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 Postmarketing Pharmacovigilance Review

Date: April 8, 2021

Safety Evaluator: Omayma Kishk, PharmD, BCPPS
Division of Pharmacovigilance I

Medical Officer: Ivone Kim, MD, FAAP
Division of Pharmacovigilance I

Team Leader: Carmen Cheng, PharmD
Division of Pharmacovigilance I

Division Director: Cindy Kortepeter, PharmD
Division of Pharmacovigilance I

OSE RCM #: 2020-2351

Product Name	**Application Type/Number**	**Applicant**	**Pediatric Labeling Approval Date**
Enbrel (etanercept)	BLA 103795	Amgen	November 4, 2016
Erelzi (etanercept-szzs)	BLA 761042	Sandoz	-
Eticovo (etanercept-ykro)	BLA 761066	Samsung Bioepis Co. Ltd	-

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for etanercept, etanercept-szzs, and etanercept-ykro in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with etanercept in pediatric patients.

The FDA first approved etanercept on November 2, 1998, and it is indicated for reduction in signs and symptoms of moderately to severely active rheumatoid arthritis in patients who have had an inadequate response to one or more disease-modifying antirheumatic drugs. The approved pediatric labeling is for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in patients aged 2 and older. On November 4, 2016, the FDA approved etanercept for the treatment of patients 4 years or older with chronic moderate to severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy. This pediatric postmarketing review was stimulated by the November 4, 2016 pediatric labeling change.

We reviewed all serious U.S. FAERS reports with etanercept, etanercept-szzs, and etanercept-ykro in the pediatric population (ages 0 to <18 years) during the period of November 4, 2015 – September 30, 2020. Our FAERS search did not identify reports with etanercept-szzs or etanercept-ykro in pediatric patients. Of the 476 reports for etanercept, we excluded 465 reports from the case series for various reasons, such as if the adverse event was unlikely to be causally related to the use of etanercept (e.g., the report was confounded by co-morbid diseases or concomitant medications), reporting lack of efficacy, event occurred prior to etanercept exposure, duplicates, transplacental exposures, labeled adverse events, miscoded age reports, or no exposure to etanercept. Of the 11 cases that were included for the case series, there were no pediatric deaths. There were single cases for events identified for the majority of the cases, and no specific pattern of adverse events was identified.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for etanercept, etanercept-szzs, and etanercept-ykro in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with etanercept in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Product Information and Dosing

Etanercept is a dimeric soluble form of the p75 tumor necrosis factor (TNF) receptor that binds TNF molecules. Etanercept works by inhibiting TNF-α and TNF-β binding to the TNF receptor cell surface which makes the TNF biologically inactive. The FDA initially approved Enbrel (etanercept) on November 2, 1998 for the reduction in signs and symptoms of moderately to severely active rheumatoid arthritis in patients who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs).[1]

Etanercept is currently approved for the following indications:

- Rheumatoid arthritis (RA),
- Psoriatic arthritis (PsA),
- Ankylosing spondylitis (AS)
- Plaque psoriasis (PsO) in patients aged ≥4 years old, and
- Polyarticular juvenile idiopathic arthritis (JIA) in patients aged ≥2 years old

On May 17, 1999, the FDA approved etanercept for use in pediatric patients 4 years and older for polyarticular juvenile rheumatoid arthritis (now JIA).[1] On November 18, 2010, the approval for etanercept was expanded to include pediatric patients 2 years and older for JIA. On November 4, 2016, the FDA approved etanercept for the treatment of patients 4 years or older with chronic moderate to severe PsO who are candidates for systemic therapy or phototherapy.

There are currently two biosimilars to etanercept approved in the U.S. The FDA approved the first biosimilar, Erelzi (etanercept-szzs), on August 30, 2016. The FDA approved the second biosimilar, Eticovo (etanercept-ykro), on April 25, 2019. The currently approved pediatric indications for etanercept-szzs and etanercept-ykro are: 1) polyarticular JIA in patients aged 2 year or older and 2) PsO in patients 4 years and older.

The recommended pediatric dosing of etanercept for PsO or JIA for pediatric patients who weigh less than 63 kg is 0.8 mg/kg weekly and for patients who weigh 63 kg or more is 50 mg weekly.[2] The pediatric dosing of etanercept-szzs and etanercept-ykro for PsO or JIA is 50 mg weekly in patients who weigh 63 kg or more (there is no dosage form for these two products that allows weight based-dosing for pediatric patients who weigh less than 63 kg). Etanercept and its biosimilars are administered by subcutaneous injection.[2-4]

Most Recent Pediatric Labeling Change

This pediatric postmarketing review was stimulated by the November 4, 2016 pediatric labeling change for etanercept with its approval for the treatment of chronic moderate to severe PsO in patients ≥4 years old.[2]

The efficacy of etanercept to support this pediatric indication was supported by a 48-week, randomized, double-blind, placebo-controlled study that enrolled 211 pediatric subjects 4 to 17 years old with moderate to severe PsO. Subjects received Enbrel 0.8 mg/kg (maximum dose of 50 mg) or placebo once weekly for the first 12 weeks. Evaluated outcomes included the Static Physician's Global Assessment (sPGA) and Psoriasis Area and Severity Index (PASI). The sPGA is a 6-category scale ranging from "5 = severe" to "0 = none" indicating the physician's overall assessment of the PsO severity focusing on induration, erythema, and scaling. Treatment success of "clear" or "almost clear" consisted of none or minimal elevation in plaque, up to faint red coloration in erythema and none or minimal fine scale over < 5% of the plaque. PASI is a tool used to measure the severity and extent of psoriasis.

A total of 106 subjects received Enbrel with 60 subjects (57%) who achieved a PASI score reduction of at least 75% from baseline, 29 subjects (27%) who achieved a PASI score reduction of at least 90% from baseline, and 55 subjects (52%) who had a sPGA of "clear" or "almost clear."

After the first 12 weeks, subjects entered a 24-week open-label period in which all subjects received the same Enbrel dose. In order to evaluate maintenance or response, subjects achieving PASI 75 response at Week 36 were re-randomized to Enbrel or placebo during a 12-week randomized withdrawal period. The maintenance of PASI 75 response was evaluated at Week 48. The proportion of subjects who maintained PASI 75 response at Week 48 was higher for subjects treated with Enbrel (65%) compared to those treated with placebo (49%).[2]
The adverse reactions reported in this 48-week clinical study in 211 pediatric subjects were similar to those seen in previous studies in adults with PsO. No new safety signals were identified in an open-label extension study (up to 264 additional weeks).[2]

Past Pediatric Review

DPV has not previously presented a pediatric evaluation on etanercept to the Pediatric Advisory Committee (PAC).

1.2 RELEVANT LABELED SAFETY INFORMATION

The following are excerpts from the Enbrel[2] labeling.

From HIGHLIGHTS OF PRESCRIBING SECTION:

WARNING: SERIOUS INFECTIONS and MALIGNANCIES
See full prescribing information for complete boxed warning.

SERIOUS INFECTIONS

- **Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens. (5.1)**
- **Enbrel should be discontinued if a patient develops a serious infection or sepsis during treatment. (5.1)**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting Enbrel. (5.1)**
- **Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)**

MALIGNANCIES

- **Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including Enbrel. (5.3)**

----------**CONTRAINDICATIONS**----------

Sepsis (4)

----------**WARNINGS AND PRECAUTIONS**----------

- Do not start Enbrel during an active infection. If an infection develops, monitor carefully and stop Enbrel if infection becomes serious. (5.1)
- Consider empiric anti-fungal therapy for patients at risk for invasive fungal infections who develop a severe systemic illness on Enbrel (those who reside or travel to regions where mycoses are endemic). (5.1)
- Demyelinating disease, exacerbation or new onset, may occur. (5.2)
- Cases of lymphoma have been observed in patients receiving TNF-blocking agents. (5.3)
- Congestive heart failure, worsening or new onset, may occur. (5.4)
- Advise patients to seek immediate medical attention if symptoms of pancytopenia or aplastic anemia develop, and consider stopping Enbrel. (5.5)
- Monitor patients previously infected with hepatitis B virus for reactivation during and several months after therapy. If reactivation occurs, consider stopping Enbrel and beginning anti-viral therapy. (5.6)
- Anaphylaxis or serious allergic reactions may occur. (5.7)
- Stop Enbrel if lupus-like syndrome or autoimmune hepatitis develops. (5.9)

----------**ADVERSE REACTIONS**----------

Most common adverse reactions (incidence > 5%): infections and injection site reactions. (6.1)

From Pediatric Use subsection:

Enbrel has been studied in 69 children with moderately to severely active polyarticular JIA aged 2 to 17 years.

Enbrel has been studied in 211 pediatric patients with moderate to severe PsO aged 4 to 17 years.

Enbrel has not been studied in children < 2 years of age with JIA and < 4 years of age with PsO. For pediatric specific safety information concerning malignancies and inflammatory bowel disease, [*see Warnings and Precautions (5.3) and Adverse Reactions (6.2])*.

The clinical significance of infant exposure to Enbrel *in utero* is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to exposed infants. For pediatric specific safety information concerning vaccinations, *[see Warnings and Precautions (5.8) and Drug Interactions (7.1])*.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

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

Table 1. FAERS Search Strategy*	
Date of search	10/21/2020
Time period of search	11/04/2015† - 09/30/2020
Search type	FBIS Quick Query, Product-Manufacturer Reporting Summary
Product terms	Product Active Ingredient: Etanercept, etanercept-szzs, etanercept-ykro
MedDRA search terms (Version 23.1)	All Preferred Terms (PTs)
* See Appendix A for a description of the FAERS database. † One year prior to most recent pediatric labeling change date FBIS = FDA Business Intelligence System	

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 with etanercept, etanercept-szzs, and etanercept-ykro received by FDA from November 4, 2015 to September 30, 2020.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From 11/04/2015 to 09/30/2020 With Etanercept, Etanercept-szzs, Etanercept-ykro			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	154,249 (121,192)	56,883 (24,046)	2,897 (755)
Pediatrics (0 - <18 years)	6,963 (5,713)	1,448 (476)	79 (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, or other serious important medical events.			

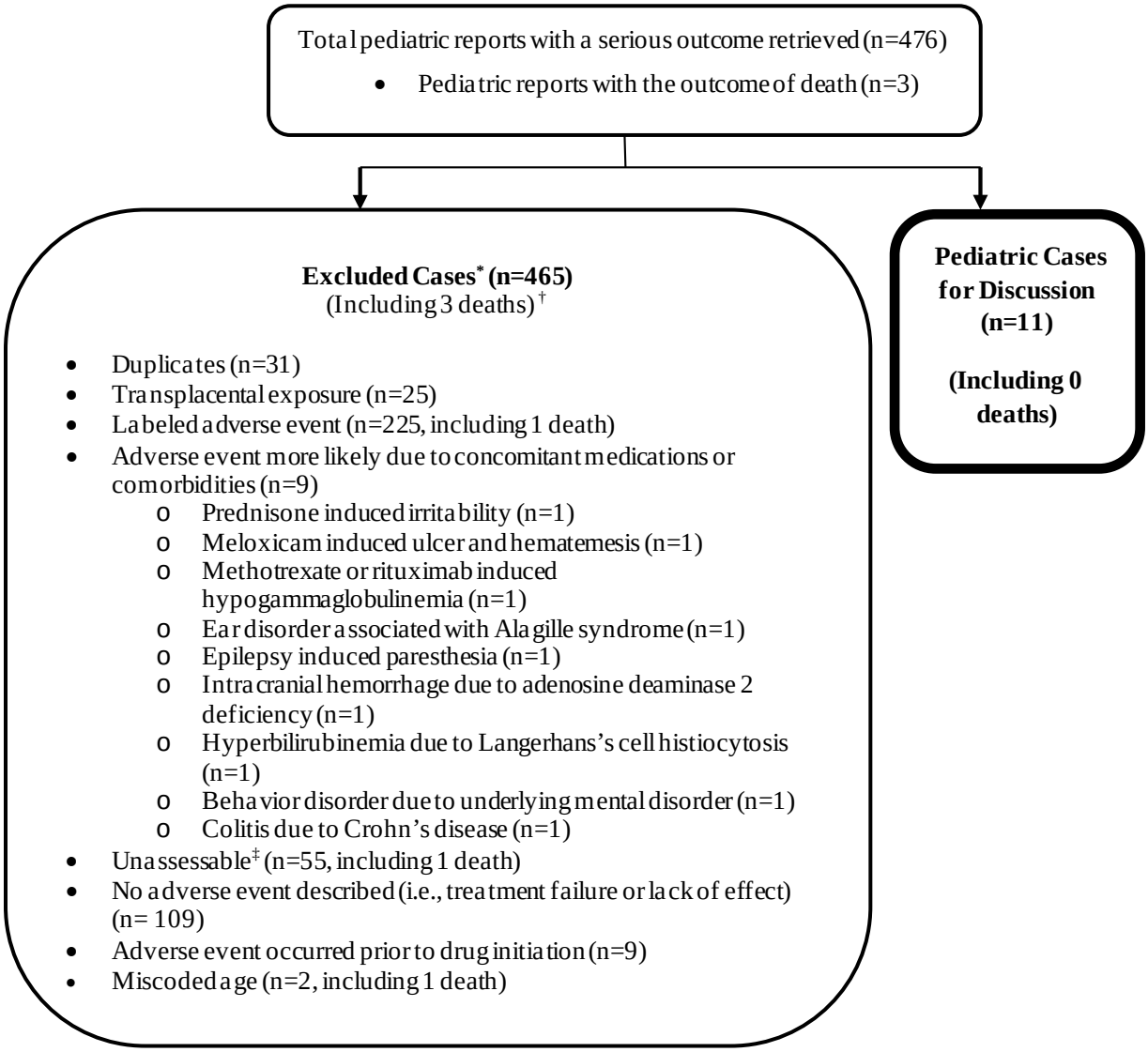
3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 476 U.S. serious pediatric reports from November 4, 2015 to September 30, 2020 for etanercept. Our FAERS search did not identify reports with etanercept-szzs or etanercept-ykro in pediatric patients.

We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded reports from the case series for various reasons, such as duplicate reporting, transplacental exposure, labeled adverse event, adverse event was unlikely to be causally related to the use of etanercept (e.g., the report was confounded by co-morbid diseases or concomitant medications), unassessable reports, no adverse event described, adverse event occurred prior to etanercept exposure, or miscoded reports.

Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious U.S. Pediatric Cases with Etanercept



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

†Three reports described fatal outcomes. One report described a neonate with exposure to etanercept via breastmilk and unknown transplacental exposure who had anencephaly and died. The second report described a 10-month-old infant who received etanercept for graft versus host disease (GVHD) after stem cell transplant for severe combined immune deficiency; the infant developed worsening GVHD and died following disseminated sepsis. The last report stated a 66-year-old patient died but offered no additional clinical details.

‡ Unassessable: Case 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.

3.1.3 Characteristics of Pediatric Cases

Appendix B contains a line listing of the 11 pediatric cases.

Table 3 summarizes the 11 FAERS U.S. pediatric cases with a serious outcome with etanercept received by FDA from 11/04/2015 to 09/30/2020.

Table 3. Characteristics of the FAERS U.S. Serious Pediatric Cases With Etanercept Received by FDA From 11/04/2015 to 09/30/2020 (N= 11)		
Age	2 – <6 years	1
	6 – <12 years	3
	12 – <18 years	7
Sex	Male	3
	Female	8
Reported reason for use	Juvenile idiopathic arthritis	5
	Psoriasis	5
	Chronic osteomyelitis	1
Serious outcome*	Hospitalization	4
	Other Serious	8
* 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. A case can have more than one serious outcome.		

3.1.4 Summary of Fatal Pediatric Cases (N=0)

There were no fatal pediatric adverse event in the final case series.

3.1.5 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=11)

We identified 11 serious FAERS cases with etanercept in the U.S. pediatric population reporting a non-fatal outcome. No clear patterns or trends suggested a new safety signal associated with the reported serious unlabeled adverse events in our pediatric cases. The cases are summarized below by System Organ Class.

Gastrointestinal Disorders (n=1)

FAERS #13748936 describes a 14-year-old male with a history of obesity (weight 106 kg) who took etanercept for psoriasis. One to two months after etanercept initiation, he developed periumbilical pain and emesis that lasted 5 days and self-resolved. Four months after etanercept initiation, he developed 5 days of nausea, vomiting, anorexia, and 9-10 /10 periumbilical abdominal pain that radiated to the lower abdominal quadrants and lower back. He was afebrile.

He had no history of liver disease, gall bladder disease, or diabetes. He was initially diagnosed with food poisoning and acute gastroenteritis with constipation and therefore treated with a laxative, which resulted in non-bloody diarrhea. He presented to care where evaluation revealed lipase was 700 (units not reported), blood glucose "high 200s," A1C of 5.2%, and the computerized tomography (CT) scan showed necrosis of the pancreas.

Reviewer's comment: The patient developed necrotizing pancreatitis, an unlabeled adverse event, 4 months after the initiation of etanercept. The patient's psoriasis and obesity may predispose him to pancreatitis. Although the narrative relates negative history of other known risk factors, it does not include other diagnostic data to assess for other, common etiologies for pancreatitis. Pancreatitis affects 1 in 10,000 children[5] and most cases are self-limited but approximately 20% of cases are associated with necrosis of the pancreatic gland.[5,6] A search of all FAERS data for additional cases coded with the PT Pancreatic necrosis with etanercept retrieved four additional reports; however, all reports had unassessable or unlikely causal association with etanercept.

Immune System Disorders (n=1)
FAERS #12279230 involves a 9-year-old female on etanercept for JIA. After an unspecified length of therapy, etanercept was discontinued for an unspecified reason. One week after discontinuation, she developed respiratory failure. She had a histoplasmosis infection. She was treated with liposomal amphotericin four days prior to the diagnosis of possible immune reconstitution inflammatory syndrome (IRIS). At the time of diagnosis, the urine antigen culture was 5.08 ng/mL and at IRIS diagnosis it was <0.6 ng/mL. The patient reportedly recovered.

Reviewer's comment: IRIS is well recognized in the context of human immunodeficiency virus (HIV) treatment[7] but it has recently been recognized in non-HIV immunosuppressed patients.[8-10] However, the link between TNF blockers and IRIS is not well described. This case was part of a multicenter, retrospective study on histoplasmosis associated with the use of TNF-α blockers.[7] This case was published in the form of a line listing without a narrative to describe the patient's clinical course and presence or absence of additional symptoms; therefore, it is not possible to confirm the IRIS diagnosis. This singular, limited case does not support a signal of IRIS and etanercept at this time.

Metabolism and Nutrition Disorders (n=1)
FAERS # 17537066 describes a 15-year-old female on etanercept 25 mg subcutaneously twice weekly for JIA. The patient's comorbidities included severe juvenile insulin dependent diabetes mellitus requiring insulin therapy. Approximately 1 month after the initiation of etanercept, she experienced a 9-pound weight gain, facial swelling, increased insulin resistance, and alopecia. Etanercept was permanently discontinued, and all events resolved after etanercept discontinuation.

Reviewer's note: There is a temporal relationship between the patient's symptoms and etanercept use. Symptom resolution following etanercept discontinuation may represent a positive dechallenge. Clinically, the constellation of symptoms can be explained by worsening insulin resistance, which is increasingly recognized in the setting of type 1 diabetes mellitus.[11, 12] However, lack of information about the patient's clinical course and lack of objective diagnostic

data precludes robust assessment of causality for the reported events. TNF-α has been implicated in the development of insulin resistance and published data suggest TNF blockers may have a role in improving insulin resistance and sensitivity.[13-15] Additionally, the etanercept labeling (Section 8.6 Use in Diabetics) states "there have been reports of hypoglycemia following the initiation of etanercept in patients receiving medication for diabetes. which required a reduction of dose in the anti-diabetic medication in some patients."[2] The mechanism by which etanercept could contribute to the reported events is unclear and establishing a strong argument for causality between etanercept and the reported adverse events remains difficult.

Nervous System Disorder (n=2)
Two cases described facial paralysis.

FAERS #13264402 describes a 15-year-old male with JIA who received etanercept. The etanercept dose increased from 25 mg to 40 mg for an unspecified reason. At an unspecified time relative to etanercept initiation or dose change, the patient was diagnosed with Bell's palsy.

FAERS #15100071 describes a 12-year-old female with a history of psoriasis and psoriatic arthritis who developed Bell's palsy while on etanercept for an unspecified length of time. Subsequently the patient was treated with topical steroids and presented to the Emergency Department for care. The treating physician was concerned that this could be due to the "demyelinating effects of TNF medications." Etanercept was discontinued and outcome for the adverse event was not reported.

Reviewer's comment: The two cases reported Bell's palsy after an unknown time after etanercept initiation. A search of all FAERS data for additional cases coded with the LLT Bell's palsy with etanercept did not identify any additional pediatric cases. Bell's palsy is common, affecting about 1 in 60 to 70 people in a lifetime with peak incidence between ages 10 and 40 years.[16] The condition describes acute facial palsy and activation of herpes simplex or zoster viruses are considered to be the most common etiologic factors. The differential for clinical symptoms for Bell's palsy includes other conditions such as complications from infections (e.g. Lyme disease, otitis media, HIV), tumor, or granulomatous conditions (e.g., sarcoid). While Bell's palsy is not specifically labeled, etanercept may be potentially causally related to Bell's palsy through development of demyelinating disease, which is labeled.[2] Another possibility is through immunosuppression, which can predispose to reactivation of dormant zoster infection. Given the lack of clinical detail including information about disease outcome or diagnostic evaluations, it is difficult to assess etanercept's role in the development of this common event.

Psychiatric Disorders (n=6)
- Tics (n=1):

FAERS #14392724 describes a 7-year-old female with a history of psoriasis, dwarfism, and optic neuritis who developed tics after being on etanercept for a "few months." The tics were described as "noises from the back of her throat" and "nervous tic when clears throat" that seemed to be worse for a couple of days after etanercept injection. The mother noted that her daughter did not have tics before etanercept initiation. The patient required physical restraining during injections because "she was not getting used to injections." The mother noted the patient

had "less tics" when she missed a dose of etanercept. The etanercept was stopped due to the tics. At the time of the report, the tics were not resolved.

Reviewer's comment: Tics can be transient (duration of less than one year) or chronic. Up to 20% of children may develop transient tics.[17] Tics may be exacerbated by stressful events.[18] The narrative suggests that etanercept administration was a stressful event; it is possible that the patient's symptoms were associated with the injection procedure rather than pharmacological properties of etanercept. In an expanded search of the FAERS database performed on February 3, 2021, we identified 21 U.S. FAERS reports of tics reported with etanercept in all ages. We did not identify a safety signal based on an evaluation of these reports. Two additional pediatric reports were unassessable. The remaining non-pediatric reports were either unassessable or tics were the patient's past medical history or due to another concomitant medication.

- Mood swing, emotional disorder (n=2)

FAERS #13341054 describes a 3-year-old female who received etanercept for JIA. At an unspecified time after initiating etanercept therapy, the patient experienced mood swings. The patient's preschool teachers noted that when the patient wasn't feeling well, her behavior was "worse," and her behavior was "mean." The patient's pediatrician recommended behavioral therapy. Therapy with etanercept continued.

FAERS #12118343 describes an 8-year-old male who started etanercept 20 mg once weekly for psoriasis. After starting etanercept, the patient had a change in his behavior and was noted to be "depressed and more emotional." His physician suggested that he should see a psychiatrist for his symptoms. The outcome of the adverse events was not reported.

Reviewer's comment: The cases reported behavioral and mood changes in young children. These symptoms are nonspecific and potentially induced by physiologic, developmental, psychosocial, and environmental factors. Without additional information, it is not possible to assign causality of these events to etanercept.

- Suicidal ideation (n=3)

FAERS #16389953 describes a 15-year-old female who experienced changes in her personality the same day she started etanercept for JIA. The patient's family history was notable for depression and anxiety in the mother and alcohol abuse in the father. One month after etanercept initiation, the patient was hospitalized for depression and suicidal thoughts. The patient was hospitalized for 4 to 5 days and etanercept was discontinued at discharge. One month following the discontinuation of etanercept, the patient's personality change, depression and suicidal thoughts resolved.

FAERS #15353993 describes a 13-year-old female on etanercept for chronic nonbacterial osteomyelitis of the jaw (off-label use). Her past medical history included anxiety and depression; her concomitant medications were leflunomide and indomethacin. About 1 year and 8 months after starting etanercept, the patient was hospitalized for worsening depression with suicidal ideation and new onset auditory hallucinations. About 1 month after this hospitalization, etanercept was discontinued due to an unspecified reason, and at the time of the report, the suicidal ideation was not resolved.

FAERS #13790295 describes a 15-year-old female who was hospitalized for suicidal ideation and cutting behavior. The patient had a history of self-injury with cutting behavior and psoriasis. The hospitalization occurred at an unspecified time relative to etanercept initiation and lasted 6 days. Etanercept was temporarily held while she was admitted to the behavioral health facility. Additionally, it was reported that the patient administered the etanercept incorrectly for three doses. She administered 0.7 mL (35 mg) intramuscularly instead of subcutaneously. The etanercept was continued after discharge from the behavioral health facility, but at the time of the report, the outcome for suicidal ideation and self-injury was unknown.

Reviewer's comment: The three cases reported adolescent patients with one or more risk factors for depression and suicidal ideation.[19-21] According to the Centers for Disease Control and Prevention, approximately 3.2% of children aged 3 to 17 years have diagnosed depression.[22] Suicide is the second leading cause of death for people ages 10 to 34 years,[23] with overall rates of suicide having increased 33% between 1999 and 2019.[19-21] Complex biochemical, genetic, personal, and environmental factors contribute to the development of depression and suicidality. The data available in these narratives are inadequate to attribute reported psychological events to etanercept alone.

4 DISCUSSION

We reviewed all serious U.S. FAERS reports with etanercept, etanercept-szzs, and etanercept-ykro in the pediatric population (ages 0 - < 18 years) during the period November 4, 2015 to September 30, 2020. Our search retrieved 476 reports with etanercept and no reports with etanercept-szzs or etanercept-ykro. We reviewed all reports and identified no new safety signals, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with etanercept.

We identified 11 serious pediatric cases with unlabeled adverse events for etanercept. Three cases of depression/suicidal ideation were confounded by the patient's medical or family history; additionally, the cases lacked additional information necessary for a robust causality assessment. The remaining cases reported one or more unlabeled adverse events (e.g., necrotizing pancreatitis, possible IRIS, alopecia, insulin resistance, temporary facial paralysis, tics, and mood or behavioral changes) and alternative causes could not be ruled out. Most of these adverse events were reported in singular cases.

5 CONCLUSION

DPV did not identify any pediatric safety concerns for etanercept at this time.

6 RECOMMENDATION

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

7 REFERENCES

1. Epps R. Medical Officer Clinical Review of Enbrel® (etanercept). September 2016. https://www.fda.gov/media/104763/download.
2. Enbrel®(etanercept) [Prescribing information]. Thousand Oaks, CA: Amgen; March 2020.
3. Eticovo® (etanercept-ykro) [Prescribing Information]. Cheomdan-daero, Yeonsu-gu, Incheon, Republic of Korea: Samsung Bioepis Co., Ltd.; April 2019.
4. Erelzi®(etanercept-szzs) [Prescribing Information]. Princeton, NJ: Sandoz Inc.; June 2020.
5. Pohl JF, Uc A. Paediatric pancreatitis. Curr Opin Gastroenterol. 2015;31(5):380-6.
6. Boxhoorn L, Voermans RP, Bouwense SA, Bruno MJ, Verdonk RC, Boermeester MA, et al. Acute pancreatitis. The Lancet. 2020;396(10252):726-34.
7. Vergidis P, Avery RK, Wheat LJ, Dotson JL, Assi MA, Antoun SA, et al. Histoplasmosis complicating tumor necrosis factor-alpha blocker therapy: a retrospective analysis of 98 cases. Clin Infect Dis. 2015;61(3):409-17.
8. Sueki H, Mizukawa Y, Aoyama Y. Immune reconstitution inflammatory syndrome in non-HIV immunosuppressed patients. J Dermatol. 2018;45(1):3-9.
9. Sun HY, Singh N. Immune reconstitution inflammatory syndrome in non-HIV immunocompromised patients. Curr Opin Infect Dis. 2009;22(4):394-402.
10. Aggarwal D, Bhardwaj M, Kumar A, Saini V, Sawal N. Immune reconstitution inflammatory syndrome in non-HIV patients with tuberculosis. A case series. Indian J Tuberc. 2020;67(1):143-7.
11. Kaul K, Apostolopoulou M, Roden M. Insulin resistance in type 1 diabetes mellitus. Metabolism. 2015;64(12):1629-39.
12. Greenbaum CJ. Insulin resistance in type 1 diabetes. Diabetes Metab Res Rev. 2002;18(3):192-200.
13. Akash MSH, Rehman K, Liaqat A. Tumor Necrosis Factor-Alpha: Role in Development of Insulin Resistance and Pathogenesis of Type 2 Diabetes Mellitus. J Cell Biochem. 2018;119(1):105-10. PubMed PMID: 28569437.
14. Borst SE. The Role of TNF-α in Insulin Resistance. Endocrine. 2004;23(2-3):177-82.
15. Burska AN, Sakthiswary R, Sattar N. Effects of Tumour Necrosis Factor Antagonists on Insulin Sensitivity/Resistance in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. PLoS One. 2015;10(6):e0128889.
16. Marson AG, Salinas R. Bell's palsy. West J Med. 2000;173(4):266-8.
17. Bagheri MM, Kerbeshian J, Burd L. Recognition and management of Tourette's syndrome and tic disorders. Am Fam Physician. 1999;59(8):2263-72, 74.
18. Himle MB, Capriotti MR, Hayes LP, Ramanujam K, Scahill L, Sukhodolsky DG, et al. Variables Associated With Tic Exacerbation in Children With Chronic Tic Disorders. Behav Modif. 2014;38(2):163-83.
19. Fried EI, Nesse RM, Zivin K, Guille C, Sen S. Depression is more than the sum score of its parts: individual DSM symptoms have different risk factors. Psychol Med. 2014;44(10):2067-76.
20. Oquendo MA, Baca-Garcia E. Suicidal behavior disorder as a diagnostic entity in the DSM-5 classification system: advantages outweigh limitations. World Psychiatry. 2014;13(2):128-30.
21. Groschwitz RC, Kaess M, Fischer G, Ameis N, Schulze UM, Brunner R, et al. The association of non-suicidal self-injury and suicidal behavior according to DSM-5 in adolescent psychiatric inpatients. Psychiatry Res. 2015;228(3):454-61.
22. Centers for Disease Control and Prevention- National Center on Birth Defects and Developmental Disabilities. Anxiety and depression in children: Get the facts [cited 2021 February 22]. Available from: https://www.cdc.gov/childrensmentalhealth/features/anxiety-depression-children.html#ref1.
23. Centers for Disease Control and Prevention- Injury Prevention and Control. Risk and Protective Factors [cited 2021 February 22]. Available from: http://www.cdc.gov/violenceprevention/suicide/riskprotectivefactors.html.

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.

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=11)

	FDA Initial Receive Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	3/16/2017	13341054	1	US-AMGEN-USASL2017037591	Non- Expedited	3	FEMALE	USA	OT
2	1/16/2018	14392724	4	US-AMGEN-USASP2018004140	Non- Expedited	7	FEMALE	USA	OT
3	2/26/2016	12118343	1	US-AMGEN-USASL2016019884	Expedited (15-Day)	8	MALE	USA	OT
4	2/23/2017	13264402	1	US-AMGEN-USASP2017025907	Expedited (15-Day)	15	MALE	USA	OT
5	4/18/2016	12279230	1	US-AMGEN-USASP2016045674	Expedited (15-Day)	9	FEMALE	USA	OT
6	7/3/2018	15100071	1	US-AMGEN-USASP2018088360	Expedited (15-Day)	12	FEMALE	USA	OT
7	9/6/2018	15353993	2	US-AMGEN-USASP2018120216	Expedited (15-Day)	13	FEMALE	USA	HO,OT
8	7/25/2017	13790295	3	US-AMGEN-USASL2017108784	Non- Expedited	15	FEMALE	USA	HO,OT
9	3/13/2020	17537066	3	US-AMGEN-USACT2020041928	Non- Expedited	15	FEMALE	USA	OT
10	7/12/2017	13748936	1		Direct	14.02	MALE	USA	HO
11	6/4/2019	16389953	1	US-AMGEN-USASL2019079673	Expedited (15-Day)	15	FEMALE	USA	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, a congenital anomaly/birth defect, or 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, OT=other medically significant

---

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/

OMAYMA A KISHK
04/08/2021 10:09:38 AM

IVONE E KIM
04/08/2021 10:50:23 AM

CARMEN CHENG
04/08/2021 10:53:21 AM

CINDY M KORTEPETER
04/08/2021 11:02:49 AM