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Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

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Reviewers:	Jill K Logan, PharmD, BCPS, Safety Evaluator Division of Pharmacovigilance I (DPV-I) Ivone Kim, MD, Medical Officer DPV-I Tracy Pham, PharmD, Drug Utilization Analyst Division of Epidemiology II (DEPI-II)
Team Leaders:	Rajdeep Gill, PharmD DEPI-II Lisa Harinstein, PharmD, BCCCP DPV-I
Deputy Division Directors:	Travis Ready, PharmD, MS DEPI-II (Acting) Monica Muñoz, PharmD, PhD, MS, BCPS DPV-I
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports and drug utilization patterns for Orencia (abatacept) in pediatric patients. The Office of Surveillance and Epidemiology (OSE) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA). This review focuses on serious unlabeled adverse events associated with abatacept in pediatric patients. Abatacept utilization patterns in pediatric patients were also examined to provide context for the adverse event cases.

The FDA approved abatacept on December 23, 2005, as an intravenous (IV) formulation. A subcutaneous (SC) formulation was approved on July 29, 2011. Abatacept is indicated for the treatment of (1) adult rheumatoid arthritis (RA), (2) juvenile idiopathic arthritis (JIA), and (3) adult psoriatic arthritis (PsA). The approved pediatric labeling is for JIA in ages 6 years and older for the IV formulation and 2 years and older for the SC formulation.

Based on prescription and medical claims data from a sample of pharmacies, clinics, hospitals, and physician's offices, pediatric utilization of abatacept was low relative to the utilization in adult patients. A total of 631 pediatric patients younger than 18 years of age (2% of total 37,388 patients of any age) had a prescription or medical claim for abatacept in 2018 within the assessed database. Among pediatric patients, abatacept was most used by patients ages 12 - <18 years.

OSE searched the FAERS database for all pediatric (<18 years) reports coded with a serious outcome from July 7, 2009, through December 18, 2019. The search retrieved 368 reports, many of which contained limited information for assessment, did not report an adverse event, or described labeled adverse events consistent with the known safety-profile of abatacept. No increase in severity or frequency of labeled adverse events was identified within this review. No pediatric deaths were attributed to abatacept. We identified two cases of unlabeled events with serious outcomes. One case reported the adverse event of inflammatory bowel disease; however, limited information within the case made attribution of the events to abatacept difficult. We assessed that inflammatory bowel disease did not constitute a new safety signal because of the poor quality of data within the identified case and the known association of select autoimmune conditions with inflammatory bowel disease at baseline. The second case reported adverse events consistent with angioedema, an unlabeled adverse event. FDA opened a tracked safety issue (TSI #2077) for angioedema on May 29, 2019, and notified the Applicant of the potential safety signal. This case prompted a full review of postmarketing data in pediatric and adult patients for an association between angioedema and abatacept therapy. We identified 83 cases of angioedema with a possible (n=67) or probable (n=16) causal association with abatacept. As a result of this investigation, DPV recommended incorporation of the adverse event of angioedema into abatacept labeling within the Warnings and Precautions Section 5.2 Hypersensitivity. A full description of the angioedema and abatacept evaluation is described in a separate signal review.

Based on findings from this pediatric postmarketing pharmacovigilance review, OSE recommended further evaluation of the angioedema signal with abatacept. The angioedema signal evaluation was concurrent with the pediatric postmarketing pharmacovigilance review and is described in a separate document; the signal review led to abatacept labeling recommendations. OSE recommends no additional regulatory action based on this pediatric postmarketing pharmacovigilance review. DPV will continue to monitor all adverse events associated with abatacept use.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports and utilization patterns for Orencia (abatacept) in pediatric patients. The Office of Surveillance and Epidemiology (OSE) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA). This review focuses on serious unlabeled adverse events associated with abatacept in pediatric patients. Abatacept utilization patterns in pediatric patients were also examined to provide context for the adverse event cases.

1.1 PEDIATRIC REGULATORY HISTORY

Abatacept is a selective T cell costimulation modulator indicated for the treatment of (1) adult rheumatoid arthritis (RA), (2) juvenile idiopathic arthritis (JIA), and (3) adult psoriatic arthritis (PsA). Abatacept was initially approved for use on December 23, 2005, as an intravenous (IV) formulation. A subcutaneous (SC) formulation was approved on July 29, 2011. The following summarizes the pediatric regulatory history of abatacept.

December 23, 2005: Abatacept IV infusion was approved for the treatment of moderately to severely active RA to reduce signs and symptoms, inducing major clinical response, inhibiting progression of structural damage, and improving physical function in patients who have had an inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate or tumor necrosis factor (TNF) alpha antagonists.[1] At the time of approval, the sponsor agreed to investigate abatacept for the treatment of polyarticular JIA to fulfil their requirement under the Pediatric Research Equity Act (PREA).

April 7, 2008: The indication of abatacept was expanded to include the treatment of moderately to severely active polyarticular JIA in pediatric patients 6 years of age and older.[2] Approval in this population was based upon a randomized, double-blind, placebo-controlled trial conducted in 190 children (age 6-17 years) with JIA with at least 5 active joints and an inadequate response or intolerance to at least one DMARD.[3] All patients enrolled in this study received abatacept (10 mg/kg, maximum dose of 1000 mg) therapy for 4 months as open-label therapy. Those who achieved a 30 percent improvement according to the American College of Rheumatology (ACR) pediatric definition (n=60) were then randomized (1:1) to receive abatacept or placebo for 6 months of therapy or until an arthritis flare. At study conclusion, patients were given the option to enroll in a 5 year follow up open-label trial. The outcomes of the trial showed that the time to disease flare was shorter for patients given placebo than those given abatacept. The adverse events reported in the trial were similar to those reported with abatacept in the RA development program, and no new safety signals were identified.[3,4] The PREA study requirement was fulfilled for ages 6 to 16 with the submission of this study and remained outstanding for ages 2 to 5 years.

September 21, 2009: The Division of Pharmacovigilance (DPV) evaluated postmarketing adverse event reports for abatacept in pediatric patients ages 0-16 years.[4] DPV's evaluation, was prompted by the pediatric labeling changes on April 7, 2008, described above and DPV evaluated adverse events reported in the Adverse Event Reporting System (AERS) database from drug approval through July 7, 2009. FDA presented DPV's evaluation to the Pediatric Advisory Committee (PAC) on December 8, 2009.[5] DPV's evaluation did not identify any new safety concerns and recommended routine monitoring for adverse events with abatacept.[4,6]

July 29, 2011: The SC formulation of abatacept was approved for RA with the use of an initial IV loading dose.[7] The requirement for an IV loading dose prior to SC therapy for RA patients was removed on December 20, 2013.[8] The labeling was further updated on December 30, 2014, to state that the safety and efficacy of SC abatacept had not been studied in patients under 18 years of age.[9]

September 13, 2013: A Written Request was issued by FDA to the Applicant to conduct study IM101301, a pharmacokinetic (PK) and safety study of SC abatacept in patients with JIA ages 6 to 17 years of age.[10]

March 30, 2017: The weight-tiered dosing SC formulation was approved for the treatment of moderately to severely active polyarticular JIA in patients 2 years of age and older.[11] This pediatric labeling change stimulated the current pediatric postmarketing review. At this time, the Applicant's study commitment under PREA for ages 2 to 17 years was considered fulfilled and was waived for ages birth to less than 2 years. To support this supplemental Biologics License Application (sBLA), the Applicant submitted the following data:[10,12]

- NCT01844518[13] (Study IM101301): an open-label, PK, safety, and efficacy study of SC abatacept in 205 children (age 2 to 17 years) with active JIA. Thirty-two of the enrolled children were ages 2 to 5 years and were enrolled to fulfill a requirement from other regulatory agencies. Weight based dosing (10 to < 25 kg received 50 mg, 25 to < 50 kg received 87.5 mg, and ≥ 50 kg received 125 mg) was administered weekly for 4 months. The PK data supported the approval of SC abatacept for JIA. The safety analysis from this study did not identify any new safety signals. The open-label efficacy response over time secondary endpoint portion of the study was ongoing at the time of submission.

- NCT01357668[14] (Study IM101240) interim analysis: an observational, multicenter registry to describe long-term safety of IV abatacept treatment for JIA in routine clinical practice entitled, "An Observational Registry of Abatacept in Patients with Juvenile Idiopathic Arthritis." The interim analysis included 226 JIA patients, including 165 patients, within the safety analysis cohort that were exposed to abatacept for 12 or more months of therapy. There were 22 reported adverse events in 18 (8%) patients. The FDA

clinical reviewer noted that the incidence rates of adverse events observed were within the range of published incidence rates and no new safety signals were identified.

- Observational registry studies: observational data of JIA patients receiving abatacept from the administrative healthcare claims data base (Truven Health MarketScan) and the Swedish Pediatric Registry of Rheumatology were submitted to FDA. The FDA reviewer found the datasets to be similar between the two sources as well as the interim analysis of NCT01357668.

June 30, 2018: Abatacept was approved for the indication of PsA in adult patients.[15]

1.2 HIGHLIGHTS OF LABELED SAFETY INFORMATION

Select safety information from the Orencia labeling (revised 3/2019) is included below:[16]

5 WARNINGS AND PRECAUTIONS

5.1 Concomitant Use with TNF Antagonists

In controlled clinical trials in patients with adult RA, patients receiving concomitant intravenous ORENCIA and TNF antagonist therapy experienced more infections (63%) and serious infections (4.4%) compared to patients treated with only TNF antagonists (43% and 0.8%, respectively). These trials failed to demonstrate an important enhancement of efficacy with concomitant administration of ORENCIA with TNF antagonists; therefore, concurrent therapy with ORENCIA and TNF antagonists is not recommended. While transitioning from TNF antagonist therapy to ORENCIA therapy, patients should be monitored for signs of infection.

5.2 Hypersensitivity

In clinical trials of 2688 adult RA patients treated with intravenous ORENCIA, there were two cases (<0.1%) of anaphylaxis or anaphylactoid reactions. Other reactions potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in less than 0.9% of ORENCIA-treated patients. Of the 190 patients with juvenile idiopathic arthritis treated with ORENCIA in clinical trials, there was one case of hypersensitivity reaction (0.5%). Appropriate medical support measures for the treatment of hypersensitivity reactions should be made available for immediate use in the event of a reaction. Anaphylaxis or anaphylactoid reactions can occur after the first infusion and can be life threatening. In postmarketing experience, a case of fatal anaphylaxis following the first infusion of ORENCIA has been reported. If an anaphylactic or other serious allergic reaction occurs, administration of ORENCIA should be stopped immediately with appropriate therapy instituted, and the use of ORENCIA should be permanently discontinued.

5.3 Infections

Serious infections, including sepsis and pneumonia, have been reported in patients receiving ORENCIA. Some of these infections have been fatal. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy which in addition to their underlying disease, could further predispose them to infection. Physicians should exercise caution when considering the use of ORENCIA in patients with a history of recurrent infections, underlying conditions with may predispose them to infection, or chronic, latent, or localized infections. Patients who develop a new infection while undergoing treatment with ORENCIA should be monitored closely. Administration of ORENCIA should be discontinued if a patient develops a serious infection. A higher rate of serious infections has been observed in RA patients treated with concurrent TNF antagonists and ORENCIA.

Prior to initiating immunomodulatory therapies, including ORENCIA, patients should be screened for latent tuberculosis infection with a tuberculin skin test. ORENCIA has not been studied in patients with a positive tuberculosis screen, and the safety of ORENCIA in individuals with latent tuberculosis infection is unknown.

Patients testing positive in tuberculosis screening should be treated by standard medical practice prior to therapy with ORENCIA.

Antirheumatic therapies have been associated with hepatitis B reactivation. Therefore, screening for viral hepatitis should be performed in accordance with published guidelines before starting therapy with ORENCIA. In clinical studies with ORENCIA, patients who screened positive for hepatitis were excluded from study.

5.4 Immunizations
Live vaccines should not be given concurrently with ORENCIA or within 3 months of its discontinuation. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving ORENCIA. The efficacy of vaccination in patients receiving ORENCIA is not known. Based on its mechanism of action, ORENCIA may blunt effectiveness of some immunizations.

It is recommended that patients with juvenile idiopathic arthritis be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating ORENCIA therapy.

5.5 Use in Patients with Chronic Obstructive Pulmonary Disease (COPD)
Adult COPD patients treated with ORENCIA developed adverse events more frequently than those treated with placebo, including COPD exacerbations, cough, rhonchi, and dyspnea. Use of ORENCIA in patients with RA and COPD should be undertaken with caution and such patients should be monitored for worsening of their respiratory status.

5.6 Immunosuppression
The possibility exists for drugs inhibiting T cell activation, including ORENCIA, to affect host defenses against infections and malignancies since T cells mediate cellular immune responses. The impact of treatment with ORENCIA on the development and course of malignancies is not fully understood. In clinical trials in patients with adult RA, a higher rate of infections was seen in ORENCIA-treated patients compared to placebo.

6 ADVERSE REACTIONS
6.1 Clinical Studies Experience in Adult RA Patients Treated with Intravenous Orencia

- Most commonly reported adverse events (occurring in ≥10% of patients treated with Orencia) were headache, upper respiratory tract infection, nasopharyngitis, and nausea.
- The adverse events most frequently resulting in clinical intervention (interruption or discontinuation were due to infection. The most frequently reported infections resulting is dose interruption were upper respiratory tract infection (1.0%), bronchitis (0.7%), and herpes zoster (0.7%). The most frequent infections resulting in discontinuation were pneumonia (0.2%), localized infection (0.2%), and bronchitis (0.1%).
- Adverse events occurring in 3% or more of patients and at least 1% more frequently in Orencia-treated patients during placebo-controlled RA studies: headache, nasopharyngitis, dizziness, cough, back pain, hypertension, dyspepsia, urinary tract infection, rash, pain in extremities.

6.3 Clinical Studies Experience in Juvenile Idiopathic Arthritis Patients Treated with Intravenous Orencia

- In general, the adverse events in pediatric patients were similar in frequency and type to those seen in adult patients.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategies described in Table 1.

Table 1. FAERS Search Strategy*		
	Query 1	**Query 2**
Date of Search	December 27, 2018	December 19, 2019
Time Period of Search	July 7, 2009† - November 26, 2018	November 27, 2018 – December 18, 2019
Search Type	Drug Safety Analytics Dashboard Quick Search	
Product Terms	Product Active Ingredient: Abatacept	
MedDRA Search Terms (Version 21.1)	All Preferred Terms (PTs)	

* See Appendix A for a description of the FAERS database.
† DPV previously assessed the pediatric postmarketing safety of abatacept from December 26, 2005, to July 7, 2009. Therefore, a data lock date of July 7, 2009, was used to inform the start date of this review.

2.2 DRUG UTILIZATION

Proprietary databases available to the FDA were used to conduct the drug utilization analyses in this review. See Appendix B for full database descriptions.

2.2.1 Determining Settings of Care

The IQVIA National Sales Perspectives™ (NSP) database was used to determine the primary setting of care for abatacept utilization based on the estimated number of abatacept vials and syringes sold from the manufacturer to various settings of care in 2018.

2.2.2 Patient Data

The Symphony Health Integrated Dataverse (IDV) database was used to provide the annual number of patients who had a prescription or a medical claim (J0129) for abatacept, stratified by patient age (<2, 2 - <12, 12 - <18, and ≥18 years), from 2015 to 2018 based on a sample of 8,049 pharmacies such as retail and mail-order/specialty, and 2,534 clinics, hospitals, and physician's offices in the United States. Patients' claims histories were searched based on the occurrence of one or more abatacept prescription or medical claim(s) during the study period. In addition, a 90-days look-back period was used to identify the number of patients with a prior prescription or medical claim that allowed for at least one day of abatacept therapy during the study period. For example, patients who did not have a prescription filled during the study period would also be counted as using abatacept if they filled a prescription during the 90 days prior to the study period, and the fill date of their prescription plus its day supply extended into the study period by one day or more. In addition, a 50% grace period was added to the prescription total days supplied time window to allow for delays in prescription filling. For example, if the total days supplied for a prescription is 30 days, a 50% grace period would add 15 more days to the prescription days supplied time window for a total of 45 days of therapy.

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from July 7, 2009, through December 18, 2019, with abatacept.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA from July 7, 2009, through December 18, 2019, with Abatacept

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	27,704 (11,964)	19,744 (816)	1,221 (326)
Pediatrics (0 - <18 years)	473 (172)	**368 (71)**	**9** (3)

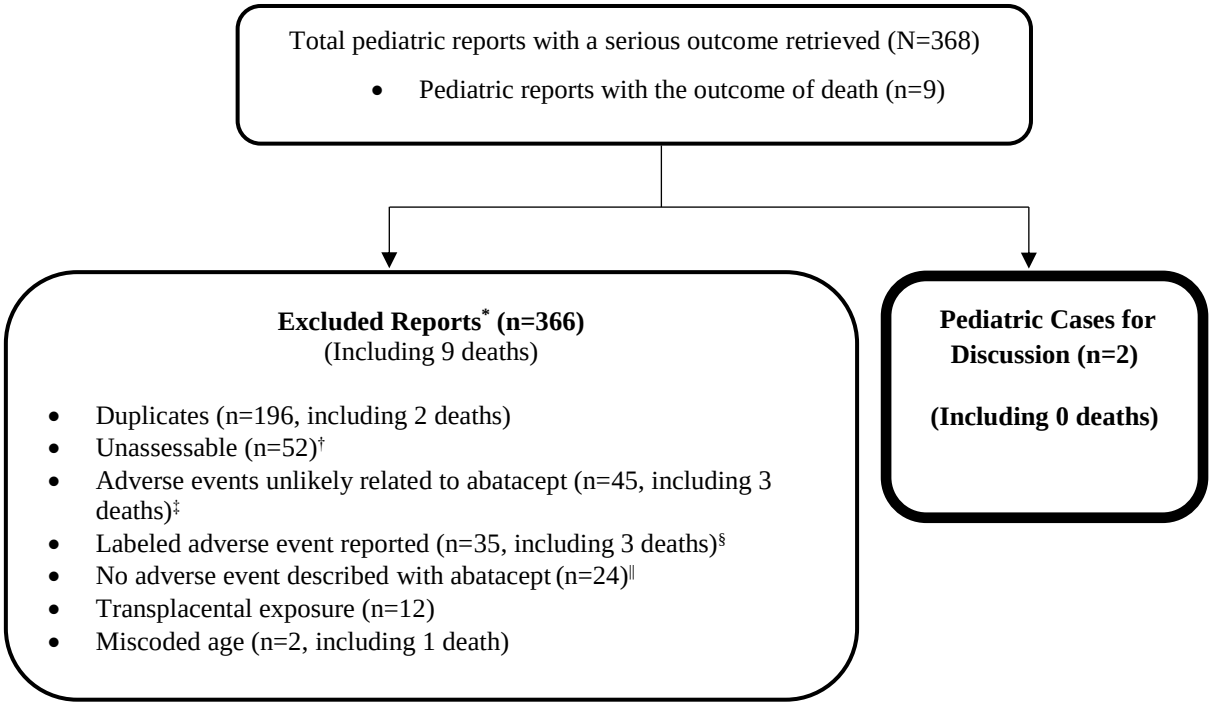
* May include duplicates and transplacental exposures, and have not been assessed for causality

† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS searches retrieved a combined total of 368 serious pediatric reports from July 7, 2009, through December 18, 2019. Results from these searches are as seen in Figure 1.

Figure 1. Selection of Serious Pediatric Cases with Abatacept



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

† 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), the information is contradictory, or the information provided in the report cannot be supplemented or verified.

‡ The 45 reports assessed to have an "unlikely" relationship to abatacept therapy described the following:

- complications of bone marrow transplantation (n=16, including 2 deaths),
- JIA symptoms and complications (n=14; uveitis (n=5), arthritis (n=4), joint destruction (n=1), inflammation (n=1), increased erythrocyte sedimentation rate (n=1), arthralgias and decreased range of motion (n=1), JIA flair not otherwise specified (n=1)),
- presence of a strong alternative cause for the reported event (n=9; broken bone attributed to sports injuries (n=2), erythema multiforme in the presence of a viral infection (n=1), colitis symptoms reported in a patient with lipopolysaccharide-responsive vesicle trafficking for which the physician planned to increase the abatacept dose (n=1), renal impairment attributed to amyloidosis (n=1), thrombotic microangiopathy due to nephrotic syndrome (n=1), exacerbation of underlying pulmonary arterial hypertension (n=1), death attributed to congenital heart disease (n=1), suicide attempt in a patient with strong psychiatric history (n=1)),
- adverse events where the symptoms preceded abatacept initiation (n=4; anemia and inflammatory bowel disease (IBD) (n=1), ulcerative colitis (n=1), hemorrhage and thrombocytopenia (n=1), and anemia (n=1)),
- development of an abscess 4-months after abatacept discontinuation (n=1),
- and elevated transaminase levels that resolved despite continued abatacept therapy (n=1).

§ The 35 reports of labeled adverse events included infections (n=18, including 3 deaths), hypersensitivity (n=6), abdominal pain (n=3), neoplasms (n=2), rash (n=2), headache (n=2), pyrexia (n=1), and psoriasis with multiple sclerosis (n=1).

‖ The 24 reports where no adverse event was described with abatacept reported lack of abatacept efficacy (n=20), central venous catheter insertion (n=1), device malfunction (n=1), accidental exposure to abatacept (n=1), and blood hemolysis in a test tube (n=1).

3.1.3 Characteristics of Pediatric Cases

Our FAERS searches retrieved two serious cases from July 7, 2009, through December 18, 2019. Both cases reported IV administration of abatacept; one for the treatment of spondyloarthritis

and the other for an unreported indication. See Appendix C for a line listing of the 2 serious pediatric cases.

3.1.4 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event cases.

3.1.5 Summary of All Pediatric Serious Cases (N=2)

We identified two FAERS cases with abatacept in the pediatric population reporting a non-fatal unlabeled serious adverse event. One case was reported from the United States and the other was a case from Finland. Both cases are summarized below.

3.1.5.1 Throat and Tongue Swelling (N=1)

FAERS Case#13557016, serious outcome—life threatening, United States, 2017: A 16-year-old female received a total of five infusions of IV abatacept therapy (administered every 4 weeks, dose not reported) for a 3-year history of spondyloarthritis. Concomitant medications included contraception with medroxyprogesterone and as needed acetaminophen and ibuprofen. She had previously been treated with infliximab; however, she was unable to tolerate this medication because of a "delayed anaphylactic reaction." She presented to the emergency department 3 days after her fifth abatacept infusion with complaints of eye and tongue swelling and tingling. She was treated with methylprednisolone 125 mg IV and famotidine 20 mg (route not specified). The following day, the patient returned to the emergency department with tongue swelling and a feeling of "throat closing off." She was drooling slightly but did not have any wheezing or respiratory distress. She was admitted to the hospital for evaluation and reportedly improved after treatment with epinephrine (dose and route not reported), methylprednisolone 80 mg IV, diphenhydramine 25 mg (route not reported), famotidine (dose and route not reported), and an unspecified IV fluid bolus. Her symptoms of lip and tongue swelling returned without respiratory distress or drooling and she required three doses of intramuscular epinephrine over 6-8 hours followed by an epinephrine infusion of 0.1-0.16 mcg/kg/min. She was intubated for airway protection. Three days after her initial symptom development, her swelling was noted to continue to be unresponsive to clinical interventions and she remained intubated.

Reviewer comment: This is a well-documented direct report from a healthcare professional (pharmacist) with aspects consistent with angioedema. The symptoms reported are clinically significant as the patient required hospitalization, multiple pharmacologic interventions, and intubation for airway protection. Angioedema may be related to abatacept therapy; however, this patient was also being treated with as needed ibuprofen. Non-steroidal anti-inflammatory

drugs have been associated with the development of angioedema[17] and this concomitant medication represents a possible alternative etiology for the reported adverse event.

3.1.5.2 Inflammatory Bowel Disease (N=1)

FAERS Case#8664359, serious outcome—hospitalization, Finland, 2012: An 11-year-old female patient initiated abatacept 500 mg IV monthly for an unknown indication. Concomitant medications included leflunomide 20 mg tablets and cyclosporine 100 mg capsules (frequencies and indications not reported). Approximately 6 months after abatacept initiation, the patient was hospitalized for bloody diarrhea and mild anemia. Laboratory tests for infection (bacterial and viral) were negative and a "scopy" examination revealed "serious colitis" in the distal colon. Abatacept was discontinued and the patient was initiated on sulfasalazine and infliximab. It was reported that the patient experienced an allergic reaction to the new medication regimen, however, it is unclear if sulfasalazine and infliximab were continued. Approximately 4 months after abatacept discontinuation, a follow-up "scopy" showed the colitis to be in remission.

Reviewer comment: Although the association between abatacept administration and the development of colitis would represent a new safety signal, the causality within this case is difficult to assess. Autoimmune diseases such as ankylosing spondylitis and RA have been associated with IBD.[18] Because the indication for abatacept was not reported, it is unclear if the patient was treated with abatacept for IBD as an off-label therapy or for a disease state which has been associated with IBD. Additionally, the patient reported concomitant leflunomide, which has been associated with the development of colitis[19] and potentially could have contributed to disease development. Based upon this single case, colitis does not represent a new safety signal with abatacept, and the potential signal will be monitored through continued pharmacovigilance.

3.2 DRUG UTILIZATION DATA

3.2.1 Settings of Care

In 2018, approximately 82% and 11% of abatacept vials were sold to the clinics and non-federal hospitals, respectively, while 75% and 17% of abatacept syringes were sold to the mail-order/specialty and retail settings, respectively. Therefore, this review examined abatacept utilization from various U.S. settings of care such as clinics, hospitals, and retail settings.[20]

3.2.2 Patient Data

Table 3 below provides the annual number of patients who had a prescription or medical claim (J0129) for abatacept based on a sample of pharmacies, clinics, hospitals, and physician's offices in the United States. Abatacept utilization in pediatric patients younger than 18 years of age was considerably lower than utilization in adult patients. In 2018, a total of 37,388 patients had a prescription or medical claim for abatacept; of these, pediatric patients younger than 18 years of

age accounted for approximately 2% (631 patients). Among pediatric patients, 72% were patients ages 12 - <18 years in 2018.

Table 3. Annual Number of Patients who had a Prescription or Medical Claim (J0129) for Abatacept Based on a Sample of Pharmacies, Clinics, Hospitals, and Physician's Offices in the U.S., 2015-2018

	Year							
	2015		2016		2017		2018	
	Patients	%	Patients	%	Patients	%	Patients	%
Total Abatacept Patients	31,276	*100.0%*	32,588	*100.0%*	34,232	*100.0%*	37,388	*100.0%*
0 - <18 years	362	*1.2%*	375	*1.2%*	493	*1.4%*	631	*1.7%*
0 - <2 years	--	--	2	*0.5%*	2	*0.4%*	8	*1.3%*
2 - <12 years	83	*22.9%*	92	*24.5%*	146	*29.6%*	171	*27.1%*
12 - <18 years	279	*77.1%*	281	*74.9%*	345	*70.0%*	452	*71.6%*
≥ 18 years	30,911	*98.8%*	32,211	*98.8%*	33,735	*98.5%*	36,752	*98.3%*
Unknown Age	3	*<0.1%*	2	*<0.1%*	4	*<0.1%*	5	*<0.1%*

Source: Symphony Health Integrated Dataverse, 2015-2018. Data extracted July 2019.
*Patients may not sum exactly and may be counted more than once across time periods. Therefore, summing patients across time periods is not advisable and will result in overestimates of patient counts.
Patient estimates were obtained from a sample of 8,049 pharmacies such as retail and mail-order/specialty, and 2,534 clinics, hospitals, and physician's offices in the U.S.

4 DISCUSSION

For this Pediatric Postmarketing review, we analyzed the pediatric drug utilization patterns with abatacept from 2015 to 2018, and all 368 pediatric (age < 18 years) FAERS reports with a serious outcome reported with abatacept from July 7, 2009, through December 18, 2019.

Abatacept utilization in pediatric patients younger than 18 years of age was low relative to the utilization in adult patients. A total of 631 pediatric patients younger than 18 years of age had a prescription or medical claim for abatacept in 2018 within the IDV database. Drug use findings should be interpreted in the context of the known limitations of the database used. Patient counts were obtained from a robust sample of pharmacies, clinics, hospitals, and physician's offices; however, the data cannot be validated due to lack of access to medical records in the database. Additionally, data are not nationally projected and may not represent abatacept utilization patterns in the United States.

Many of the pediatric reports identified within the FAERS database contained limited information for assessment, did not report an adverse event, or described labeled adverse events consistent with the known safety-profile of abatacept. No increase in severity or frequency of labeled adverse events was identified within this review. No pediatric deaths were attributed to abatacept. Of the 368 reports reviewed, we identified two cases of unlabeled events with serious

outcomes. One case reported the adverse event of IBD; however, limited information within the case made attribution of the events to abatacept difficult. We determined that IBD does not constitute a new safety signal because of the poor quality of data within the identified case and the known association of select autoimmune conditions with IBD at baseline. The second case reported adverse events consistent with angioedema, an unlabeled adverse event. FDA opened a tracked safety issue (TSI #2077) for angioedema on May 29, 2019, and notified the Applicant of the potential safety signal. This case prompted a full review of postmarketing data in pediatric and adult patients assessing for an association between angioedema and abatacept therapy. DPV evaluated the safety signal of angioedema and abatacept through an extended search of the FAERS database and medical literature. We identified 83 cases of angioedema with a possible (n=67) or probable (n=16) causal association with abatacept. As a result of this investigation, DPV recommended incorporation of the adverse event of angioedema into abatacept labeling within the Warnings and Precautions Section 5.2 Hypersensitivity. A full description of the angioedema and abatacept evaluation is described in a separate signal review.

5 CONCLUSION

OSE identified angioedema as a safety signal with abatacept therapy and labeling has been updated accordingly. Although only one adverse event was identified, the use of abatacept in the pediatric population was low when compared to the adult population and continued pharmacovigilance is recommended to ensure continued safe medication use. The labeled adverse events reported in FAERS for abatacept in the pediatric population are consistent with the known adverse events described in labeling; there is no evidence of increased frequency or severity for these labeled events. The FAERS database analysis and the drug utilization data do not suggest a change in the overall benefit-risk profile for pediatric abatacept use.

6 RECOMMENDATION

Based on findings from this pediatric postmarketing pharmacovigilance review, OSE recommended further evaluation of the angioedema signal with abatacept. The angioedema signal evaluation was concurrent with the pediatric postmarketing pharmacovigilance review and is described in a separate document; the signal review led to abatacept labeling recommendations. OSE recommends no additional regulatory action based on this pediatric postmarketing pharmacovigilance review. DPV will continue to monitor all adverse events associated with abatacept use.

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

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 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.

8.2 APPENDIX B. DRUG UTILIZATION DATABASE DESCRIPTIONS AND LIMITATIONS

IQVIA National Sales Perspectives™ (NSP)

The IQVIA 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.

The manufacturer sales distribution data do not provide an estimate of direct patient use but do provide a national estimate of units sold from the manufacturer to various retail and non-retail settings of care. The amount of product purchased by these settings of care may be a possible surrogate for use if we assume that facilities purchase drugs in quantities reflective of actual patient use.

Symphony Health IDV® (Integrated Dataverse)

IDV (Integrated Dataverse) from Symphony Health contains longitudinal patient data sources that capture adjudicated prescription, medical, and hospital claims across the United States for all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. The IDV contains over 10 billion prescriptions claims linked to over 280 million unique prescription patients of with an average of 5 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-9/10 diagnosis history of which nearly 180 million prescription drug patients are linked to a diagnosis. The overall sample represents over 65,000 pharmacies, 1,500 hospitals, 800 outpatient facilities, and 80,000 physician practices.

8.3 APPENDIX C. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES WITH ABATACEPT (N=2)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	5/17/2017	13557016	1		Direct	16	Female	United States	LT
2	7/13/2012	8664359	1	FI-BRISTOL-MYERS SQUIBB COMPANY-16742744	Expedited	11	Female	Finland	HO

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case may have more than one serious outcome.
Abbreviations: HO=Hospitalization, LT= Life-threatening

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JILL K LOGAN
03/04/2020 09:57:28 AM

IVONE E KIM
03/04/2020 10:15:03 AM

TRACY M PHAM
03/04/2020 10:29:19 AM

RAJDEEP K GILL
03/04/2020 10:46:59 AM

LISA M HARINSTEIN
03/04/2020 11:32:53 AM

TRAVIS W READY
03/06/2020 09:30:25 AM

MONICA MUNOZ
03/06/2020 11:38:26 AM