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:	June 9, 2022
Reviewers:	Debra Ryan, PharmD, MBA, Safety Evaluator Ivone Kim, MD, FAAP, Medical Officer Division of Pharmacovigilance I (DPV-I)
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Product Name:	Benlysta (belimumab)
Pediatric Labeling Approval Date:	April 26, 2019
Application Type/Number:	BLA 125370
Applicant:	Human Genome Sciences, Inc.
OSE RCM #:	2022-591

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EXECUTIVE SUMMARY

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

Belimumab was approved by the FDA on March 9, 2011, for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy. On December 16, 2020, belimumab was approved for the treatment of adult patients with active lupus nephritis who are receiving standard therapy.

This review was prompted by a pediatric labeling change on April 26, 2019, that expanded the indication from adults to pediatric patients aged 5 years and older with active, autoantibody-positive SLE who are receiving standard therapy.

We identified five FAERS cases and no literature reports with belimumab in the pediatric population. Our case series includes five cases that describe unlabeled adverse events that occurred following initiation of therapy with belimumab. The five cases do not provide a complete medical history or a potential history of the clinical features of the reported adverse event prior to receiving belimumab; therefore, it is not possible to establish drug causality versus manifestation of SLE and/or disease progression.

DPV-I did not identify any new pediatric safety signals for belimumab 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 belimumab.

1 INTRODUCTION

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

1.1 PEDIATRIC REGULATORY HISTORY

Belimumab is a B-lymphocyte stimulator (BLyS)-specific inhibitor, approved by the FDA on March 9, 2011, for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy. On December 16, 2020, belimumab was approved for the treatment of adult patients with active lupus nephritis who are receiving standard therapy.

This review was prompted by the pediatric labeling change on April 26, 2019, that expanded the indication from adults to pediatric patients aged 5 years and older with active, autoantibody-positive SLE who are receiving standard therapy.

The determination of efficacy in pediatric patients was based on pharmacokinetic (PK) and efficacy results from a pediatric SLE study (NCT01649765), as well as PK exposure and extrapolation of the established efficacy of belimumab plus standard therapy from the Phase 3 intravenous studies in adults; the adverse event profile in pediatric patients aged 5 years and older were consistent with those observed in adults.[1] The results of clinical trial NCT01649765 are summarized in the USE IN SPECIAL POPULATIONS, *Pediatric Use,* section of the product labeling and provided in Section 1.2 of this review.[2]

Belimumab has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION[2]

The following provides safety information and information on use in pediatrics excerpted from the pertinent sections of the belimumab labeling.

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

- Previous anaphylaxis to belimumab.

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

- Serious Infections: Serious and sometimes fatal infections have occurred in patients receiving immunosuppressive agents, including BENLYSTA. Use with caution in patients with severe or chronic infections. Consider interrupting therapy with BENLYSTA if patients develop a new infection during treatment with BENLYSTA.

- Progressive Multifocal Leukoencephalopathy (PML): Evaluate patients with new-onset or deteriorating neurological signs and symptoms for PML. If confirmed, consider discontinuation of immunosuppressant therapy, including BENLYSTA.

- Hypersensitivity Reactions, including Anaphylaxis: Serious and fatal reactions have been reported. BENLYSTA for intravenous use should be administered by healthcare providers prepared to manage anaphylaxis. Monitor patients during infusion and for an appropriate period of time after intravenous administration of BENLYSTA.

- Depression and Suicidality: Depression and suicidality have been reported in trials with BENLYSTA. Assess for depression and risk of suicide before treatment with BENLYSTA and monitor during treatment. Instruct patients to contact their healthcare provider if new or worsening depression, suicidal thoughts, or other mood changes occur.

- Immunization: Live vaccines should not be given concurrently with BENLYSTA.

---------- ADVERSE REACTIONS ----------

- Common adverse reactions in adults (≥5%): nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, pharyngitis, and injection site reactions (subcutaneous administration).

- Adverse reactions in pediatric patients aged 5 years and older were consistent with those observed in adults.

----------USE IN SPECIAL POPULATIONS----------

Intravenous administration of BENLYSTA in patients with SLE is indicated in children aged 5 years and older. Determination of efficacy in pediatric patients was based on pharmacokinetic (PK) and efficacy results from a pediatric SLE study, as well as PK exposure and extrapolation of the established efficacy of BENYLSTA plus standard therapy from the Phase 3 intravenous studies in adults with SLE. A randomized, double-blind, placebo-controlled, PK, efficacy, and safety study to evaluate intravenously administered BENLYSTA 10 mg/kg plus standard therapy compared with placebo plus standard therapy over 52 weeks was conducted in 93 pediatric patients with SLE. The proportion of pediatric patients achieving an SRI-4 response was higher in patients receiving BENLYSTA plus standard therapy compared with placebo plus standard therapy. Pediatric patients receiving BENLYSTA plus standard therapy also had a lower risk of experiencing a severe flare compared with placebo plus standard therapy.

The adverse event profile in pediatric patients was consistent with the overall population in the Phase 3 studies in adults.

Pharmacokinetics were evaluated in a total of 53 pediatric patients and were consistent with the adult population. The safety and effectiveness of BENLYSTA have not been established in pediatric patients younger than 5 years of age.

The safety and effectiveness of intravenous administration of BENLYSTA have not been established in pediatric patients with active lupus nephritis younger than 18 years of age.

The safety and effectiveness of subcutaneous administration of BENLYSTA have not been established in pediatric patients younger than 18 years of age.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

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

Table 1. FAERS Search Strategy*	
Date of search	March 23, 2022
Time period of search	March 9, 2011† through March 22, 2022
Search type	RxLogix PV Reports Quick Query
Product terms	Belimumab
MedDRA search terms (Version 24.1)	All PT terms

* See Appendix A for a description of the FAERS database.
† U.S. approval date for Benlysta (belimumab)
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term

2.2 LITERATURE SEARCH STRATEGY

DPV-I searched the medical literature with the strategy described in Table 2.

Table 2. Literature Search Strategy		
Database	Embase	PubMed
Date of search	April 4, 2022	
Time period of search	All dates through April 4, 2022	
Search terms	'belimumab'/exp	Belimumab
Limits	Adolescent, children, infant, newborn, English, human	Newborn, infant, preschool child, child, adolescent, English, human

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 3 presents the number of adult and pediatric FAERS reports from March 9, 2011, through March 22, 2022, with belimumab.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA From March 9, 2011 through March 22, 2022 with Belimumab			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	7685 (5989)	3813 (2141)	295 (193)
Pediatrics (0 - <18 years)	106 (56)	75 (25)	4 (0)

* 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 Pediatric Cases in FAERS

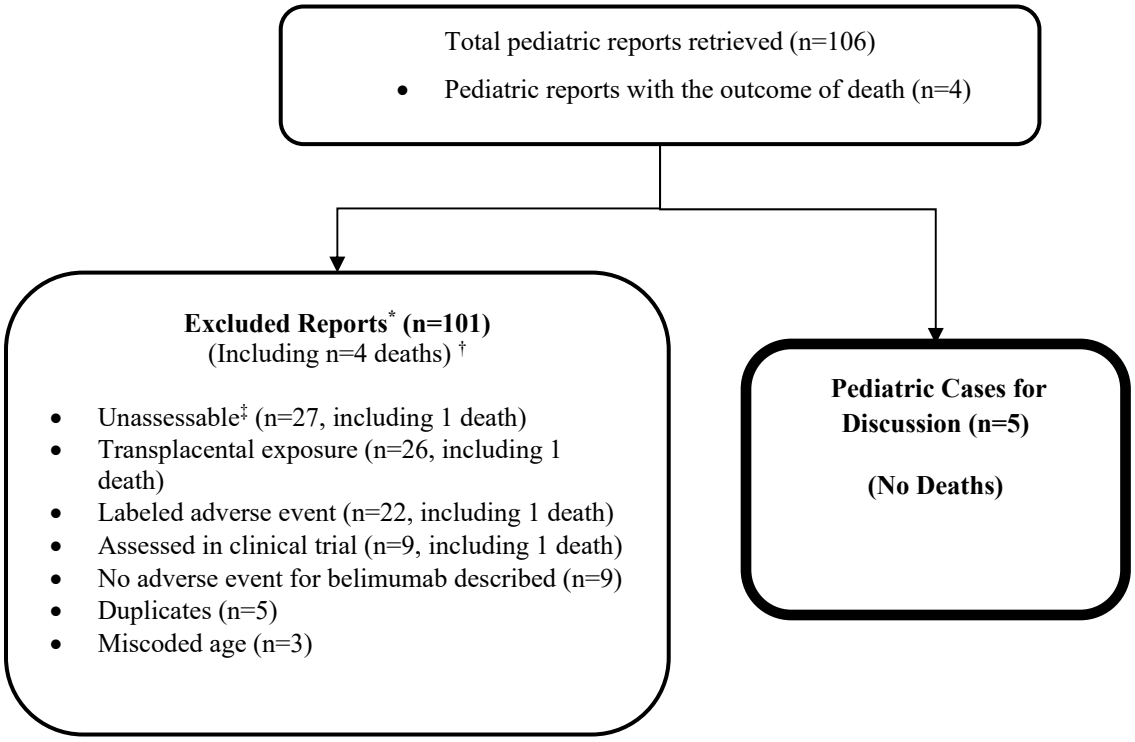
Our FAERS search retrieved 106 pediatric reports from March 9, 2011, through March 22, 2022, with belimumab.

We reviewed all FAERS pediatric reports. We excluded reports from our case series for various reasons such as unassessable reports (n=27), transplacental exposure (n=26), labeled adverse event (n=22), no adverse event for belimumab described (n=9), report previously assessed in clinical trial (n=9), duplicate reporting (n=5), or miscoded age reports (n=3).

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

Appendix B contains a line listing of the 5 cases in this case series.

Figure 1. Selection of Pediatric Cases with Belimumab



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

† Four excluded reports described a fatal outcome as follows:

- A 10-year-old male patient received belimumab for SLE and died; however, no clinical information about events leading to death were available.
- A premature neonate born at 25 weeks gestation to a mother with a history of antiphospholipid syndrome, eclampsia, assisted reproductive technology use, and belimumab use during the first trimester for SLE and lupus nephritis. The neonate died perinatally and no additional clinical information is available.
- A 4-year-old female received belimumab for SLE; the child died at an unspecified time relative to belimumab exposure after developing a "chest infection" that was complicated by septic shock. It was not reported if belimumab therapy was ongoing at time of death.
- A 17-year-old female participated in a clinical trial and received belimumab for the treatment of SLE. Almost two years after initiating belimumab, she developed infectious gastroenteritis complicated by septic shock and cardiopulmonary arrest. Her concomitant medications included azathioprine, hydroxychloroquine, and prednisone. The patient died despite resuscitative efforts.

‡ 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.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

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

3.1.4 Summary of Pediatric Cases (N=5)

We identified five FAERS cases that reported a temporal relationship with belimumab in the pediatric population. The unlabeled adverse events reported in each of the five cases are: arthritis (n=1); menstrual cycle disorder (n=1); vomiting, weight loss (n=1); vomiting, myocardial infarction and troponin increase (n=1); alopecia, hair texture abnormal, and hair discolored (n=1).

FAERS Case# 10299476 (Foreign): A physician reported that a 17-year-old female experienced knee arthritis after starting therapy with belimumab for the treatment of SLE. Medical history and concomitant medications were not reported. Time-to-onset was not reported. The patient was hospitalized and belimumab was discontinued. The outcome of the knee arthritis was not reported.

Reviewer comment: Approximately 95% of patients with lupus experience arthritis or arthralgia during the course of their illness. There is insufficient information to determine whether the arthritis in this case represents lupus disease progression, lack of efficacy, or drug reaction.[3]

FAERS Case# 15390760 (Domestic): A parent reported that a 17-year-old female experienced "menstrual cycle disorders" described as only having "spotting" three months after starting therapy with belimumab for the treatment of SLE. Medical history, concomitant medications, or other clinical information was not reported. The outcome of the reported event, menstrual cycle disorder was not reported.

Reviewer comment: Dysfunctional uterine bleeding (DUB) is common in adolescence.[4] *It is unclear whether DUB described was pre-existing. Female patients with SLE receiving treatment report menstrual irregularities and amenorrhea.*[5] *There is insufficient information provided in this case to determine the cause of the menstrual disorder.*

FAERS Case #15905186 (Foreign): A physician reported that an 11-year-old female experienced nausea, vomiting, and weight decreased four months after starting therapy with belimumab for the treatment of SLE. Medical history was not reported. Concomitant drug therapy included azathioprine, hydroxychloroquine, mycophenolic acid, and unspecified steroids. Nausea and vomiting required hospitalization. The patient experienced a weight loss of 10 kilograms, over an unreported timeframe. Belimumab was discontinued and three months following discontinuation the reported events of nausea and vomiting had not resolved, no outcome was reported for weight decreased.

Reviewer comment: Nausea and vomiting are common symptoms that may represent varied conditions ranging from non-serious and self-limited, to serious and chronic. The accompanying symptom of significant weight loss elevates the concern for a clinically serious etiology. In the absence of additional clinical information, it is difficult to interpret the negative dechallenge with belimumab and the relatively long latency from belimumab exposure to symptom onset and to perform a meaningful causality assessment.

FAERS Case# 16119498 (Foreign): A physician reported that an 8-year-old male experienced nausea and vomiting two months after starting therapy with belimumab for the treatment of SLE. Medical history included dyslipidemia. Concomitant drug therapy included azathioprine, hydroxychloroquine, an unspecified steroid, and an unspecified statin. Nausea and vomiting persisted and treatment with belimumab was continued due to improvement of SLE symptoms. Approximately five months after belimumab initiation, the patient experienced myocardial infarction with troponin elevation and on an unreported date experienced disease progression. Belimumab was discontinued and the patient continued on standard therapy. The outcome for nausea, vomiting, myocardial infarction, troponin increased, and disease progression are reported as recovered.

Reviewer comment: Patients with SLE have higher risk for coronary artery disease (CAD), which is attributable to known CAD risk factors including hypertension, diabetes, and dyslipidemia.[6,7] SLE may lead to cardiac complications in as many as 50% of affected individuals[8] and childhood-onset SLE may be associated with substantially higher incidence of myopericardial manifestations compared to adult-onset disease.[9] A search of the FAERS database from March 23, 2022, through April 21, 2022 for belimumab and the MedDRA Preferred Term Myocardial infarction retrieved no additional reports of myocardial infarction in pediatric patients.

FAERS Case# 19891284 (Foreign): A health care professional reported that a 13-year-old male experienced alopecia, abnormal hair texture, and hair discoloration four months after starting therapy with belimumab for the treatment of SLE and lupus nephritis. The patient experienced alopecia and his hair was described as yellowing and fragile. No treatment was administered and belimumab treatment continued. The outcome for the reported adverse events of hair color changes, alopecia, and hair texture abnormal is reported as not recovered.

Reviewer comment: SLE can be associated with different patterns of hair loss.[10] There is insufficient information to discern whether the reported symptoms are related to underlying SLE, belimumab, or another condition.

3.2 LITERATURE SEARCH RESULTS

DPV-I performed a literature search for additional case reports for adverse events with belimumab in pediatric patients using the strategy delineated in Table 2. We identified no additional cases for inclusion in the case series.

4 DISCUSSION

We reviewed all FAERS reports with belimumab in the pediatric population (ages 0 - < 18 years) during the period from March 9, 2011, through March 22, 2022, and five cases were included in our case series. There were no new safety signals identified, no increased severity or frequency of any labeled adverse events and there were no deaths directly attributable to belimumab. No additional cases were identified in the medical literature.

Our case series includes five cases that describe unlabeled adverse events that occurred following initiation of therapy with belimumab. The five cases do not provide a complete medical history or a potential history of the clinical features of the reported adverse event prior to receiving belimumab; therefore, it is not possible to establish drug causality versus manifestation of SLE and/or disease progression.

5 CONCLUSION

DPV-I did not identify any new pediatric safety signals for belimumab 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 belimumab.

7 REFERENCES

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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.

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=5)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	11-JUL-2014	10299476	1	BR-GLAXOSMITHKLINE-A1080425A	Expedited (15-Day)	17	FEMALE	Brazil	HO
2	10-SEP-2018	15390760	1	FDA-CDER-CTU-2018-84311	Direct	17	FEMALE	USA	
3	04-FEB-2019	15905186	1	AE-GLAXOSMITHKLINE-AE2019GSK017252	Expedited (15-Day)	11	FEMALE	United Arab Emirates	HO
4	26-MAR-2019	16119498	2	AE-GLAXOSMITHKLINE-AE2019GSK017624	Expedited (15-Day)	8	MALE	United Arab Emirates	HO, OT
5	28-SEP-2021	19891284	1	CN-GLAXOSMITHKLINE-CN2021APC202447	Expedited (15-Day)	12	MALE	China	OT

*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

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/s/

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