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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

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Product Name	**Pediatric Labeling Approval Date**	**Application Type/Number**	**Applicant**
Nucala (mepolizumab) injectable subcutaneous	June 6, 2019; September 12, 2019	BLA 761122	GlaxoSmithKline
Nucala (mepolizumab) injectable subcutaneous lyophilized powder	September 12, 2019	BLA 125526	GlaxoSmithKline

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) for mepolizumab in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with mepolizumab in pediatric patients.

Mepolizumab is an interleukin-5 inhibitor that was initially approved by the FDA on November 4, 2015, as a lyophilized powder in a single-dose vial administered subcutaneously. Mepolizumab is also available as a single-dose prefilled autoinjector and single-dose prefilled syringe. Mepolizumab is currently indicated for:

- Add-on maintenance treatment of adult and pediatric patients aged 6 years and older with severe asthma and with an eosinophilic phenotype.
- Add-on maintenance treatment of adult patients 18 years and older with chronic rhinosinusitis with nasal polyps.
- The treatment of adult patients with eosinophilic granulomatosis with polyangiitis.
- The treatment of adult and pediatric patients aged 12 years and older with hypereosinophilic syndrome for ≥6 months without an identifiable non-hematologic secondary cause.

This pediatric postmarketing pharmacovigilance review was prompted by two pediatric labeling changes for mepolizumab:

- June 6, 2019: new liquid formulation approved for subcutaneous injection via Autoinjector or Safety Syringe Device
- September 12, 2019: expanded the indication for add-on maintenance treatment of patients with severe asthma, and with an eosinophilic phenotype to include patients aged 6 to 11 years

DPV reviewed all U.S. serious FAERS reports for mepolizumab in the pediatric population (ages 0 to <17 years) from August 1, 2017, through December 11, 2022. Our evaluation did not identify any cases reporting unlabeled adverse event associated with mepolizumab in the pediatric population. There were no increased severity or frequency of labeled adverse events, and no pediatric deaths that could be attributed to mepolizumab. We identified no new safety signals and no deaths directly associated with mepolizumab.

DPV will continue to monitor all adverse events associated with the use of mepolizumab.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) for mepolizumab in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with mepolizumab in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Mepolizumab is an interleukin-5 (IL-5) inhibitor that was initially approved by the FDA on November 4, 2015 as a lyophilized powder in a single-dose vial administered subcutaneously. Mepolizumab is also available as a single-dose prefilled autoinjector and single-dose prefilled syringe. Mepolizumab is currently indicated for:[1]

- Add-on maintenance treatment of adult and pediatric patients aged 6 years and older with severe asthma and with an eosinophilic phenotype.
- Add-on maintenance treatment of adult patients 18 years and older with chronic rhinosinusitis with nasal polyps.
- The treatment of adult patients with eosinophilic granulomatosis with polyangiitis.
- The treatment of adult and pediatric patients aged 12 years and older with hypereosinophilic syndrome for ≥ 6 months without an identifiable non-hematologic secondary cause.

Table 1 shows the pediatric labeling changes for mepolizumab.

Table 1. Timeline of Pertinent Mepolizumab Pediatric Labeling Changes

Date	Labeling Change
November 4, 2015	• Initial drug approval[2, 3] • New indication: Add-on maintenance treatment of patients with severe asthma with an eosinophilic phenotype in patients age 12 years and older[2, 3]
June 6, 2019	• New liquid formulation approved for subcutaneous injection via Autoinjector or Safety Syringe Device[4-6]
September 12, 2019	• Indication extended: Add-on maintenance treatment of patients with severe asthma, and with an eosinophilic phenotype to include patients aged 6 to 11 years[7, 8]
September 25, 2020*	• New indication: treatment of adult and pediatric patients aged 12 years and older with hypereosinophilic syndrome for ≥ 6 months without an identifiable non-hematologic secondary cause[9, 10]

*This labeling change is exempt from the Pediatric Research Equity Act because mepolizumab has orphan drug designation for this indication.

DPV previously evaluated postmarketing adverse event reports for mepolizumab in pediatric patients for the Pediatric Advisory Committee. DPV's evaluation, dated December 15, 2017, was prompted by the pediatric labeling on November 4, 2015. DPV's evaluation did not identify

any new safety concerns and recommended return to routine monitoring for adverse events with mepolizumab.[11]

This pediatric postmarketing pharmacovigilance review was prompted by the pediatric labeling changes on June 6, 2019, and September 12, 2019.

1.2 RELEVANT LABELED SAFETY INFORMATION

The mepolizumab labeling contains the following safety information excerpted from the Highlights section of the labeling as well as the Pediatric Use subsection.[1] For further labeling information, please refer to the full prescribing information.

---------- **CONTRAINDICATIONS** ----------
History of hypersensitivity to mepolizumab or excipients in the formulation. (4)

---------- **WARNINGS AND PRECAUTIONS** ----------
• Hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of NUCALA. Discontinue NUCALA in the event of a hypersensitivity reaction. (5.1)
• Do not use to treat acute bronchospasm or status asthmaticus. (5.2)
• Herpes zoster infections have occurred in patients receiving NUCALA. Consider vaccination if medically appropriate. (5.3)
• Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with NUCALA. Decrease corticosteroids gradually, if appropriate. (5.4)
• Treat patients with pre-existing helminth infections before therapy with NUCALA. If patients become infected while receiving treatment with NUCALA and do not respond to anti-helminth treatment, discontinue NUCALA until parasitic infection resolves. (5.5)

---------- **ADVERSE REACTIONS** ----------
Most common adverse reactions (incidence ≥5%) include headache, injection site reaction, back pain, and fatigue. (6.1)

8.4 Pediatric Use
Severe Asthma
The safety and efficacy of NUCALA for severe asthma, and with an eosinophilic phenotype, have been established in pediatric patients aged 6 years and older.

Use of NUCALA in adolescents aged 12 to 17 years is supported by evidence from adequate and well-controlled trials in adults and adolescents. A total of 28 adolescents aged 12 to 17 years with severe asthma were enrolled in the Phase 3 asthma trials. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 2, NCT #01691521) and had a mean age of 14.8 years. Patients had a history of 2 or more exacerbations in the previous year despite regular use of medium- or high-dose ICS plus additional controller(s) with or without OCS and had blood eosinophils of ≥150 cells/mcL at screening or ≥300 cells/mcL within 12 months prior to enrollment. [See Clinical Studies (14.1).] Patients had a reduction in the rate of exacerbations that trended in favor of NUCALA. Of the 19 adolescents who received NUCALA, 9 received 100 mg and the

mean apparent clearance in these patients was 35% less than that of adults. The safety profile observed in adolescents was generally similar to that of the overall population in the Phase 3 studies [see Adverse Reactions (6.1)].

Use of NUCALA in children aged 6 to 11 years with severe asthma, and with an eosinophilic phenotype, is supported by evidence from adequate and well-controlled trials in adults and adolescents with additional pharmacokinetic, pharmacodynamic, and safety data in children aged 6 to 11 years. A single open-label clinical trial (NCT #02377427) was conducted in 36 children aged 6 to 11 years (mean age: 8.6 years, 31% female) with severe asthma. Enrollment criteria were the same as for adolescents in the 32-week exacerbation trial (Trial 2). Based upon the pharmacokinetic data from this trial, a dose of 40 mg subcutaneous every 4 weeks was determined to have similar exposure to adults and adolescents administered a dose of 100 mg subcutaneous [see Clinical Pharmacology (12.3)].

The efficacy of NUCALA in children aged 6 to 11 years is extrapolated from efficacy in adults and adolescents with support from pharmacokinetic analyses showing similar drug exposure levels for 40 mg administered subcutaneously every 4 weeks in children aged 6 to 11 years compared with adults and adolescents [see Clinical Pharmacology (12.3)]. The safety profile and pharmacodynamic response observed in this trial for children aged 6 to 11 years were similar to that seen in adults and adolescents [see Adverse Reactions (6.1), Clinical Pharmacology (12.2)].

The safety and efficacy in pediatric patients aged younger than 6 years with severe asthma have not been established.

Eosinophilic Granulomatosis with Polyangiitis

The safety and efficacy in patients aged younger than 18 years with EGPA have not been established.

Hypereosinophilic Syndrome

The safety and effectiveness of NUCALA for HES have been established in adolescent patients aged 12 years and older. The safety and effectiveness in pediatric patients aged younger than 12 years with HES have not been established.

Use of NUCALA for this indication is supported by evidence from an adequate and well-controlled study (NCT #02836496) in adults and adolescents and an open-label extension study (NCT #03306043). One adolescent received NUCALA during the controlled study and this patient and an additional three adolescents received NUCALA during the open-label extension study [see Clinical Studies (14.3)]. The one adolescent treated with NUCALA in the 32-week trial did not have a HES flare or an adverse event reported. All adolescents received 300 mg of NUCALA for 20 weeks in the open-label extension.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

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

Table 2 FAERS Search Strategy*	
Date of search	December 12, 2022
Time period of search	August 1, 2017† - December 11, 2022
Search type	RxLogix PV Signal Quick Query
Product terms	Product Active Ingredient: Mepolizumab
MedDRA search terms (Version 25.1)	All PT terms
* See Appendix A for a description of the FAERS database. † Data lock date from last Pediatric Postmarketing Pharmacovigilance Review 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

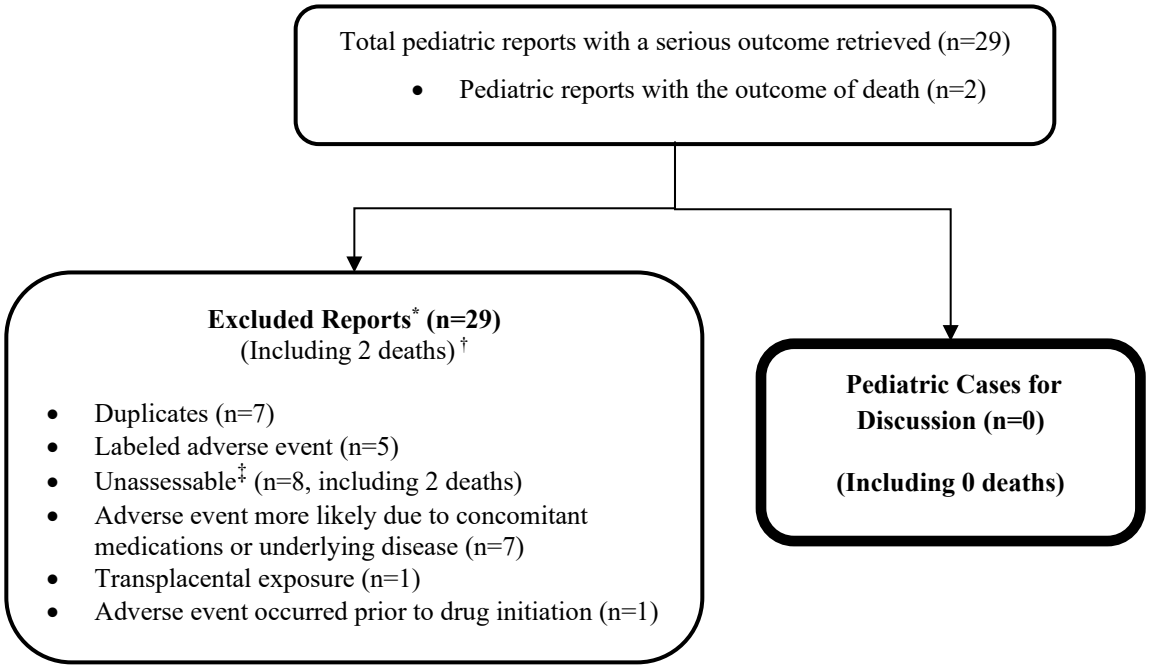
Table 3 presents the number of adult and pediatric FAERS reports August 1, 2017, through December 11, 2022, with mepolizumab.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA From August 1, 2017, through December 11, 2022 With Mepolizumab			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	9,182 (2,935)	7,043 (817)	298 (133)
Pediatrics (0 - <17 years)	138 (89)	78 (29)	5 (2)
* 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 29 U.S. serious pediatric reports from August 1, 2017, through December 11, 2022. We excluded all 29 reports from the case series for the following reasons: duplicate reports (n=7), labeled adverse event (n=5), unassessable reports (n=8), adverse event more likely due to concomitant medications or underlying disease (n=7), transplacental exposure report (n=1), or adverse event occurred prior to drug initiation (n=1). **Figure 1** presents the selection of cases for the pediatric case series.

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



* DPV reviewed these reports, but they were excluded from further discussion for the reasons listed above.
† Two reports described fatal outcomes but were unassessable, including one report of death due to difficulty breathing, and one report with no clinical details.
‡ 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 information provided in the report cannot be supplemented or verified.

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 Non-Fatal Pediatric U.S. Serious Cases (N=0)

We did not identify any FAERS U.S. serious, unlabeled, non-fatal adverse event cases associated with mepolizumab in the pediatric population.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports for mepolizumab in the pediatric population (ages 0 to <17 years) from August 1, 2017, through December 11, 2022. Our evaluation did not identify any cases reporting unlabeled adverse event associated with mepolizumab in the pediatric population. There were no increased severity or frequency of labeled adverse events, and no pediatric deaths that could be attributed to mepolizumab.

5 CONCLUSION

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

6 RECOMMENDATION

DPV will continue to monitor all adverse events associated with the use of mepolizumab.

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.

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