Department of Health and Human Services
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	December 15, 2017
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Product Name:	Nucala (mepolizumab)
Pediatric Labeling Approval Date:	November 4, 2015
Application Type/Number:	Biologics License Application (BLA) 125526
Applicant/Sponsor:	GlaxoSmithKline LLC
OSE RCM #:	2017-1650

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports for Nucala (mepolizumab) in pediatric patients.

Mepolizumab is an interleukin-5 (IL-5) inhibitor and was approved in the United States on November 4, 2015 for add-on therapy for severe asthma with an eosinophilic phenotype in patients age 12 years and older.

The Division of Pharmacovigilance I (DPV-I) evaluated all pediatric adverse event reports with mepolizumab in the FDA Adverse Event Reporting System (FAERS) database from the U.S. approval date on November 4, 2015 to July 31, 2017. The review of the FAERS pediatric reports resulted in the identification of two non-fatal cases containing unlabeled adverse events, of which one was associated with a serious outcome. The two cases reported the unlabeled adverse events of histiocytic necrotizing lymphadenitis (n=1, serious) and varicella infection (n=1, nonserious); however, no new safety signals were identified after review of the cases with mepolizumab.

The one case associated with a serious outcome of hospitalization reported a patient who developed histiocytic necrotizing lymphadenitis after receiving mepolizumab and another drug that inhibits IL-5 production (suplatast tosilate). Therefore, we are unable to attribute causality to mepolizumab alone. For completeness, we searched the FAERS database for reports of histiocytic necrotizing lymphadenitis with mepolizumab in the adult population; we did not retrieve any additional reports. The one nonserious case reported the unlabeled adverse event of varicella infection; this single case does not represent a new safety signal at this time. However, because of the known association between mepolizumab and shingles, we will continue close postmarketing surveillance of all varicella zoster virus infections.

DPV will continue postmarketing surveillance of all adverse events with the use of mepolizumab.

1 INTRODUCTION

This review evaluates postmarketing adverse event reports for Nucala (mepolizumab, BLA 125526) subcutaneous (SC) injection in pediatric patients. The approval of mepolizumab for patients 12 years of age or older on November 4, 2015 triggered this review.

Mepolizumab is an interleukin-5 (IL-5) inhibitor and was approved in the United States on November 4, 2015 as an add-on therapy for severe asthma with an eosinophilic phenotype in patients age 12 years and older. Another IL-5 inhibitor, reslizumab, has also been approved for the same indication since the approval of mepolizumab; however, it is not indicated for pediatric patients.[1]

Eosinophils are suggested to have a role in the pathogenesis of asthma with data showing that higher amounts of eosinophils—in peripheral blood samples as well as bronchoalveolar lavage fluids—are associated with higher severity of asthmatic disease.[2] IL-5 is an important cytokine in the regulation of eosinophils and key in their recruitment.[3] Mepolizumab blocks the recruitment of eosinophils to the lung reducing disease burden via inhibition of IL-5.

Mepolizumab is supplied as 100 mg of lyophilized powder in a single-dose vial and the approved dosing is 100 mg given SC in the upper arm, thigh, or abdomen, once every 4 weeks.

1.1 PEDIATRIC REGULATORY HISTORY

The clinical development program for mepolizumab consisted of three pivotal trials described in Table 1.1.

Table 1.1 Pivotal Trials from Mepolizumab Clinical Development Program [4]

Study Number	Patient Population	Treatments	Primary Endpoint
NCT01000506[5]	Ages 12-65 years on inhaled corticosteroids (ICS) with a history of two or more exacerbations within the past year, in patients that had markers of eosinophilic inflammatory airway disease.	616 patients randomized 1:1:1:1 to: 1) mepolizumab 75 mg intravenous (IV) 2) mepolizumab 250 mg IV 3) mepolizumab 750 mg IV 4) placebo	Exacerbation rate over 52-week study duration
NCT01691521[6]	Ages 12 years and older on ICS and an additional controller medication with a history of two or more exacerbations within the past year. Patients must have biomarker based on blood eosinophil counts.	576 patients randomized 1:1:1 to: 1) mepolizumab 75 mg IV 2) mepolizumab 100 mg SC 3) placebo	Exacerbation rate over 32-week study duration

Table 1.1 Pivotal Trials from Mepolizumab Clinical Development Program [4]			
NCT01691508[7]	Ages 12 years and older on ICS and an additional control medication and oral corticosteroids (OCS). Patients must have biomarker based on blood eosinophil counts.	132 patients randomized 1:1 to: 1) mepolizumab 100 mg SC 2) placebo	Percent reduction in OCS during weeks 20-24 in the 24-week study

Although the studies demonstrated efficacy and safety in the adult population, there were only 28 pediatric patients (12 years to 17 years of age) in the clinical development program, with the majority (n = 25) enrolled in pivotal trial study 88.[8]

A Pulmonary Allergy Drugs Advisory Committee (PADAC) Meeting was held on June 11, 2015, to discuss the following topics: 1) asthma severity most likely to benefit from mepolizumab, 2) role of eosinophils in initiating treatment with mepolizumab, 3) adequacy of the efficacy and safety data in children 12 to 17 years of age, and 4) ethnicity of the study population.[9]

Overall the committee felt that mepolizumab demonstrated a reduction in exacerbations and OCS use when use is limited to a severe asthma population, with eosinophil counts guiding who should initiate treatment. No specific eosinophil cutoff values were endorsed by then panel, but general concern regarding the utility of the historical threshold value ≥ 300 cells/mcL was raised. In general, the committee noted the lack of data in the adolescent and African American population. However, some members voiced concern regarding restricting use in either of these populations given the unmet medical need in both.

The committee was asked to vote individually on the efficacy and safety of mepolizumab (see Table 1.2 for the PADAC voting results). Each voting question was subdivided by age with a vote in adults ≥ 18 years of age and in adolescents 12 to 17 years of age. Overall, the committee voted strongly in favor of the demonstration of efficacy and safety with a favorable risk benefit in the adult population; however, the majority of the panel felt that the data were too limited to demonstrate efficacy and safety in the adolescent population. Further evaluation in adolescent population was recommended.

Table 1.2 PADAC Voting Results[6]				
Voting Question	Age	Yes	No	Abstain
Do the efficacy data provide substantial evidence of a clinically meaningful benefit of mepolizumab 100 mg SC once every 4 weeks for the treatment of severe asthma?	Adults (≥ 18 years)	14	0	0
	Children (12-17 years)	5	9	0
Has the safety of mepolizumab 100 mg SC administered once every 4 weeks been adequately demonstrated for treatment of patients with severe asthma?	Adults (≥ 18 years)	13	1	0
	Children (12-17 years)	2	12	0

Based upon this information, the clinical reviewer recommended approval in subjects ≥ 18 years of age and a complete response for patients 12 to 17 years of age.[5] However, the Division

Director[10] of Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) and Office Director[4] agreed with approval in patients 12 years of age and older.

On November 4, 2015, mepolizumab was approved in the United States for add-on therapy for severe asthma with an eosinophilic phenotype in patients age 12 years and older. The required pediatric assessments under the Pediatric Research Equity Act (PREA) were waived for patients less than 6 years of age because it is unlikely that there will be high enough numbers of patients to allow clinical studies. Studies for pediatrics ages 6 years to 11 years have been deferred.[11] The final reports for the following trials are to be submitted in September 2019:

- Open label pediatric pharmacokinetic and pharmacodynamics study of mepolizumab (ages 6 years to 11 years), 12 week duration.
- Pediatric safety and pharmacodynamics extension study of mepolizumab (ages 6 years to 11 years), 12 month duration.

On December 12, 2017, an additional indication for mepolizumab—the treatment of adult patients with eosinophilic granulomatosis with polyangiitis—was approved. Additional pediatric studies under PREA were waived because mepolizumab was designated as an orphan drug for this indication.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

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

- History of hypersensitivity to mepolizumab or excipients in the formulation.

----------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.
- Do not use to treat acute bronchospasm or status asthmaticus.
- Herpes zoster infections have occurred in patients receiving NUCALA. Consider varicella vaccination if medically appropriate prior to starting therapy with NUCALA.
- Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with NUCALA. Decrease corticosteroids gradually, if appropriate.
- 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.

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

- Most common adverse reactions (incidence greater than or equal to 5%) include headache, injection site reaction, back pain, and fatigue.

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

- Pediatric Use: The safety and efficacy in pediatric patients younger than 12 years have not been established. A total of 28 adolescents aged 12 to 17 years with asthma were enrolled in the phase 3 studies. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 2) and had a mean age of 14.8 years. Subjects has a history of 2 or more exacerbations in the previous year despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) with or without oral corticosteroids and had blood eosinophils of greater than or equal to 150 cells/mcL at screening or greater than or equal to 300 cells/mcL within 12 months prior to enrollment. Subjects had a reduction in the rate of exacerbations that trended in favor of mepolizumab. Of the 19 adolescents who received mepolizumab, 9 received NUCALA and the mean apparent clearance in these subjects was 35% less than that of adults. The adverse event profile in adolescents was generally similar to the overall population in the phase 3 studies.

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

The Division of Pharmacovigilance I (DPV-I) searched the FAERS database with the strategy described in Table 2.1.1. See Appendix A for a description of the FAERS database.

Table 2.1.1 FAERS Search Strategy	
Date of Search	September 1, 2017
Time Period of Search	November 4, 2015* - July 31, 2017
Search Type	Product-Manufacturer Reporting Summary (Profile report)
Product Name(s)	Product active ingredient: Mepolizumab
Search Parameters	All ages, all outcomes, worldwide

** Start data selected is U.S. approval date for mepolizumab.*

2.2 RESULTS

2.2.1 Total number of FAERS reports by Age

Table 2.2.1 Total Adult and Pediatric FAERS Reports* from November 4, 2015 through July 31, 2017 with Mepolizumab

	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	659 (370)	421 (134)	14 (5)
Pediatrics (0 - <17 years)	15‡ (8)	8 (1)	0 (0)

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

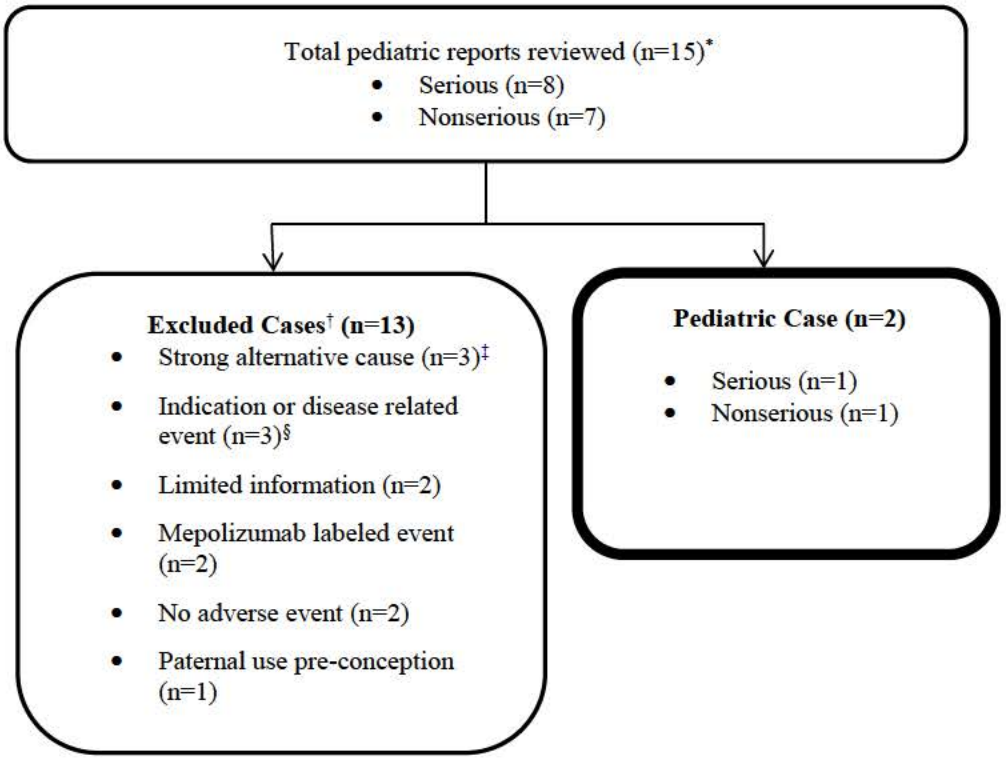
† For the purposes of this review, the following outcomes qualify as serious: ***death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.***

‡ See figure 2.2.2

2.2.2 Selection of Pediatric Cases in FAERS

We identified 15 pediatric adverse event reports, of which eight were associated with a serious outcome; there were no pediatric deaths reported with mepolizumab. See **Figure 2.2.2** below for the specific selection of cases to be summarized in **Sections 2.3 and 2.4.**

Figure 2.2.2 Selection of Pediatric Cases with Mepolizumab



* There were no pediatric reports with the outcome of death.
† DPV reviewed these cases, but they were excluded from the case series for the reasons listed above.
‡ Three reports described strong alternative causes for the adverse events: one reported back pain associated with a concomitant viral illness, one reported a peanut allergic patient that developed anaphylaxis after exposure to peanuts, and one reported a labeled event for a concomitant medication (skin fragility and abrasions associated with corticosteroid use).
§ Three reports resulted in adverse events that were indication- or disease- related (asthma exacerbations (n=2), pneumonia (n=1)).

See Appendix B for the FAERS case numbers, manufacturer control numbers, and FAERS version numbers included in the pediatric case series (n=2).

2.3 Summary of Fatal Pediatric Adverse Event Cases (N=0)

No pediatric deaths were reported with mepolizumab in the FAERS database from November 4, 2015 through July 31, 2017.

2.4 SUMMARY OF NON-FATAL PEDIATRIC ADVERSE EVENT CASES (N=2)

We reviewed two cases that described non-fatal unlabeled pediatric adverse events for mepolizumab, of which one was associated with a serious outcome. The two cases are summarized below:

Unlabeled Events

2.4.1 Blood and lymphatic system disorder (N=1)

Histiocytic necrotizing lymphadenitis (N=1)

Case # 13204190, serious outcome-hospitalization, Japan, 2017: A physician reported that a 12-year-old male receiving mepolizumab for asthma developed subacute necrotizing lymphadenitis. The patient's concomitant medical condition included food allergies and concomitant medications included fluticasone, salmeterol, montelukast, and suplatast tosilate.[a] Prior to the patient's third dose of mepolizumab 100 mg (42 days after mepolizumab initiation), he developed a fever requiring hospitalization and received unspecified antibiotics. Fever resolution was not achieved and he was later diagnosed with subacute necrotizing lymphadenitis. A lymphadenectomy was performed and he was initiated on prednisolone 1 mg/kg/day; subacute necrotizing lymphadenitis resolved approximately one month after the patient's initial diagnosis. The patient's third dose of mepolizumab was given (delayed by approximately two weeks) and he continues to receive monthly injections (through the 5th dose reported) without further adverse events reported.

Reviewer's Comments: This case reports a temporal relationship between mepolizumab and the adverse event of subacute necrotizing lymphadenitis. However, the patient was also receiving suplatast tosilate, which has a similar mechanism of action to mepolizumab with suppression of IL-5; therefore, we are unable to attribute causality to mepolizumab alone. For completeness, we searched the FAERS database for reports of histiocytic necrotizing lymphadenitis with mepolizumab in the adult population; we did not retrieve any additional reports. DPV will continue postmarketing surveillance of this adverse event.

2.4.2 Infections and infestations (N=1)

Varicella (N=1)

Case # 12481465, United States, 2016: A physician reported that a 12-year-old female developed chickenpox 21 days after receiving her third dose of mepolizumab 100 mg monthly for the treatment of asthma.[b] The patient was exposed to the virus one week prior to disease onset (exposure source not specified) and was previously vaccinated. The patient had mild symptoms and was treated successfully with valacyclovir. The patient's mepolizumab was held for one month and was subsequently resumed on her normal scheduled.

Reviewer's Comments: Varicella zoster virus (VZV) is the causative virus for two diseases; varicella (which is also known as chickenpox) and herpes zoster (which is also known as shingles). VZV is addressed in the mepolizumab labeling; however, the labeling is in reference only to herpes zoster (Warnings and Precautions Section 5.3 Opportunistic infections: Herpes

[a] Suplatast tosilate is a selective Th2 cytokine inhibitor that suppresses the synthesis of IL-4 and IL-5.
[b] The report initially indicated the patient received mepolizumab in utero; however, this was corrected to state that the patient did not receive the product in utero but rather by "injection."

zoster). Although the patient developed chickenpox despite vaccination, the patient experienced mild disease and the timing of varicella vaccination administration relative to event onset was not reported. Vaccination failure may be related to waning immunity with significantly higher rates of breakthrough disease reported at 5 years post-vaccination versus within 1 year of vaccination.[12] For completeness, we searched the FAERS database for reports of chickenpox with mepolizumab in the adult population; we did not retrieve any additional reports. This single case does not represent a new safety signal at this time. DPV will continue close postmarketing surveillance of all VZV infections because of the known association between mepolizumab and shingles.

3 DISCUSSION

We evaluated all FAERS reports of adverse events in the pediatric population with mepolizumab from the initial U.S. approval on November 4, 2015 through July 31, 2017. The review of the FAERS pediatric reports resulted in the identification of two non-fatal cases containing unlabeled adverse events, of which one was associated with a serious outcome. The two cases reported the unlabeled adverse events of histiocytic necrotizing lymphadenitis (n=1, serious) and varicella infection (n=1, nonserious); however, no new safety signals were identified after review of the cases with mepolizumab.

The one case associated with a serious outcome of hospitalization reported a patient who developed histiocytic necrotizing lymphadenitis after receiving mepolizumab and another drug that inhibits IL-5 production (suplatast tosilate). Therefore, we are unable to attribute causality to mepolizumab alone. For completeness, we searched the FAERS database for reports of histiocytic necrotizing lymphadenitis with mepolizumab in the adult population; we did not retrieve any additional reports. The one nonserious case reported the unlabeled adverse event of varicella infection; this single case does not represent a new safety signal at this time. However, because of the known association between mepolizumab and shingles, we will continue close postmarketing surveillance of all VZV infections.

4 CONCLUSION

We did not identify any new safety signals with mepolizumab in pediatric patients. There is no evidence from this data that there are pediatric safety concerns with mepolizumab at this time.

5 RECOMMENDATIONS

DPV will continue routine pharmacovigilance monitoring of all adverse events with mepolizumab in the pediatric population.

6 APPENDICES

6.1 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 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.

6.2 APPENDIX B. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC REPORTS WITH MEPOLIZUMAB (N=2)

FAERS CASE NUMBER	VERSION NUMBER	MANUFACTURER CONTROL NUMBER	FAERS CASE NUMBER	VERSION NUMBER	MANUFACTURER CONTROL NUMBER
13204190	3	JP-GLAXOSMITHKLINE-JP2017JPN014630	12481465	3	US-GLAXOSMITHKLINE-US2016GSK080849

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