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:	July 12, 2021
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Product Name:	Fasenra (benralizumab)
Pediatric Labeling Approval Date:	November 14, 2017
Application Type/Number:	BLA 761070
Applicant:	AstraZeneca
OSE RCM #:	2021-964

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Fasenra (benralizumab) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with benralizumab in pediatric patients and was triggered by the pediatric indication included at the time of approval.

Benralizumab is an interleukin-5 receptor alpha-directed cytolytic monoclonal antibody (IgG1, kappa) indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. The safety and efficacy in patients younger than 12 years of age has not been established.

DPV identified no new pediatric safety signals associated with benralizumab from reports submitted to the FAERS database from November 14, 2017 through May 9, 2021.

DPV did not identify any new pediatric safety concerns for benralizumab at this time and recommends no regulatory action at this time.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Fasenra (benralizumab) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with benralizumab in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Benralizumab is an interleukin-5 receptor alpha-directed cytolytic monoclonal antibody (IgG1, kappa) approved by the FDA on November 14, 2017. It is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. The safety and efficacy in patients younger than 12 years of age has not been established. Benralizumab is available for subcutaneous injection as a 30 mg/ml solution in a single-dose prefilled syringe and in a single-dose auto injector.

Patients with severe uncontrolled asthma with an eosinophilic phenotype represent a small subset of asthmatic patients, estimated to be 3% or less of all patients with asthma. Patients with this condition experience frequent exacerbations and are at risk for increased morbidity and mortality. The pediatric study plan for benralizumab consisted of the inclusion of 108 adolescents aged 12 to 17 years old in the adult development program. Treatment benefit to adolescents was inconclusive; however, a sufficiently powered clinical trial to demonstrate treatment benefit would be impractical to conduct due to the rarity of the disease. The progression and characteristics of the disease in adults and adolescent patients is similar and there are no age-related differences in the pharmacokinetic and pharmacodynamic properties of benralizumab. No safety concerns were identified to offset the potential efficacy of benralizumab in adolescent patients and the indication for use was approved to include patients 12 years of age and older.[1]

DPV has not previously presented a benralizumab pediatric evaluation to the Pediatric Advisory Committee (PAC). This review was triggered by the pediatric indication included at the time of approval.

1.2 RELEVANT LABELED SAFETY INFORMATION

The following provides relevant safety information and information on use in pediatrics excerpted from the pertinent sections of the benralizumab labeling.[2]

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

- Known hypersensitivity to benralizumab or excipients. (4)

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

- Hypersensitivity reactions: Hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash) have occurred after administration of FASENRA. Discontinue in the event of a hypersensitivity reaction. (5.1)
- Acute asthma or deteriorating disease: FASENRA should not be used to treat acute asthma symptoms or acute exacerbations. Do not use FASENRA to treat acute bronchospasm or status asthmaticus. (5.2)
- Reduction in Corticosteroid Dosage: Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with FASENRA. Decrease corticosteroids gradually, if appropriate. (5.3)
- Parasitic (Helminth) Infection: Treat patients with pre-existing helminth infections before therapy with FASENRA. If patients become infected while receiving FASENRA and do not respond to anti-helminth treatment, discontinue FASENRA until the parasitic infection resolves. (5.4)

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

- Hypersensitivity reactions (5.1)
- Headache and pharyngitis. (6.1)

----------**USE IN SPECIFIC POPULATIONS**----------

There were 108 adolescents aged 12 to 17 with asthma enrolled in the Phase 3 exacerbation trials (Trial 1: n=53, Trial 2: n=55). Of these, 46 received placebo, 40 received FASENRA every 4 weeks for 3 doses, followed by every 8 weeks thereafter, and 22 received FASENRA every 4 weeks. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months and reduced lung function at baseline (pre-bronchodilator FEV1<90%) despite regular treatment with medium or high dose ICS and LABA with or without OCS or other controller therapy. The pharmacokinetics of benralizumab in adolescents 12 to 17 years of age were consistent with adults based on population pharmacokinetic analysis and the reduction in blood eosinophil counts was similar to that observed in adults following the same FASENRA treatment. The adverse event profile in adolescents was generally similar to the overall population in the Phase 3 studies [see Adverse Reactions (6.1)]. The safety and efficacy in patients younger than 12 years of age has not been established.

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	May 10, 2021
Time period of search	November 14, 2017† - May 9, 2021
Search type	Product-Manufacturer Reporting Summary
Product terms	Product Active Ingredient: benralizumab
MedDRA search terms (Version 24.0)	All PT terms
* See Appendix A for a description of the FAERS database. † U.S. approval date for Fasenra (benralizumab) Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term	

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 November 14, 2017 through May 9, 2021 with benralizumab.

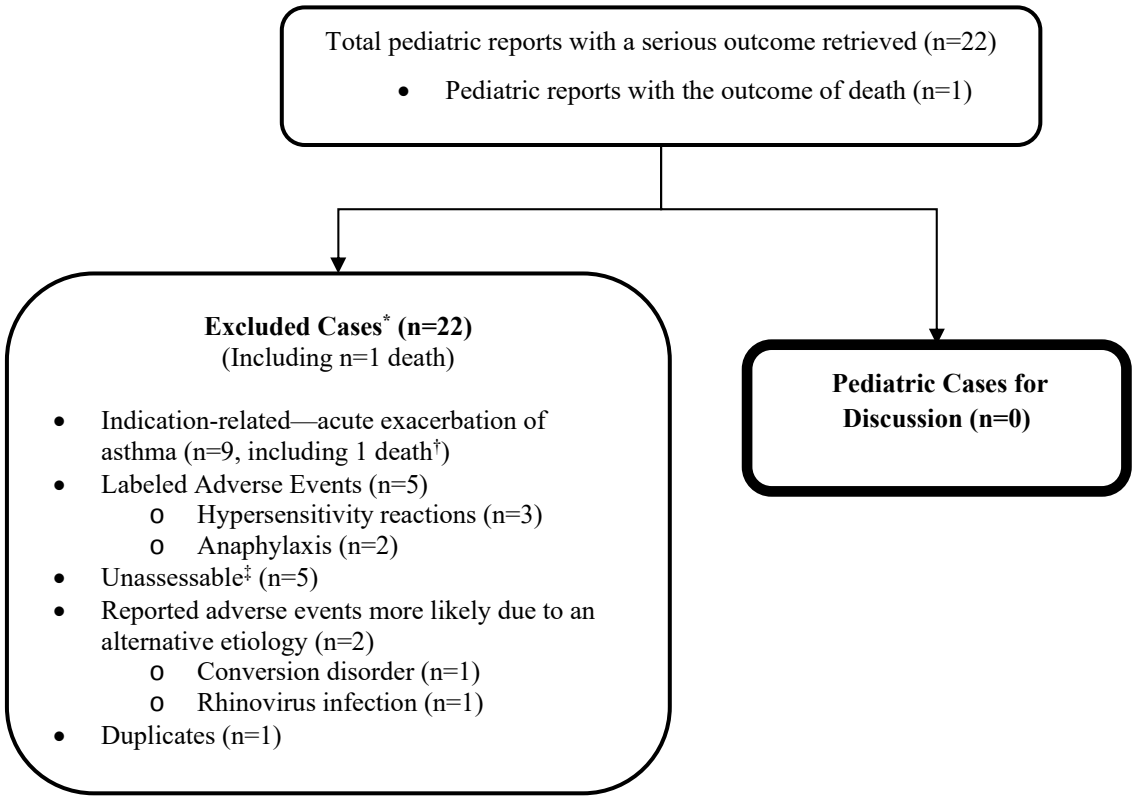
Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From November 14, 2017 – May 9, 2021 with Benralizumab			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	2,161 (1,363)	1,265 (490)	153 (72)
Pediatrics (0 - <18 years)‡	65 (62)	22 (19)	1 (1)
* May include duplicates 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. ‡ Pediatric age range conforms to ages included in the pediatric study plan.			

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved 22 serious pediatric reports from November 14, 2017 through May 9, 2021 with benralizumab.

DPV reviewed all 22 FAERS pediatric reports with a serious outcome. We excluded reports from further analysis if they were indication-related (n=9), described a labeled adverse event that did not reflect an apparent increase in severity (n=5), were unassessable reports that cannot be clinically assessed for causality because information is insufficient or lacking (n=5), if the adverse event reported was unlikely to be causally related to the use of benralizumab because a more likely alternative etiology was reported (n=2), or the report is a duplicate (n=1). **Figure 1** presents the selection and exclusion of reports for the pediatric case series. There were no reports selected for a pediatric case series.

Figure 1. Exclusion and Selection of Serious Pediatric Reports with Benralizumab



*DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above
† Patient cause of death due to acute exacerbation of asthma 36 days following discontinuation of benralizumab
‡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 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event cases where the cause of death was likely related to the use of benralizumab.

3.1.4 Summary of Non-Fatal Pediatric Serious Cases (N=0)

We did not identify any reported serious unlabeled non-fatal adverse events causally associated with benralizumab in the pediatric population.

4 DISCUSSION

DPV identified no new pediatric safety signals associated with benralizumab from reports submitted to the FAERS database from November 14, 2017 through May 9, 2021. Of the 22 serious reports reviewed in pediatric patients (ages 0 to < 18 years) there were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly attributed to the use of benralizumab.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for benralizumab 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 benralizumab.

7 REFERENCES

1. Chaudhry S Clinical Review BLA: 761070 (Benralizumab). 2017. Retrieved from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761070Orig1s000MedR.pdf

2. Fasenra (benralizumab) [package insert]. Wilmington, DE: AstraZeneca. Revised 03Oct19.

8 APPENDICES

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

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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