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

Pediatric Postmarketing Pharmacovigilance Review

Date:	September 12, 2022
Safety Evaluator:	Laura Kangas, PharmD Division of Pharmacovigilance-I (DPV-I)
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Product Name:	Actemra (tocilizumab)
Pediatric Labeling Approval Dates:	May 11, 2018; September 12, 2018
Application Type/Number:	BLA 125276 (injectable; injection); BLA 125472 (injectable; intravenous, subcutaneous)
Applicant:	Genetech (Roche subsidiary)
OSE RCM #:	2022-689

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EXECUTIVE SUMMARY

This review evaluates reports in the FDA Adverse Event Reporting System (FAERS) and the medical literature for tocilizumab in pediatric patients through age 17 years. The Division of Pharmacovigilance-I (DPV-I) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA), Best Pharmaceuticals for Children Act (BPCA), and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with tocilizumab in pediatric patients.

The FDA approved tocilizumab on January 8, 2010, for the treatment of adult patients with moderately-to severely-active rheumatoid arthritis (RA) who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies; since that time, it has received approval for multiple adult indications: giant cell arteritis, systemic sclerosis-associated interstitial lung disease, cytokine release syndrome. The approved pediatric labeling is for polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, and cytokine release syndrome in patients two years of age and older. This pediatric postmarketing pharmacovigilance review was triggered by the pediatric labeling changes on May 11, 2018, and September 12, 2018.

We reviewed all medical literature cases and FAERS U.S. serious cases with tocilizumab in the pediatric population (ages 0 -< 18 years) for the period of July 1, 2012, through April 3, 2022. Our evaluation identified one case describing posterior reversible encephalopathy syndrome with tocilizumab; however, there is insufficient evidence to support a new signal at this time. We did not identify any additional safety signals, increased severity or frequency of any labeled adverse events, or deaths directly associated with tocilizumab.

DPV-I did not identify any new pediatric safety concerns for tocilizumab at this time. DPV-I recommends no regulatory action at this time, and will continue to monitor all adverse events associated with the use of tocilizumab.

1 INTRODUCTION

This review evaluates reports in the FDA Adverse Event Reporting System (FAERS) and the medical literature for tocilizumab in pediatric patients through age 17 years. The Division of Pharmacovigilance-I (DPV-I) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA), Best Pharmaceuticals for Children Act (BPCA), and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious, unlabeled adverse events associated with tocilizumab in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Actemra® (tocilizumab), an interleukin-6 (IL-6) receptor inhibitor, was initially approved by the FDA on January 8, 2010 as an intravenous formulation for rheumatoid arthritis in adults.[1] It is currently indicated for the treatment of:[2]

- Rheumatoid Arthritis (RA): adult patients with moderately to severely active RA who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs); intravenous (IV) and subcutaneous (SC) formulations are approved
- Giant Cell Arteritis (GCA): adult patients with GCA; IV and SC formulations are approved
- Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD): slowing the rate of decline in pulmonary function in adult patients with SSc-ILD; SC formulation is approved
- Polyarticular Juvenile Idiopathic Arthritis (PJIA): patients 2 years of age and older with active PJIA; IV and SC formulations are approved
- Systemic Juvenile Idiopathic Arthritis (SJIA): patients 2 years of age and older with active SJIA arthritis; IV and SC formulations are approved
- Cytokine Release Syndrome (CRS): adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening CRS; IV formulation is approved

Table 1 shows the pediatric labeling changes for tocilizumab.

Table 1. Timeline of Pertinent Tocilizumab Pediatric Labeling Changes

Date	Population	Labeling Change
April 15, 2011	Pediatric	IV dosing approved for treatment of active SJIA in patients 2 years of age and older[3,4]
April 29, 2013	Pediatric	IV dosing approved for treatment of active PJIA in patients 2 years of age and older[5,6]

August 30, 2017	Adult and pediatric	IV dosing approved for treatment of CAR T cell-induced severe or life-threatening CRS in adults and pediatric patients 2 years of age and older[7,8]
May 11, 2018	Pediatric	Adverse events in SJIA patients updated: serious adverse events, hypersensitivity, and infections; [9,10] SC dosing approved for treatment of PJIA in patients 2 to 17 years of age [9,10]
September 12, 2018	Pediatric	SC dosing approved for treatment of SJIA in patients 2 to 17 years of age[11,12,13]
November 19, 2018	Adult and pediatric	SC autoinjector formulation approved[14,15]
May 28, 2020	Pediatric	Updated information on autoinjector use in the pediatric population[16,17]
Abbreviations: CAR= chimeric antigen receptor, IV=intravenous, PJIA=Polyarticular Juvenile Idiopathic Arthritis, SC=subcutaneous, SJIA= Systemic Juvenile Idiopathic Arthritis		

This pediatric postmarketing pharmacovigilance review was triggered by the pediatric labeling changes on May 11, 2018, and September 12, 2018.

OSE previously evaluated pediatric postmarketing adverse event reports with tocilizumab; Drug Use's evaluation, dated November 16, 2012, and DPV-I's evaluation, dated December 4, 2012, were prompted by the pediatric labeling change on April 15, 2011. DPV-I's evaluation did not identify any new safety concerns, and recommended return to routine monitoring for adverse events with tocilizumab.[18,19,20] FDA presented their results to the Pediatric Advisory Committee (PAC) on March 14, 2013.[21]

Actemra® is supplied as 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL individually packaged 20 mg/mL single-dose vials for intravenous infusion and as 162 mg/0.9 mL single-dose prefilled syringes and ACTPen® autoinjectors for subcutaneous injection.

1.2 RELEVANT LABELED SAFETY INFORMATION

A summary of the safety information from the HIGHLIGHTS OF PRESCRIBING INFORMATION section of the tocilizumab product labeling is reproduced below.[2]

---------- CONTRAINDICATIONS ----------

- ACTEMRA is contraindicated in patients with known hypersensitivity to ACTEMRA. (4)

---------- 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. (5.1)

- Gastrointestinal (GI) perforation—use with caution in patients who may be at increased risk. (5.2)
- Hepatotoxicity- Monitor patients for signs and symptoms of hepatic injury. Modify or discontinue ACTEMRA if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop. (2.10, 5.3)
- Laboratory monitoring—recommended due to potential consequences of treatment-related changes in neutrophils, platelets, lipids, and liver function tests. (2.10, 5.4)
- Hypersensitivity reactions, including anaphylaxis and death have occurred. (5.6)
- Live vaccines—Avoid use with ACTEMRA. (5.9, 7.3)

---------- ADVERSE REACTIONS----------
Most common adverse reactions (incidence of at least 5%): upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased ALT, injection site reactions. (6)

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategy described in **Table 2**.

Table 2. FAERS Search Strategy*

Date of search	April 25, 2022
Time period of search	July 1, 2012† - April 3, 2022
Search type	RxLogix PV Reports Quick Query
Product terms	PAI: tocilizumab
MedDRA search terms (Version 25)	All PT terms

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

† DPV-I previously assessed the pediatric postmarketing safety of tocilizumab from January 8, 2010, to June 30, 2012.

Abbreviations: PAI=Product Active Ingredient, MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term

2.2 LITERATURE SEARCH STRATEGY

DPV-I searched the literature with the strategy described in **Table 3**.

Table 3. Literature Search		
Database	PubMed	Embase
Date of Search	May 3, 2022	
Search Terms	Tocilizumab	'tocilizumab'/exp
Limits	Publication dates 2012/7/1 – 2022/4/3, Humans, English, Case reports, Child: birth-18 years	Publication years 2012-2022 Humans, English, Case reports, Newborn, infant, child, preschool child, school child, adolescent

3 RESULTS

3.1 FAERS AND THE MEDICAL LITERATURE

3.1.1 Total Number of FAERS Reports by Age

Table 4 presents the number of adult and pediatric FAERS reports from July 1, 2012, through April 3, 2022 with tocilizumab.

Table 4. Total Adult and Pediatric FAERS Reports* Received by FDA From July 1 2012, through April 3, 2022 With Tocilizumab

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	34,419 (8,319)	29,687 (3,847)	2,691 (708)
Pediatrics (0 - <18 years)	1,071 (251)	933 (120)	72 (21)‡

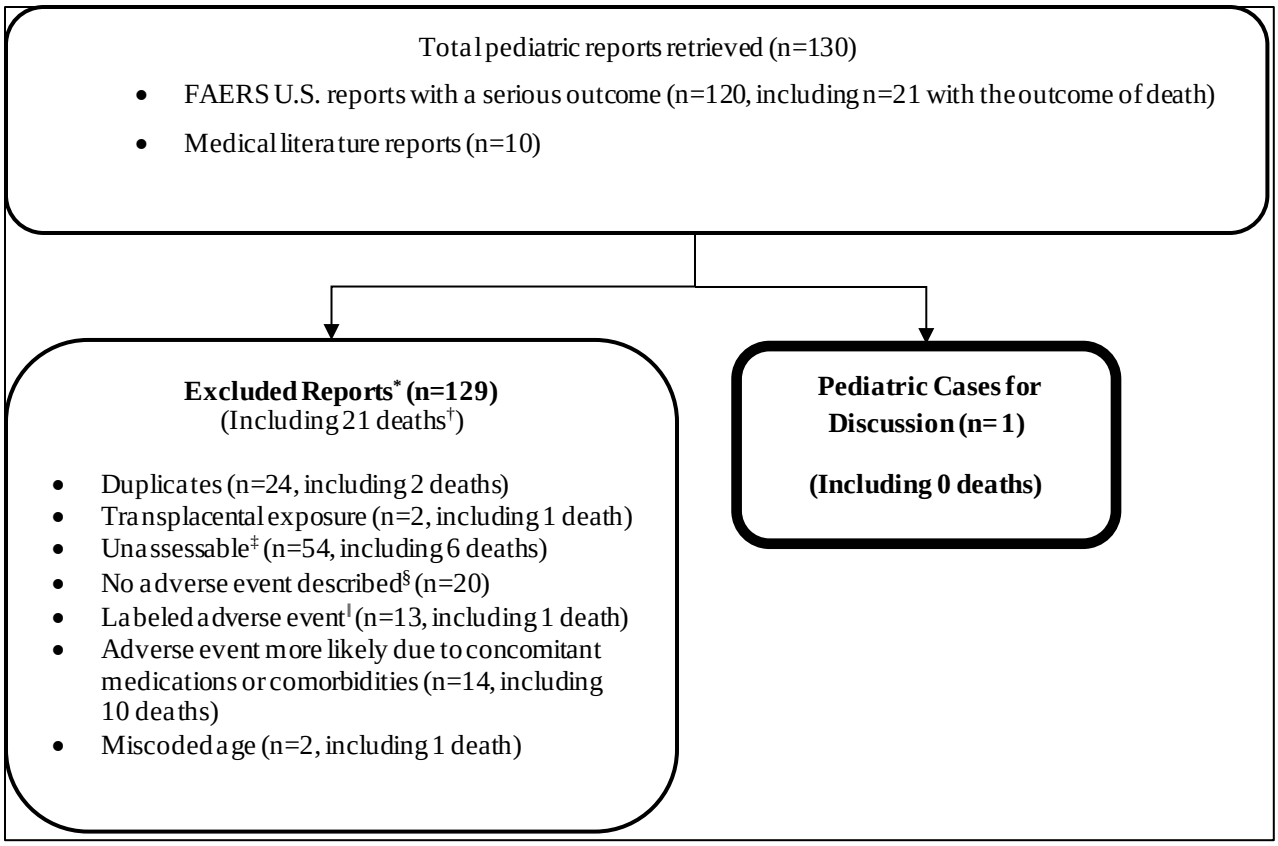
* May include duplicates and transplacental exposures, and have not been assessed for causality.
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.
‡ See Figure 1. Nine additional reports of pediatric deaths were identified among U.S. reports not reporting an age. These nine reports are reflected in the counts of pediatric reports.

3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS and the Medical Literature

Our FAERS search retrieved 120 U.S. serious pediatric reports from July 1, 2012, through April 3, 2022. The search of the medical literature retrieved ten additional pediatric adverse event reports with tocilizumab.

We reviewed all U.S. FAERS and medical literature pediatric reports with a serious outcome with tocilizumab. We excluded reports from the case series for various reasons: duplicate reports, unassessable reports, no adverse event described; labeled adverse event without new features, adverse event not causally related to tocilizumab use, age miscoded as pediatric, or transplacental exposure. **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious U.S. Pediatric Cases with Tocilizumab in FAERS and the Medical Literature



* DPV-I reviewed these reports, but they were excluded from further discussion for the reasons listed above.

† The FAERS search identified 21 fatal pediatric reports. After accounting for duplicate reports (n=2) and reports with miscoded age (n=1), there were 18 unique cases with a fatal outcome. One case described a 9-year-old female who received tocilizumab, developed the labeled adverse event of sepsis, and later died from septic complications. Ten cases involved patients 7-16 years old who received tocilizumab and died secondary to complications from underlying conditions (cytokine release syndrome n=3, juvenile idiopathic arthritis n=2, Still's disease n=2, graft versus host disease n=1, stem cell transplant n=1, and malignant atrophic papulosis n=1). The remaining seven cases did not report any substantive clinical information to perform causality assessments. These cases included a case describing a neonate with transplacental exposure to tocilizumab and died in the perinatal period, and six cases describing patients aged 1-16 years who received tocilizumab and died from unspecified conditions.

‡ Unassessable: Report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome) or the information is contradictory or information provided in the case cannot be supplemented or verified.

§ Reports of treatment failure, lack of effect, or administration error.

‖ Labeled adverse events include: serious infection, hypersensitivity, gastrointestinal perforation, elevated liver function tests, and infusion reaction.

3.1.3 Summary of Fatal Pediatric Cases in FAERS (N=0) and the Medical Literature (N=0)

There are no fatal pediatric adverse event cases for further discussion.

3.1.4 Summary of Non-Fatal Pediatric U.S. Serious Cases in FAERS (N=0) and the Medical Literature (N=1)

We did not identify any FAERS U.S. serious, unlabeled, non-fatal adverse event cases associated with tocilizumab in the pediatric population. We identified one case report in the medical literature describing an adverse event with tocilizumab in a pediatric patient.[22] The case is summarized below:

A 17-year-old male was treated with tocilizumab for juvenile idiopathic arthritis (JIA). Two days after treatment with tocilizumab, he developed acute bilateral blindness and retro-orbital pain. He had normal blood pressure and magnetic resonance imaging (MRI) was notable for "cortical and subcortical FLAIR hyperintense signals involving the occipital lobes with restricted diffusion and contrast enhancement." Findings were consistent with posterior reversible encephalopathy syndrome (PRES). Tocilizumab was discontinued and the patient's imaging findings improved with partial recovery of the visual symptoms.

Reviewer Comments: This case describes temporal association between tocilizumab exposure and onset of PRES symptoms as well as positive dechallenge. However, causality assessment is limited by missing information regarding prior exposures to tocilizumab, prior exposure to medications with known risks of PRES, concomitant medications, treatments given for PRES, and rechallenge attempts. Notably, JIA is also a risk factor for PRES. Additional risk factors of PRES include, but are not limited to: blood pressure fluctuations, renal failure, cytotoxic agents, and autoimmune conditions.[23] *For completeness, we searched the FAERS database for all reports of PRES through June 7, 2022, with the Product Active Ingredient tocilizumab and the MedDRA Preferred Term Posterior reversible encephalopathy syndrome. Our search identified two cases of PRES with tocilizumab in pediatric patients; the causality for both cases was unassessable. We do not have sufficient evidence to support a signal of PRES with tocilizumab at this time.*

4 DISCUSSION

We reviewed all medical literature cases and FAERS U.S. serious cases with tocilizumab in the pediatric population (ages 0 -< 18 years) during the period of July 1, 2012, through April 3, 2022. Our evaluation identified one case describing PRES with tocilizumab, however, there is insufficient evidence to support a new signal at this time.

5 CONCLUSION

DPV-I did not identify any new pediatric safety concerns for tocilizumab at this time.

6 RECOMMENDATION

DPV-I recommends no regulatory action at this time, and will continue to monitor all adverse events associated with the use of tocilizumab.

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

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 FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council 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 tradenames or active ingredients in the FAERS Product Dictionary (FPD).

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.

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