In the 12 week double-blind, controlled portion of the clinical study 75 patients received treatment with ACTEMRA (8 or 12 mg per kg based upon body weight). After 12 weeks or at the time of escape, due to disease worsening, patients were treated with ACTEMRA in the open-label extension phase.

The most common adverse events (at least 5%) seen in ACTEMRA treated patients in the 12 week controlled portion of the study were: upper respiratory tract infection, headache, nasopharyngitis and diarrhea.

Infections
In the 12 week controlled phase, the rate of all infections in the ACTEMRA group was 345 per 100 patient-years and 287 per 100 patient-years in the placebo group. In the open label extension over an average duration of 73 weeks of treatment, the overall rate of infections was 304 per 100 patient-years.

In the 12 week controlled phase, the rate of serious infections in the ACTEMRA group was 11.5 per 100 patient years. In the open label extension over an average duration of 73 weeks of treatment, the overall rate of serious infections was 11.4 per 100 patient years. The most commonly reported serious infections included pneumonia, gastroenteritis, varicella, and otitis media.

Macrophage Activation Syndrome
In the 12 week controlled study, no patient in any treatment group experienced macrophage activation syndrome (MAS) while on assigned treatment; 3 per 112 (3%) developed MAS during open-label treatment with ACTEMRA. One patient in the placebo group escaped to ACTEMRA 12 mg per kg at Week 2 due to severe disease activity, and ultimately developed MAS at Day 70. Two additional patients developed MAS during the long-term extension. All 3 patients had ACTEMRA dose interrupted (2 patients) or discontinued (1 patient) for the MAS event, received treatment, and the MAS resolved without sequelae. Based on a limited number of cases, the incidence of MAS does not appear to be elevated in the ACTEMRA SJIA clinical development experience; however no definitive conclusions can be made.

Infusion Reactions
Patients were not premedicated, however most patients were on concomitant corticosteroids as part of their background treatment for SJIA. Infusion related reactions were defined as all events occurring during or within 24 hours after an infusion. In the 12 week controlled phase, 4% of ACTEMRA and 0% of placebo treated patients experienced events occurring during infusion. One event (angioedema) was considered serious and life-threatening, and the patient was discontinued from study treatment.

Within 24 hours after infusion, 16% of patients in the ACTEMRA treatment group and 5% of patients in the placebo group experienced an event. In the ACTEMRA group the events included rash, urticaria, diarrhea, epigastric discomfort, arthralgia and headache. One of these events, urticaria, was considered serious.

Anaphylaxis
Anaphylaxis was reported in 1 out of 112 patients (less than 1%) treated with ACTEMRA during the controlled and open label extension study *[see Warnings (5.5)]*.

Immunogenicity
All 112 patients were tested for anti-tocilizumab antibodies at baseline. Two patients developed positive anti tocilizumab antibodies: one of these patients experienced serious adverse events of urticaria and angioedema consistent with an anaphylactic reaction which led to withdrawal; the other patient developed macrophage activation syndrome while on escape therapy and was discontinued from the study.

Laboratory Tests

Neutrophils
During routine monitoring in the 12 week controlled phase, a decrease in neutrophil below 1 × 109 per L occurred in 7% of patients in the ACTEMRA group, and in no patients in the placebo group. In the open label extension over an average duration of 73 weeks of treatment, a decreased neutrophil count occurred in 17% of the ACTEMRA group. There was no clear relationship between decrease in neutrophils below 1 × 109 per L and the occurrence of serious infections.

Platelets
During routine monitoring in the 12 week controlled phase, 1% of patients in the ACTEMRA group and 3% in the placebo group had a decrease in platelet count to no more than 100 × 103 per mcL.

In the open label extension over an average duration of 73 weeks of treatment, decreased platelet count occurred in 4% of patients in the ACTEMRA group, with no associated bleeding.

Liver Function Tests
During routine laboratory monitoring in the 12 week controlled phase, elevation in ALT or AST at or above 3x ULN occurred in 5% and 3% of patients, respectively in the ACTEMRA group and in 0% of placebo patients.

In the open label extension over an average duration of 73 weeks of treatment, the elevation in ALT or AST at or above 3x ULN occurred in 13% and 5% of ACTEMRA treated patients, respectively.

Lipids
During routine laboratory monitoring in the 12 week controlled phase, elevation in total cholesterol greater than 1.5x ULN – 2x ULN occurred in 1.5% of the ACTEMRA group and in 0% of placebo patients. Elevation in LDL greater than 1.5x ULN – 2x ULN occurred in 1.9% of patients in the ACTEMRA group and 0% of the placebo group.

In the open label extension study over an average duration of 73 weeks of treatment, the pattern and incidence of elevations in lipid parameters remained consistent with the 12 week controlled study data.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Safety and effectiveness of ACTEMRA in pediatric patients with conditions other than SJIA have not been established. Children under the age of two have not been studied. Testing of a murine analogue of tocilizumab did not exert toxicity in juvenile mice. In particular, there was no impairment of skeletal growth, immune function and sexual maturation.

8.2 APPENDIX B. STANDARD SEARCHES

A. Adults (18 yrs and above)
   1. All outcomes from approval date (no set criteria)
   2. Serious outcomes from approval date
   3. Death as an outcome from approval date

B. Ages 0-17 yrs ONLY
   1. Same as above 1-3

8.3 APPENDIX C. ADVERSE EVENT REPORTING SYSTEM (AERS)

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do 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 all adverse event reports that occur 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, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

8.4 APPENDIX D. AERS CASE NUMBERS, AERS ISR NUMBERS AND MANUFACTURER CONTROL NUMBERS

CSENUM	ISRNUM	MFRCNTRL	Duplicate CSENUM
7250049	6634921	JP-ROCHE-588086	
7256135	8213426	JP-ROCHE-680309	
7256142	6551395	JP-ROCHE-611714	
7257889	6723499	JP-ROCHE-599216	
7257890	6553931	JP-ROCHE-648512	
7258017	6554138	ES-ROCHE-678487	
7260492	6612239	JP-ROCHE-597778	
7267462	6836078	JP-ROCHE-634393	
7275064	7488062	JP-ROCHE-672587	
7294323	6963760	JP-ROCHE-576461	7369005
7307000	6616319	RU-ROCHE-688506	
7315395	6628299	JP-ROCHE-634266	
7322883	6848257	JP-ROCHE-623197	7323841
7339095	6661241	EC-ROCHE-693839	
7340968	6937442	JP-ROCHE-694358	
7345561	8402785	JP-ROCHE-694959	
7371967	6704009	US-ROCHE-661417	
7372151	6711725	JP-ROCHE-699881	
7372886	6965621	JP-ROCHE-597910	
7383577	6769705	ES-ROCHE-701720	
7389671	6786247	FR-ROCHE-702488	
7393201	6732362	JP-ROCHE-575719	
7398409	7244148	IT-ROCHE-671906	
7401270	8008470	JP-ROCHE-705278	
7419759	7191375	CA-ROCHE-707609	
7424807	6828163	JP-ROCHE-709552	
7491753	6862680	JP-ROCHE-575919	
7503035	7024146	JP-ROCHE-717354	
7507519	6882580	JP-ROCHE-591901	
7511911	8014946	JP-ROCHE-717171	
7536983	7177197	IN-ROCHE-719957	
7538296	6920988	CL-ROCHE-662204	
7552320	6979960	CA-US-EMD SERONO, INC.-7013879	
7554828	6942823	CZ-ROCHE-722040	
7554832	6942837	IT-ROCHE-718264	
7605467	7178245	JP-ROCHE-629362	
7621777	7081053	DK-ROCHE-730630	
7621821	7275235	JP-ROCHE-730872	
7663589	7094601	US-ROCHE-738990	
7668302	7102160	ZA-ROCHE-738888	
7696294	7287262	BR-ROCHE-745670	
7711829	8393471	IT-ROCHE-741874	
7722822	7177260	CO-ROCHE-748231	
7723476	7269978	US-ROCHE-746681	

CSENUM	ISRNUM	MFRCNTRL	Duplicate CSENUM
7757060	7221671	US-ROCHE-751999	
7763723	7757521	JP-ROCHE-752800	
7771742	7241466	NO-ROCHE-754642	
7809205	7288373	SA-ROCHE-757659	
7812766	7293100	JP-ROCHE-756981	
7835169	7323671	GR-ROCHE-761176	
7843673	7335032	SE-ROCHE-763314	
7860242	7509436	JP-ROCHE-765641	
7889538	7540732	JP-ROCHE-769051	
7902795	7519154	JP-ROCHE-770655	
7913123	7587244	AU-ROCHE-771896	
7956666	8476809	JP-BAYER-2011-042696	
7962030	7519083	AU-ROCHE-778197	
7969411	7540742	ID-ROCHE-779855	
7975438	7647777	LB-ROCHE-779685	
7975472	7531811	ID-ROCHE-780656	
7975485	7531812	ID-ROCHE-780678	
7983548	7536765	CA-ROCHE-631537	
7993547	7551149	DE-SANOFI-AVENTIS-2011SA037559	
8001761	7817477	JP-ROCHE-782250	
8002260	7752638	JP-ROCHE-782499	
8007172	7722632	JP-MERCK-1106USA02760	
8010430	7603964	JP-ROCHE-785205	
8013186	7562413	CTU 457171	
8016838	7650173	DE-ROCHE-768876	8001803
8018619	7746179	JP-ROCHE-779717	
8026575	7914997	JP-ROCHE-787619	
8028505	7600558	NO-ROCHE-787199	
8045187	7817468	JP-ROCHE-610049	
8049716	7769229	JP-ROCHE-790963	
8067742	8475520	JP-ROCHE-785720	
8088155	7754468	JP-ROCHE-789745	
8097930	7693652	JP-ROCHE-794693	7441609
8137529	7752743	SY-ROCHE-801402	
8146193	7806938	SE-ROCHE-802889	
8153972	7812001	CZ-ROCHE-804358	
8181503	7814842	SE-ROCHE-798687	8171421
8220669	8053266	JP-ROCHE-1006194	
8237744	8005375	JP-ROCHE-1009308	
8244050	7913283	CO-ROCHE-1011887	
8248661	8174020	JP-ROCHE-1013516	
8271743	7953265	US-ROCHE-1014239	
8282686	8393254	JP-ROCHE-1009763	
8290984	7979647	KW-ROCHE-1020170	
8292750	8054205	SE-ROCHE-1020213	
8315656	8407091	FR-ROCHE-1016060	

CSENUM	ISRNUM	MFRCNTRL	Duplicate CSENUM
8341932	8115907	GB-ROCHE-1030603	
8391762	8146544	BR-ROCHE-1035759	
8392700	8117317	NZ-ROCHE-1033578	
8405532	8136503	HU-ROCHE-1037810	8327464
8437956	8180737	JP-ROCHE-750172	
8448107	8192159	GB-BAUSCH-2012BL001364	8401358, 8433801
8454857	8203212	JP-ROCHE-1034847	
8468883	8257446	CA-ROCHE-1046563	
8477086	8235894	CA-ROCHE-1051593	
8485511	8266385	JP-ROCHE-1046377	
8490942	8245866	CTU 472547	
8516061	8473099	JP-ROCHE-1057932	
8522480	8299349	JP-ROCHE-576448	
8528507	8309018	JP-ROCHE-1058658	
8531973	8344338	BR-ROCHE-1063028	
8533955	8318207	JP-ROCHE-1061940	
8535108	8435928	JP-ROCHE-1061844	
8537991	8325242	CA-ROCHE-1043973	
8602822	8418843	DZ-ROCHE-1072551	
8605064	8422290	CA-ROCHE-1073828	
8635579	8471370	RU-ROCHE-1080193	
8638499	8471812	JP-ROCHE-764578	

8.5 APPENDIX E. SUMMARY OF REMAINING NON-FATAL PEDIATRIC ADVERSE EVENTS (N=29)

Event Type	Adverse Event	N	Labeling Status	Comments
Blood	lymphopenia, splenic injury	1	not labeled	
Blood	white blood cell count increased	1	not labeled	
Cardiac	pericarditis	1	not labeled	
Cardiac	arrhythmia	1	not labeled	
Dermatologic	panniculitis	1	not labeled	
Dermatologic	vasculitis	1	not labeled	cutaneous
Dermatologic	rosaceiform dermatitis	1	not labeled	rosaceiform dermatitis
Dermatologic	acute febrile neutrophilic dermatitis	1	not labeled	"Sweet's Syndrome"
Dermatologic	pyoderma, erythema multiforme	1	not labeled	
Eye	papilloedema	1	not labeled	optic nerve swelling
Eye	uveitis	1	not labeled	bilateral
General	disease progression, juvenile arthritis, arthritis, ill-defined disorder, fatigue	5	not labeled	describe progression of underlying disease
General	dysphagia	1	not labeled	
Immune	Behcet's syndrome	1	not labeled	intestinal
Musculoskeletal	systemic sclerosis	1	not labeled	pre-existing disease
Musculoskeletal	spondylitis	1	not labeled	
Musculoskeletal	radius fracture	1	not labeled	from fall
Pregnancy	abortion spontaneous	1	not labeled; Section 8.1 describes increase abortion in animal model	Pregnancy Category C
Psychiatric	tic, scan abnormal	1	not labeled	MRI abnormalities
Renal	nephrolithiasis, calculus urinary	3	labeled for adult RA studies (AR)	
Respiratory	asthma, pericardial effusion	1	not labeled	
Vascular	hypertension	1	not labeled for pediatrics; labeled for adults (AR)	140/110
Vascular	thrombosis	1	not labeled	right atrium

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