Reslizumab(CINQAIR)

National Drug Monograph

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Indication(s) Under Review	Reslizumab is an interleukin-5 antagonist monoclonal antibody indicated for add-on maintenance treatment of patients with severe asthma aged 18 years and older, **and with an eosinophilic phenotype.** Reslizumab is not indicated for treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus.
Dosage Form(s) Under Review	For intravenous infusion: 100mg /10mL solution in single-use vials
REMS	☐ REMS ☒ No REMS *See Other Considerations for additional REMS information*
Pregnancy Rating	Data on pregnancy exposure are insufficient to inform on drug-associated risks.

	Executive Summary
Efficacy	• Reslizumab was FDA approved for add-on maintenance treatment of patients with severe asthma aged 18 or older with an eosinophilic phenotype the based upon 4 pivotal phase III trials • Reslizumab vs. placebo as add-on to at least medium-dose inhaled corticosteroids ± controller drug ± oral corticosteroids was shown to reduce the risk of exacerbations by about half. • Reslizumab improved symptoms, quality of life, and pulmonary function (FEV1) compared to placebo. • There was no significant decrease in rescue inhaler use • Oral glucocorticoid sparing effect and ability to step-down other asthma medications were not evaluated.
Safety	• Anaphylaxis occurred with reslizumab infusion in 0.3% of patients in placebo-controlled trials. Anaphylaxis events were observed during or within 20 minutes after completion of the reslizumab infusion and reported as early as the second dose of reslizumab. Manifestations included dyspnea, decreased oxygen saturation, wheezing, vomiting, and skin and mucosal involvement, including urticaria. • At least one malignant neoplasm was reported in 0.6% patients receiving reslizumab and 0.3% patients in the placebo group. The malignancies reported in the reslizumab group were diverse in nature and without clustering of any particular tissue type. The majority were diagnosed within less than six months of exposure to reslizumab. • It is unknown if reslizumab will influence a patient's response against parasitic infections (patients with known parasitic infections were excluded from the clinical trials). • CPK elevation >10x ULN regardless of baseline value were reslizumab (0.8%) and placebo (0.4%). Elevations >10 x ULN were asymptomatic and did not lead to treatment discontinuation.
Other Considerations	• There has been a relatively small number of patients and a short duration of follow-up of studies; durability of treatment uncertain and whether relatively uncommon adverse events, such as opportunistic infections or anaphylaxis, will emerge with greater patient exposure • Reslizumab is administered as 3mg/kg every 4 weeks by IV infusion over 20-50 minutes. Reslizumab should be administered in a healthcare setting by a healthcare professional prepared to manage anaphylaxis

Projected Place in Therapy	Severe asthma that is not controlled on at least medium-dose ICS + at least one controller drug ± oral corticosteroids with evidence of eosinophilic inflammation

Background

Purpose for Review

The purpose of this monograph is to evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating reslizumab for possible addition to the VA National Formulary

Other Therapeutic Options

Formulary Alternatives	Other Considerations
N/A	
Non-formulary Alternatives	**Other Considerations**
Omalizumab	For those who meet eligibility criteria for reslizumab AND omalizumab, either SINGLE agent could be selected
Mepolizumab	Administered subcutaneously Lower risk of anaphylaxis?? Based on limited clinical trial data, there were no cases of anaphylaxis; however, it is unknown if cases will emerge with wider usage.

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to, June 30, 2016) using the search term reslizumab and asthma. The search was limited to studies performed in humans and published in the English language.

Review of Efficacy

This review will discuss the four primary efficacy trials comparing reslizumab and placebo; two 52-week and two 16-week trials (**Table 1).** Reslizumab was administered as 3mg/kg via intravenous infusion. The study by Bjermer was a dose-ranging trial that included a reslizumab 0.3mg/kg arm. Efficacy results are not shown for the unapproved 0.3mg/kg dose. All treatments were administered every 4 weeks.

Inclusion/Exclusion Criteria

The key inclusion criteria in the primary trials were diagnosis of asthma, ages 12-75 years (18-75 in Corren et al), airway reversibility ≥ 12% to a short-acting beta-agonist, Asthma Control Questionnaire (ACQ) score ≥ 1.5; additional inclusion criteria specific to each trial are shown in **Table 1**.

Key exclusions for the 52-week trials were current smoker; other underlying lung disorder; known hypereosinophilic syndrome; any clinically meaningful comorbidity that could interfere with study, current use of systemic immunosuppressive, immunomodulation or other biologic agents within prior 6 months; HIV, AIDS or congenital immunodeficiency; active parasitic infection within prior 6 months; receipt of live attenuated vaccines within prior 12-weeks; infection in prior 4 weeks necessitating hospitalization for ≥24 hours or treatment with IV/oral antibiotics; treatment for asthma exacerbation in prior 4 weeks; pregnant/nursing (see original publications for a list of complete inclusion/exclusion criteria).

Earlier studies with reslizumab indicate that eosinophilic asthma can be characterized by a sputum eosinophil count of ≥3% and that reslizumab is expected to benefit patients with asthma with sputum eosinophil count of ≥3%. The sponsor chose blood eosinophil as a surrogate of sputum eosinophilia because of the ease of obtaining in clinical practice. The sponsor selected ≥400 cells/μL as the threshold based on a secondary analysis of datasets from asthma patients that indicated blood eosinophil count of ≥400 cells/μL had a high positive predictive value for the presence of sputum eosinophils of ≥3%, and a count of <400 cells/μL identified the majority of patients without sputum eosinophilia. It should be noted that a definitive threshold value of eosinophilia has not been defined.

Table 1: Inclusion Criteria for Primary Trials

Study	Duration (weeks)	Treatment arms	n	Baseline medications	Exacerbation history	Eosinophilic inflammation criteria
Castro 2015	52	RSLZ PBO	245 244	At least medium dose ICS* ± other controller drugs ±oral steroids	≥1 exacerbation requiring systemic steroids in previous year	Blood eosinophil count ≥ 400 cells/mcL within 3-4 weeks of dosing
Castro 2015	52	RSLZ PBO	232 232	At least medium dose ICS ± other controller drugs ±oral steroids	≥1 exacerbation requiring systemic steroids in previous year	Same as above
Bjermer 2016	16	RSLZ 3 RSLZ 0.3 PBO	103 103 105	At least medium dose ICS ± other controller drugs Maintenance oral steroids not allowed	No exacerbation requirements	Same as above
Corren 2016	16	RSLZ PBO	398 98	At least medium dose ICS ± other controller drugs Maintenance oral steroids not allowed	No exacerbation requirements	None (in trial, 20% had eosinophil count ≥ 400 cells/mcL)

Abbreviations: ICS=inhaled corticosteroid; PBO=placebo; RSLZ=reslizumab
*Medium dose ICS fluticasone propionate ≥440mcg/day or equivalent)

Baseline Characteristics

In the 52-week studies, 63% were female, 73% were white, the approximate mean values were as follows; age 47 years, duration of asthma 19 years, FEV1 % predicted 66%, and eosinophil count 654 cells per mcL. Approximately 84% were using a LABA, 57% were using medium-dose and 43% high-dose ICS at baseline. The mean number of exacerbation in the prior year was 2; approximately 41% had ≥2 and 21% had ≥3 exacerbations in the prior year.

In the 16-week studies, 61% were female, 73% were white, the approximate mean values were as follows; age 45 years, , duration of asthma 20-26 years, FEV1 % predicted 68%, and eosinophil count 614 cells per mcL (Bjermer) and 280 (Corren) cells per mcL. Approximately 82% were using a LABA. Medium-dose ICS was used in 67% (Bjermer) and 76% (Corren) of patients; the remainder of patients were using high-dose ICS. The mean number of exacerbation in the prior year was 2; approximately 20% had ≥2 and 12% had ≥3 exacerbations in the prior year.

Exacerbations

The primary endpoint of the Castro trials was exacerbations. Exacerbation was defined as worsening of asthma that required at least ONE of the following: systemic steroids or 2-fold increase in ICS for ≥ 3 days AND/OR asthma-related emergency treatment (unscheduled visit to provider, ER visit, hospitalization). The medical intervention had to be corroborated with at least ONE of the following: ≥20% decrease from baseline in FEV1, ≥30% decrease from baseline in peak expiratory flow rate on two consecutive days, worsening of symptoms or other clinical signs per physician evaluation of event. Exacerbations were not evaluated in the 16-week trials.

Reslizumab reduced the risk of all exacerbations compared to placebo (**Table 2**). This was mainly driven by reduction in events requiring systemic steroids. Although a numerical difference was noted, there was no statistically significant difference between the 2 groups for events requiring hospitalization/ER visit.

Table 2: Exacerbations

Study	Duration (weeks)	Tx arms	n	Mean # exacerbations in prior year	No exacerbation during tx period (%)	Exacerbation Rate(per patient-year)		
						All episodes	Requiring systemic steroids	Hospitalization/ ED visit
Castro 2015	52	RSLZ PBO	245 244	1.99	62 46	0.90* 1.80	0.72* 1.60	0.14 0.21
Castro 2015	52	RSLZ PBO	232 232	1.94	75 55	0.86* 2.11	0.65* 1.66	0.03 0.05

*significant vs. placebo

A pooled post-hoc analysis of the Castro studies evaluated exacerbation outcomes according to age of asthma onset. Those who were diagnosed with asthma after the age of 40 years (late-onset asthma) had a greater reduction in asthma exacerbation and improvement in FEV1 at 52 weeks than those diagnosed with asthma before the age of 40

(**Table 3**) These results were presented as a late-breaking abstract at the 2015 ERS International Congress in Amsterdam.

Table 3: Exacerbations According to Age of Asthma Diagnosis

	Asthma exacerbations Rate ratio [95% CI]	FEV1 (mL) treatment difference vs. placebo [95%CI]
Overall	0.46 [0.37, 0.58]	110 [66-154]
Age <40 years	0.58 [0.44, 0.76]	88 [34, 142]
Age≥ 40 years	0.25 [0.16, 0.40]	167 [89, 245]

Symptom control/Quality of Life

The Asthma Control Questionnaire-7 (ACQ-7) consists of seven questions regarding frequency and severity of symptoms over the past week. Each response is graded on a 0-6 scale with higher scores indicating poorer control. The minimum clinically important difference (MID) for the mean score is 0.5 points.

The Asthma Quality of Life Questionnaire (AQLQ) measures physical and emotional impact of asthma. There are 32 items within the 4 domains: symptoms, activity limitation, emotional function, and environmental stimuli. The MID for the AQLQ for the mean score is 0.5 points.

Asthma Symptom Utility Index (ASUI) is an 11 item questionnaire with scores range from 0 (worst possible symptoms) to 1 (no symptoms). This instrument assesses frequency and severity of cough, wheezing, dyspenia, and nighttime awakening, and medication side effects. The MID has not been well established. One study has determined the MID to be 0.09 and another to be 0.15.

In the 52 week trials, there was significantly greater improvement in the ACQ-7, AQLQ, and ASUI scores with reslizumab compared to placebo. A greater proportion of patients in the reslizumab groups achieved the MID of ≥ 0.5 for ACQ and AQLQ (**Table 4**).

The improvement in ACQ score was significant in both 16 week trials with reslizumab versus placebo; however, the proportion of patients achieving the MID did not differ between groups in the trial by Bjermer (not discussed in Corren). In Bjermer, the improvement in the AQLQ score and the proportion of patients meeting the MID was significantly greater with reslizumab. There was no significant improvement in the ASUI score (**Table 4**).

Table 4: Asthma Symptoms and Quality of Life

Study	Tx arms	Baseline ACQ-7	ACQ-7 Δ score (% pts MID)	Baseline AQLQ	AQLQ Δ score (% pts MID)	Baseline ASUI	ASUI Δ score
Castro 2015	RSLZ	2.66	-1.02* (76)*	4.30	1.09* (74)*	0.63	0.19*
	PBO	2.76	-0.76 (63)	4.16	0.79 (65)	0.61	0.13
Castro 2015	RSLZ	2.57	-1.04* (77)*	4.35	1.12* (73)*	0.66	0.15*
	PBO	2.61	-0.80 (61)	4.22	0.89 (62)	0.65	0.11
Bjermer 2016	RSLZ 3	2.59	-0.85* (64)	4.18	1.14* (64)*	0.66	0.13
	PBO	2.47	-0.49 (58)	4.37	0.78 (48)	0.67	0.08
Corren 2016	RSLZ	2.55	-0.84*	N/A	N/A	N/A	N/A
	PBO	2.56	-0.65				

*significant vs. placebo

Data for Castro trials are at week 52 and Bjermer and Corren at week 16

Pulmonary Function

The primary endpoint in the 16 week trials was change in FEV1. The 52-week trials evaluated FEV1 at 16 weeks as a secondary endpoint; data were also collected at 52 weeks. There was significant improvement in FEV1 at week 16 compared to placebo in all the trials except for the trial by Corren (**Table 5**). Recall that the Corren trial did not require baseline eosinophils ≥400 cells/μL as an inclusion criterion; therefore, patients with values above and below 400cells/μL were included. A subgroup analysis showed those with eosinophils ≥400cells/μL, had significant improvement in FEV_1 compared to placebo (treatment difference 0.270L [95%CI 0.008, 0.532; p=0.043]). Comparatively, the subgroup of patients with baseline eosinophils <400cells/μL, did not have significant improvement in FEV_1 with reslizumab vs. placebo (treatment difference 0.033L [95%CI -0.073, 0.0539; p=NS]).

Longer-term data show that improvement in FEV1 at week 52 is maintained.

Table 5: Change from Baseline in FEV1 (mL) and Rescue Inhaler Use

Study	Treatment arms	Baseline FEV1 (L)	ΔFEV1 (L) Week 16	ΔFEV1 (L) Week 52	SABA use in past 3 days (% pts)	Baseline SABA (puffs/day)^	SABA (puffs/day)
Castro 2015	RSLZ	1.89	0.248*	0.235*	78	2.4	-0.58
	PBO	1.93	0.110	0.109	78	2.7	-0.42
Castro 2015	RSLZ	2.13	0.187*	0.201*	69	1.9	-0.73
	PBO	2.00	0.094	0.11	77	2.1	-0.55
Bjermer 2016	RSLZ 3	2.19	0.286*	N/A	N/A	2.2	-0.9*
	PBO	2.22	0.126			2.3	-0.3
Corren 2016	RSLZ	2.10	-0.256	N/A	N/A	1.9	-0.3
	PBO	2.18	-0.187			2.0	-0.4

^Mean SABA use in the past 3 days

Short-acting beta-agonist use
Only the trial by Bjermer showed a small, but statistically significant decrease in as needed SABA use (**Table 5**).

Oral glucocorticoid sparing effect
Oral glucocorticoid sparing effects were not evaluated.

Ability to step-down background medications
Not assessed

Long-term Studies
There is an ongoing long-term open-label extensions study from both Castro trials and the trial by Bjermer.

Potential Off-Label Use

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

Hypereosinophilic syndrome, eosinophilic esophagitis, nasal polyposis, COPD

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	Anaphylaxis occurred with reslizumab infusion in 0.3% of patients in placebo-controlled trials. Patients should be observed for an appropriate period of time after reslizumab infusion; healthcare professionals should be prepared to manage anaphylaxis that can be life-threatening. Discontinue reslizumab immediately if the patient experiences anaphylaxis.
Contraindications	History of hypersensitivity to reslizumab or any of its excipients
Warnings/ Precautions	• Anaphylaxis: See boxed warning. Anaphylaxis events were observed during or within 20 minutes after completion of the reslizumab infusion and reported as early as the second dose of reslizumab. Manifestations included dyspnea, decreased oxygen saturation, wheezing, vomiting, and skin and mucosal involvement, including urticaria. In all 3 cases, reslizumab was discontinued. • Acute asthma symptoms or deteriorating disease: Do not use reslizumab to treat acute asthma symptoms or acute asthma exacerbations • Malignancy: in the placebo-controlled trials, 6/1028 (0.6%) patients receiving reslizumab had at least one malignant neoplasm reported compared to 2/730 (0.3%) patients in the placebo group. The malignancies reported in the reslizumab group were diverse in nature and without clustering of any particular tissue type. The majority were diagnosed within less than six months of exposure to reslizumab. • Reduction of corticosteroid dosage: no clinical studies have been conducted to assess

reduction of maintenance corticosteroid dosages following administration of reslizumab. Do not abruptly discontinue systemic or inhaled steroids upon initiation of reslizumab. If appropriate, reduction should be done gradually and under the care of a physician.

- Parasitic (helminth) infection: It is unknown if reslizumab will influence a patient's response against parasitic infections (patients with known parasitic infections were excluded from the clinical trials). Pre-existing infection should be treated prior to initiating therapy with reslizumab. If an infection occurs while being treated with reslizumab and does not respond to anti-helminth therapy, discontinue reslizumab until infection resolves.

Safety Considerations

CPK elevation and muscle-related events

At baseline, elevated CPK was more frequent in the reslizumab groups (14%) than placebo (9%). Transient elevation in CPK in those with normal baseline values occurred in 20% and 18% of the reslizumab and placebo groups respectively during routine laboratory assessment. CPK elevation >10x ULN regardless of baseline value were reslizumab (0.8%) and placebo (0.4%). Elevations >10 x ULN were asymptomatic and did not lead to treatment discontinuation.

Myalgia was reported in 1% of the reslizumab 3mg/kg group compared to 0.5% of the placebo group. On the day of infusion, musculoskeletal AEs were reported in 2.2% of the reslizumab 3mg/kg and 1.5% of the placebo groups. These reactions included musculoskeletal chest pain, neck pain, muscle spasm, extremity pain, muscle fatigue and musculoskeletal pain.

Infection

Infections, including serious infections and opportunistic infections, were reported in 41% and 53% of the reslizumab and placebo-treated groups respectively. The most commonly reported infection events were nasopharyngitis (14%), upper respiratory tract infection (12%), sinusitis (7%), and bronchitis (6%). No opportunistic infections were reported, including helminthic infections. Reslizumab clinical studies included regions where helminthic parasitic infections are prevalent.

Immunogenicity

Anti-drug antibodies (ADA) were mostly low titer and transient. About 5% of reslizumab treated patients developed at least one positive ADA during the treatment period. The ADA-positive and ADA-negative patients had similar adverse event profile and positive antibody status was not associated anaphylaxis or hypersensitivity reactions to reslizumab. Change in blood eosinophils and efficacy was not affected by antibody status.

Adverse Reactions

Common adverse reactions

Common adverse reactions were reported more frequently in the placebo group with the exception of oropharyngeal pain. Only oropharyngeal pain was reported more often with reslizumab.

Table 6 : Adverse Reactions (≥2%) from Primary Trials

	RSLZ (%) (n=1028)	Placebo (%) (n=730)
Asthma	22.6	39.6
Nasopharyngitis	10.0	14.1
URI	9.3	9.5
Headache	7.6	8.5
Sinusitis	5.5	7.0
Bronchitis	3.3	7.1
UTI	3.3	3.3
Back pain	3.2	3.4
Influenza	3.2	5.1
Allergic rhinitis	2.7	3.0
Oropharyngeal pain	**2.6**	**2.2**
Pharyngitis	2.2	3.4
Cough	2.1	3.2

	Dyspnea	2.1	2.7
	FDA Briefing Document		

Death/Serious adverse reactions (SAE)	**Deaths**: 1 death in the placebo group (52-week trial); there were no deaths in either group in the 16-week trials. Four deaths were reported in the open-label extension studies. None were considered related to study drug. The cause of death was progressive anal cancer (1), hemoptysis/aspiration pneumonia, cardiac arrest (1), cardiac arrest (1), and accidental drug overdose (1). **Non-fatal SAE** 52-week trials: Reslizumab 42/477 (8.8%); placebo 57/475 (12%) 16-week trials: Reslizumab 20/501 (4%); placebo 5/203 (2.5%) Most reports were asthma-related.
Discontinuations due to adverse reactions	52-week trials: Reslizumab 12/477 (2.5%); placebo 17/475 (3.6%) 16-week trials: Reslizumab 39/501 (7.8%); placebo 21/203 (10.3%)

Drug Interactions

Drug-drug interactions	Formal drug interaction trials have not been conducted. However, possibility of drug interactions should be considered based on class of drug (e.g., vaccines, other biologics, etc.)
Drug-food interactions	None
Drug-lab interactions	None
Pharmacogenomics	None

Risk Evaluation

As of June 2016

Sentinel event advisories	Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Reslizumab	None	None	None	Ranibizumab Raxibacumab
Cinqair	None	None	None	Cinryze Cimzia Singulair

Other Considerations

- Supplied as 100mg/10mL vial
- Refrigerate at 2°C to 8°C (36°F to 46°F). Do not freeze. Do not shake. Protect from light by storing in the original package until time of use

- Reslizumab is only available to VA through ASD Healthcare. ASD Healthcare will accept wholesale orders for the product and no specialty pharmacy services are required. Details are posted on PBM's SharePoint site: https://vaww.cmopnational.va.gov/cmop/PBM/Special%20Handling%20Drugs/Forms/AllItems.aspx

Dosing and Administration

See product labeling for complete instructions

- 3mg/kg every 4 weeks by IV infusion over 20-50 minutes
- If refrigerated prior to administration, allow diluted reslizumab to reach room temperature
- Reslizumab should be administered in a healthcare setting by a healthcare professional prepared to manage anaphylaxis

Special Populations (Adults)

	Comments
Elderly	There were 122 patients enrolled in the clinical trials who were ≥ 65 years old that received reslizumab. Overall differences in safety or effectiveness were not observed between younger and older patients. No dosage adjustment is required.
Pregnancy	Data on pregnancy exposure are insufficient to inform on drug-associated risks. Transfer of monoclonal antibodies across the placenta increases in a linear fashion as pregnancy progresses (greater during 2nd and 3rd trimesters). Reslizumab has a long half-life (approximately 24 days). This needs to be taken into consideration. There was no evidence of adverse effects on embryo-fetal development in mice and rabbits at doses ~6 times the exposure at the maximum recommended human dose (MRHD) in mice and ~17 times the MRHD in rabbits.
Lactation	It is not known if reslizumab is present in human milk. However, reslizumab is a monoclonal antibody (IgG4 kappa), and IgG is present in human milk in small amounts. In lactating mice (at 1.5 and 6 times exposures achieved at the MRHD levels) during gestation day 6 and 18 and postnatal day 14, the levels of reslizumab in milk were approximately 5-7% of maternal serum concentration. The benefits of breastfeeding and mother's clinical need for reslizumab versus any potential adverse effects should be considered.
Renal Impairment	None
Hepatic Impairment	None
Pharmacogenetics/genomics	None

Projected Place in Therapy

Severe asthma that is not controlled on at least medium-dose ICS + at least one controller drug ± oral corticosteroids with evidence of eosinophilic inflammation

References:

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Prepared by Deb Khachikian, PharmD