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Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	March 7, 2018
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Product Name:	Cinqair (Reslizumab)
Approval Date:	March 23, 2016
Application Type/Number:	BLA 761033
Applicant/Sponsor:	Teva Branded Pharmaceutical Products R&D, Inc.
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EXECUTIVE SUMMARY

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

Reslizumab is an interleukin-5 (IL-5) antagonist monoclonal antibody that was first approved in the United States on March 23, 2016. It was approved for add-on maintenance treatment of patients with severe asthma and an eosinophilic phenotype, aged 18 years and older. Safety and efficacy of reslizumab in the pediatric patient population was not established at the time of approval; however, the sponsor fulfilled pediatric study requirements for patients 12 to 17 years of age because pediatric data included in the original BLA application showed the drug was ineffective in these patients.

The Division of Pharmacovigilance I (DPV-I) evaluated all pediatric adverse event reports with reslizumab in the FDA Adverse Event Reporting System (FAERS) database from the U.S. approval date on March 23, 2016 through December 20, 2017. This search resulted in the identification of three pediatric reports, two with a reported serious outcome. The review of these reports identified one report as a duplicate, one without an adverse event, and one non-fatal serious report resulting in hospitalization that was attributable to a strong alternative cause (chronic cholecystitis with MRI evidence of a narrow cystic duct). No new safety signals were identified from this review.

DPV-I will continue postmarketing surveillance of all adverse events with the use of reslizumab.

1 INTRODUCTION

This review evaluates pediatric postmarketing adverse event reports for Cinqair (reslizumab, BLA 761033) intravenous injection. This review was triggered by the approval of reslizumab in patients 18 years and older on March 23, 2016; although safety and efficacy of reslizumab in pediatric patients was not established, the Pediatric Research Equity Act (PREA) study requirements were met (see Section 1.1 for details of the PREA study requirements).

Reslizumab is an interleukin-5 (IL-5) antagonist monoclonal antibody (IgG4 kappa) indicated for add-on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype.[1] Two other IL-5 antagonist monoclonal antibodies are available on the U.S. market, but vary from reslizumab by approved indications and population for use. See Table 1.1 for additional information regarding available IL-5 antagonist monoclonal antibodies.

Table 1.1. Approved IL-5 Antagonist Monoclonal Antibodies in the U.S.

Drug	**Initial U.S. Approval Date**	**Indication**
Nucala[2] (Mepolizumab)	November 4, 2015	• Add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. • The treatment of adult patients with eosinophilic granulomatosis with polyangiitis.
Cinqair[1] (Reslizumab)	March 23, 2016	• Add-on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype.
Fasenra[3] (Benralizumab)	November 14, 2017	• Add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.

Reslizumab is available as 100 mg/10 mL solution in a single use vial. The approved dosing is 3 mg/kg intravenously once every four weeks.

1.1 PEDIATRIC REGULATORY HISTORY

On April 15, 2015, the Sponsor submitted Biologics Licensing Application (BLA) 761033 under section 351(a) of the Public Health Service Act. The clinical development program consisted of four efficacy and safety trials and a long-term extension trial described in Table 1.2.

Table 1.2. Pivotal Trials from Reslizumab Clinical Development Program

Study Number	**Patient Population**	**Treatments**	**Primary Objective**
NCT00587288[4]	Asthmatic patients ages 18 to 75 years with: • Symptoms consistent with poorly controlled disease	Participants were randomized to the following IV treatment every 28 days for a total of 4 doses: • Reslizumab 3 mg/kg	To determine the effectiveness and safety of reslizumab in the treatment of subjects with poorly controlled asthma.

Table 1.2. Pivotal Trials from Reslizumab Clinical Development Program			
	• Treatment with ICS • ≥ 3% sputum eosinophils at screening	• Placebo	
NCT01270464[5]	Asthmatic patients ages 12 through 75 years with: • Blood eosinophil count ≥ 400 cells/mcL • Use of ICS as asthma treatment	Participants were randomized to the following IV treatment every 4 weeks for a total of 4 doses: • Placebo • Reslizumab 0.3 mg/kg • Reslizumab 3 mg/kg	Lung function study: To determine whether reslizumab, at a dosage of 0.3 or 3 mg/kg, administered once every 4 weeks for a total of 4 doses is more effective than placebo in improving lung function in patients with eosinophilic asthma, as assessed by the overall change from baseline in forced expiratory volume in 1 second.
NCT01287039[6]	Asthmatic patients ages 12 through 75 years with: • ≥ 1 asthma exacerbation within 12 months requiring corticosteroids • Blood eosinophil count ≥ 400 cells/mcL • Requirement of ICS as asthma treatment • OCS allowed as asthma treatment if stable	Participants were randomized to the following IV treatment every 4 weeks for a total of 13 doses: • Placebo • Reslizumab 3 mg/kg	Exacerbation rate study: To evaluate the efficacy, safety, and immunogenicity of treatment with reslizumab in patients with eosinophilic asthma.
NCT01285323[7]			Exacerbation rate study: To determine whether reslizumab is more effective than placebo in reducing the number of clinical asthma exacerbations in patients with eosinophilic asthma.
NCT01290887[8]	Patients participating in NCT1270464, NCT01287039, and NCT01285323	Reslizumab 3 mg/kg IV every 4 weeks for up to 24 months	To evaluate the long-term safety of reslizumab 3 mg/kg every 4 weeks for approximately 24 months in pediatric and adult patients with eosinophilic asthma.

OCS: oral corticosteroids, ICS: inhaled corticosteroids

The FDA Clinical Review of the submitted trial data noted that the trials showed significant lung function improvement and a significant reduction in asthma exacerbations in the overall population.[9] However, findings were inconsistent in the adolescent population randomized to reslizumab, which showed an apparent decrease in lung function and increase in exacerbation rates; the number of pediatric patients in the clinical development program was small (39 patients ages 12 to 17 years). The reviewer concluded that the risk-benefit assessment did not support approval for pediatric patients ages 12 to 17 years. The following safety signals were identified for inclusion in product labeling from the clinical development program: anaphylaxis (labeled as a boxed warning), muscle toxicity (labeled in Adverse Reactions 6.1 Clinical Trials Experience), malignancy (labeled in Warnings

and Precautions), and increased risk of infection (parasitic infection labeled in Warnings and Precautions).

Reslizumab was discussed at the December 9, 2015 meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC). The committee was asked to vote on the efficacy and safety of this agent (see Table 1.3 for the PADAC voting results). Overall, the committee voted in favor of the safety and efficacy of reslizumab in adult patients; however, not in pediatrics. The committee's discussion noted an imbalance in the risk-benefit equation in the pediatric population due to the lack of demonstrated efficacy in this age group and the identified safety issues.

Table 1.3. PADAC Voting Results[10]

Voting Question	Age	Yes	No	Abstain
Do the efficacy data provide substantial evidence of a clinically meaningful benefit of reslizumab 3 mg/kg IV once every 4 weeks for the treatment of asthma?	Adults (≥ 18 years)	13	1	0
	Children (12-17 years)	0	14	0
Do the available efficacy and safety data support approval of reslizumab 3 mg/kg IV every 4 weeks for the treatment of patients with asthma?	Adults (≥ 18 years)	11	5	0
	Children (12-17 years)	0	14	0

On March 23, 2015, reslizumab was approved for patients 18 years and older for add-on maintenance treatment of patients with severe asthma and an eosinophilic phenotype. At the time of approval, the Sponsor was noted to have fulfilled the Pediatric Research Equity Act (PREA) study requirement for patients ages 12 to 17 years of age as reslizumab was not found to be effective in this age group, and the study requirements in pediatric subjects ages zero to 11 years were waived, because evidence strongly suggests the drug product would be ineffective in this pediatric group.[11] A number of postmarketing requirements at the time of approval were implemented, including testing of IgE antibodies and the development of a test for detection of other anti-drug antibodies in order to further investigate findings noted in the clinical development program.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

The labeling for reslizumab dated 03/2016 contains the following select safety information:[1]

----------WARNING: ANAPHYLAXIS----------

- Anaphylaxis occurred with CINQAIR infusion in 0.3% of patients in placebo controlled studies.
- Patients should be observed for an appropriate period of time after CINQAIR infusion; healthcare professionals should be prepared to manage anaphylaxis that can be life-threatening.
- Discontinue CINQAIR immediately if the patient experiences anaphylaxis.

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

- Known hypersensitivity to reslizumab or any of its excipients.

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

- Malignancy: Malignancies were observed in clinical studies.
- Reduction in Corticosteroid Dosage: Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with CINQAIR. Decrease corticosteroids gradually, if appropriate.
- Parasitic (Helminth) Infection: Treat patients with pre-existing helminth infections before therapy with CINQAIR. If patients become infected while receiving CINQAIR and do not respond to anti-helminth treatment, discontinue CINQAIR until the parasitic infection resolves.

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

- The most common adverse reaction (incidence greater than or equal to 2%) includes oropharyngeal pain.

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

- Pediatric Use: CINQAIR is not indicated for use in pediatric patients less than 18 years of age. The safety and effectiveness in pediatric patients (aged 17 years and younger) have not been established.

  CINQAIR was evaluated in 39 patients aged 12 to less than 18 years with asthma in two 52-week exacerbation studies and one 16-week lung function study. In the exacerbation studies, patients were required to have at least 1 asthma exacerbation requiring systemic corticosteroid use in the year prior to study entry. In these studies, the asthma exacerbation rate was higher in adolescent patients treated with CINQAIR than placebo (CINQAIR n=14, rate 2.86, 95% CI [1.02 to 8.09] and placebo n=11, rate 1.37, 95% CI [0.57 to 3.28]: rate ratio 2.09, 95% CI [0.82 to 5.36]).

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	December 20, 2017
Time Period of Search	March 23, 2016* - December 20, 2017
Search Type	Product-Manufacturer Reporting Summary (Profile Report)
Product Name(s)	Product active ingredient: Reslizumab
Search Parameters	All ages, all outcomes, worldwide

** Start date selected is U.S. approval date for reslizumab.*

2.2 RESULTS

2.2.1 Total Number of FAERS Reports by Age

Table 2.2.1 Total Adult and Pediatric FAERS Reports* from March 23, 2016 to December 20, 2017 with Reslizumab

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (> 17 years)	63 (51)	39 (27)	0 (0)
Pediatrics (0 - <17 years)	3 (3)†	**2 (2)**‡	**0** (0)

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

† See Appendix B for the FAERS cases numbers, version numbers, and manufacturer control numbers of the three retrieved cases.

‡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.***

2.2.2 Selection of Serious Pediatric Cases in FAERS

We identified three pediatric reports with reslizumab in the FAERS database from March 23, 2016 through December 20, 2017, of which one was a duplicate. Of the remaining two cases, one had a non-serious outcome and one had a serious outcome of hospitalization; no pediatric deaths were reported with reslizumab.

The case with a non-serious outcome did not report an adverse event; the non-serious report described that an 9-year-old patient with eosinophilic esophagitis had, "a lot less choking episodes since starting Cinqair."

The remaining report with a serious outcome of hospitalization was attributable to a strong alternative cause. The report described a 16-year-old female receiving reslizumab 2 mg/kg every four weeks through a compassionate use program for the treatment of eosinophilic esophagitis, albuterol inhaler, hyoscyamine sulfate, loratadine, and triamcinolone topical cream who experienced right upper quadrant and flank pain occurring several times per day (started at an unknown time relative to the initiation of all medications); magnetic resonance imaging (MRI) showed the patient's cystic duct was narrow and may be contributing to the development of chronic cholecystitis. The patient was hospitalized for an elective cholecystectomy.

Reviewer comment: For completeness, we searched the FAERS database for reports of bile duct disorders with reslizumab in the adult population for all dates through February 1, 2018 and did not retrieve any additional reports.

3 DISCUSSION

We evaluated all FAERS reports of adverse events in the pediatric population (n=3) with reslizumab from the initial U.S. approval date on March 23, 2016 through December 20, 2017. Review of the three reports revealed one was a duplicate, one did not report an adverse event, and one non-fatal serious case resulting in hospitalization was attributable to a strong alternative cause (chronic cholecystitis with MRI evidence of a narrow cystic duct). No new safety signals were identified after review of the case with reslizumab.

4 CONCLUSION

We did not identify any new safety signals with reslizumab in pediatric patients and there is no data to support a safety concern at this time.

5 RECOMMENDATIONS

DPV will continue routine pharmacovigilance monitoring of all adverse events with reslizumab.

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 LINE LISTING OF RESLIZUMAB REPORTS

	Initial FDA Received Date	FAERS Case Number	Version Number	Manufacturer Control Number
1	11/21/2016	12960324	2	US-TEVA-711267USA
2	12/2/2016	12994288	1	
3	5/16/2017	13550330	2	US-TEVA-768859USA

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