Drug Use Research & Management Program
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New Drug Evaluation: reslizumab for injection

Date of Review: July 2016
Generic Name: reslizumab
PDL Class: Misc Pulmonary Agents

End Date of Literature Search: March 2016
Brand Name (Manufacturer): Cinqair® (Teva)
AMCP Dossier Received: Yes

Research Questions:

1. Does reslizumab have superior efficacy to placebo and is it more effective than alternative drugs in clinically relevant outcomes for the treatment of severe asthma?
2. Is reslizumab safer than currently utilized drugs in the treatment of severe asthma?

Conclusions:

- Moderate quality evidence over 52 weeks supports the efficacy of reslizumab 3 mg/kg intravenous (IV) infusion every 4 weeks in reducing the number of patients experiencing at least one asthma exacerbation (an exacerbation that requires use of systemic corticosteroids, a two-times increase in the dose of either inhaled corticosteroid [ICS] or oral corticosteroids [OCS] for 3 or more days, an emergency department visit, and/or hospitalization or unscheduled physician's office visit) in adults (≥18 years) with severe eosinophilic asthma (broadly defined as peripheral blood count ≥400 cells/µL) compared to placebo (32% vs. 50%, respectively; RR 0.64; 95% CI 0.5 to 0.7) with an ARR of 18% and a NNT of 5 over 52 weeks. All patients received standard of care for severe asthma (i.e., high dose ICS, long-acting beta-agonist [LABA] and a rescue short-acting bronchodilator).
- Low quality evidence suggests reslizumab 3 mg/kg IV every 4 weeks does not reduce the rate of exacerbations that require hospitalization or emergency department visits compared with placebo (RR 0.66; 95% CI 0.38 to 1.16).
- Moderate quality evidence suggests reslizumab is associated a clinically meaningful improvement in quality life, measured by more patients achieving a 0.5 point reduction in the Asthma Control Questionnaire and the Asthma Quality of Life Questionnaire.
- There is insufficient data to support reslizumab in patients' ages 12 to 17 years of age. Although the sample size small, there was an increase in asthma exacerbation rates among adolescents. Reslizumab should not be used at this time in this patient population.
- The reslizumab and placebo groups had similar frequencies of serious adverse events, with the majority of events related to asthma exacerbations. However, patients 12 to 17 years of age, elderly patients, U.S. and non-white racial groups were underrepresented in clinical trials. Therefore, the safety of reslizumab in these populations is unclear.
- There is insufficient evidence to differentiate differences in efficacy or safety between reslizumab and other monoclonal antibodies for severe asthma of any phenotype.

Recommendations:

Designate reslizumab as a non-preferred drug subject to Prior Authorization (PA) criteria in **Appendix 2**.

Author: Herink

Date: July 2016

Background:
An estimated 22 million Americans have asthma, which affects people of all ages and can have a significant impact on quality of life and daily functioning.[1] Only 5-10% of people with asthma have severe asthma but they account for about 50% of all healthcare costs associated with asthma.[1] Severe asthma is characterized by daily symptoms, awakening most nights due to symptoms and significant limitations in normal activities.[1,2] The European Respiratory Society (ERS)/American Thoracic Society (ATS) defines severe asthma as asthma that (1) requires treatment with high dose ICS plus a second controller (e.g., LABA) during the previous year and/or use OCS for 50% or more of the previous year or (2) remains uncontrolled despite this therapy.[3] However, chronic use of OCS may result in other complications, including growth suppression in children, osteoporosis, Cushing's syndrome, adrenal insufficiency, diabetes, and increased risk for infections.[1]

Clinical trials may further define patients with severe asthma as those whose asthma worsens when high dose ICS or OCS are tapered but do not otherwise meet criteria for uncontrolled asthma and patients with evidence of any one of the 4 following criteria for uncontrolled asthma who are currently on high dose ICS therapy: (1) poor symptom control (Asthma Control Questionnaire [ACQ] score consistently greater than 1.5 or Asthma Control Test [ACT] score less than 20; (2) frequent severe exacerbations that have required use of OCS for more than 3 days on 2 separate occasions in the previous year; (3) serious exacerbations that resulted in at least 1 hospitalization in the previous year; or (4) airflow limitation (pre-bronchodilator forced expiratory volume in 1 second (FEV_1) less than 80% of the normal predicted volume with a reduced FEV_1/Forced Vital Capacity (FVC) defined as less than the lower limit of normal.[3] However, uncontrolled asthma is multifactorial, and issues such as incorrect diagnosis, comorbidities and nonadherence to prescribed therapy, and psychosocial issues are major causes for treatment failure.[2] The Global Initiative for Asthma (GINA) guidelines recommend patients with severe asthma, despite correct inhaler use and adherence to standard of care, be seen by an asthma specialist.[4] These patients should be seen 1 to 3 months after starting specific treatment for eosinophilic severe asthma, and every 3–12 months thereafter.[4] All patients should be seen within 1 week after an exacerbation.[4]

Clinically relevant outcomes for severe asthma include reduction in asthma exacerbations that result in: 1) decreased emergency department (ED) visits or hospitalizations; 2) decreased chronic use of OCS; 3) improved quality of life; and 4) improved symptom management. Four instruments are commonly used in clinical trials to assess quality-of-life and symptom management related to asthma. These tests are self-administered and subject to recall bias but have been validated with highly consistent reproducibility between users. The ACQ is a 5- or 7-item questionnaire that assesses asthma symptoms and rescue inhaler use in the preceding week.[5] Scores range from 0 (totally controlled) to 6 (severely uncontrolled), with a change in score of 0.5 the minimally clinical important difference.[5] The Asthma Quality of Life Questionnaire (AQLQ) is a 32-item quality-of-life instrument that assesses both physical and emotional impact of disease.[6] Scores range from 1 (severely impaired) to 7 (not impaired at all), with higher scores indicating better quality of life.[6] A difference of 0.5 overall and for each item is the minimally clinical important difference for this instrument.[6] The St. George's Respiratory Questionnaire (SGRQ) is a 50-item quality-of-life tool for patients with obstructive airway disease.[7] The questionnaire is composed of 2 parts. Part 1 assesses symptoms and part 2 assesses limitation of activities and its social and psychological impact.[7] Scores range from 0 to 100, with higher scores indicating more limitations.[7] A change of 4 points is associated with slightly efficacious treatment, 8 points for moderately efficacious treatment, and 12 points for very efficacious treatment.[7] Lastly, the ACT is a tool used to identify patients with poorly controlled asthma.[8] The test contains 5 items that assess the frequency of shortness of breath and general asthma symptoms, use of rescue medications, the effect of asthma on daily functioning, and overall self-assessment of asthma control.[8] Scores range from 5 (poor control of asthma) to 25 (complete control of asthma).[8] An ACT score greater than 19 indicates well-controlled asthma, with a change of 3 points the minimally clinical important difference over time.[8]

Omalizumab is a monoclonal antibody that has been available for over a decade to help manage severe allergic asthma with use of other asthma controllers (e.g., ICS, LABA, etc.).[9] Mepolizumab and reslizumab are humanized monoclonal antibodies recently approved to manage severe asthma. These agents are approved and studied in patients with severe asthma and eosinophilic phenotype, though this phenotype has not been clearly defined outside of these trials and a consensus has not been developed to identify this phenotype in a clinically useful way.[11–13] Eosinophilic asthma is found in patients with both non-severe and severe disease and is often associated with response to corticosteroids.[15,16] However, some patients with eosinophilic asthma may not sufficiently respond to OCS .[15,16] Persistence of eosinophils in the airways despite ICS therapy has been associated with severe asthma, and higher airway and blood eosinophil counts have been associated with increased risk for asthma exacerbations.[16–18] Reslizumab is an interleukin 5 antagonist approved for the add-on maintenance treatment of patients with severe asthma and with an eosinophilic phenotype.[19] It was studied as add on therapy for patients inadequately controlled on traditional controller medications, which may include inhaled corticosteroids, long-acting inhaled beta-agonists, mast cell stabilizers and leukotriene modifiers. Reslizumab was studied in patients with asthma with sputum eosinophil count ≥3%. However, in clinical trials blood eosinophil was used a surrogate to sputum eosinophilia because it is more accessible.

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Reslizumab was FDA approved based on 3 phase 3 studies (3081, 3082, and 3083).[23] Study 3081 was a lung function study and studies 3082 and 3083 were exacerbation studies. Patients were required to have a blood eosinophil count ≥400 cells/µl. This cutoff is based on data suggesting that a blood eosinophil count of at least 400 cells/µl had a high positive predictive value for the presence of sputum eosinophils of 3% or greater. However, this threshold is not widely defined or definitive.[23] The studied dose was 3 mg/kg IV every 4 weeks. However, the FDA notes that dose-ranging data are not as robust for reslizumab, and only a single dose was studied in all phase 3 studies.[23] Study sites were in the US, North America, South America, Asia and Europe. In the 3 primary studies (3081, 3082, 3083), only 20% of sites were within the US. Studies included patients with mean asthma duration of around 20 or more years with a mean of 2 exacerbations in the previous year.[23] All patients were on standard of care treatment based on disease severity, including ICS and LABA with inadequate control based on an ACQ score of ≥1.5.[23]

Study 3081 was a dose ranging lung function study over 16 weeks. It remains unpublished and cannot be adequately assessed for quality. It included patients taking medium- to high-dose ICS with or without another controller with inadequate control based on an ACQ score of ≥1.5.[23] This was the only study investigating more than one dose of reslizumab, 0.3 mg/kg and 3 mg/kg IV. Overall, both groups had a significant improvement in FEV1 from baseline compared to placebo (0.127, 0.238, and 0.286 L for placebo, 0.3 mg/kg and 3 mg/kg, respectively). While the treatment effect was larger for patients in the 3.0 mg/kg treatment group (treatment difference 0.159L) compared to the 0.3 mg/kg group (0.111 L), both demonstrated efficacy in lung function. Both doses demonstrated improvements in the ACQ and AQLQ. A dose-dependent reduction of blood eosinophil count was seen with the higher dose (92%) compared to the lower dose (68%) and placebo (14%).[23] How this relates to clinical outcomes remains unknown. An additional study was designed to evaluate for an interaction between change from baseline in FEV1 and baseline eosinophil count and no significant interaction was found.[23] Additionally, an FDA exploratory analysis of studies 3082 and 3083 found no relationship between blood eosinophil count and exacerbation benefit.[23]

Studies 3082 and 3083 were identical phase 3 studies evaluating the frequency of exacerbations over 52 weeks with similar inclusion criteria as study 3081 in addition to requiring ≥1 exacerbation during the year prior and the use of OCS was permitted.[24] Studies only included the 3 mg/kg dose despite the FDA

suggesting inclusion of more than one dose.[23] Pooled data from 3082 and 3083 demonstrated a decrease in the number of patients experiencing at least one asthma exacerbation compared to placebo (32% vs. 50%, respectively; RR 0.64; 95% CI 0.5 to 0.7) with an ARR of 18% and a NNT of 5 over 52 weeks.[24] There was no significant difference in the rate of episodes requiring hospitalization or ER visit per patient per year between reslizumab and placebo (0.077 vs. 0.12; RR 0.66; 95% CI 0.38 to 1.16).[24] However, the rates were low across all treatment groups (approximately 1 in every 5-10 exacerbations).[23] There was a significant improvement in patient-reported measures of asthma control (ACQ) (pooled mean difference -0.25; 95% CI -0.343 to 0.156) and significantly more patients achieving a clinically significant reduction of 0.5 points on the ACQ in the reslizumab group compared to placebo, despite a large placebo effect.[24] Both studies demonstrated an increased change in FEV1 over placebo at week 52 (0.145 L in study 3082 and 0.123 L in study 3083).

Study data did not show a consistent benefit in patients 12 to 17 years of age; therefore, reslizumab is only approved for adults ages 18 years or older.[23] A total of 40 pediatric patients ages 12 to 17 were included in studies 3081, 3082 and 3083 and the FDA advisory committee did not find the data adequate to support approval. In addition, findings of an increase in asthma exacerbation rates was observed for adolescents, Blacks, and US patients. This could be driven by the small sample size in these subgroups; further data is needed in these populations.

Clinical Safety:
Overall dropouts and discontinuation were low. The most common event leading to discontinuation in all groups was asthma. The most common adverse events occurring in more than 5% of patients receiving reslizumab were worsening of asthma symptoms, nasopharyngitis, upper respiratory tract infections, sinusitis, influenza and headache. The only adverse event occurring at greater than 2% incidence and more commonly than in the placebo group was oropharyngeal pain (2.6% vs. 2.2%).

Anaphylaxis as a treatment related serious adverse event was reported in 3 patients receiving reslizumab. Other findings were malignancy and a transient increase in CPK suggesting potential for muscle toxicity. CPK elevations > 10 x ULN occurred more frequently in the reslizumab arm (0.8%) compared to the placebo arm (0.4%). Musculoskeletal pain, muscle spasm, myalgia, muscle fatigue and rhabomyolysis also occurred with higher incidence 24 hours after infusion in the reslizumab group as cojpared to placebo. However, overall differences were small and there was an imbalance in baseline CPK values between the two groups.

Pharmacology and Pharmacokinetic Properties:

Parameter	
Mechanism of Action	IL-5 antagonist; thereby reducing the production and survival of eosinophils.
Distribution and Protein Binding	Volume of distribution of 5L, suggesting minimal distribution to the extravascular tissues.
Metabolism	Metabolized by enzymatic proteolysis into small peptides and amino acids.
Half-Life	Approximately 24 days.
Elimination	Clearance approximately 7ml/hour.

Abbreviations: IL-5 = interleukin 5; L = liters; ml =milliliters

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Hospitalizations due to exacerbations
2) Emergency Department visits due to exacerbations
3) Quality of life
4) Asthma symptoms
5) Reduction/elimination in systemic corticosteroid use
6) Serious adverse events
7) Discontinuations due to adverse events

Primary Study Endpoint:

1) Frequency of clinical asthma exacerbations per patient during the 52 week treatment period.

Table 1. Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Castro, et al.[24] (Study 1) MC, DB, PC, RCT Phase 3 Study 3082	1. RES 3 mg/kg IV Q 4 weeks 2. Placebo	Demographics: Mean age: 49 y Females: 62% White: 73% Chronic OCS: 19% LABA use: 85% Mean ACQ: 2.71 Key Inclusion Criteria: Age 12-75 years blood eosinophil ≥ 400 cells/ µL; ACQ-7 score ≥1.5, at least medium dose ICS, ≥1 exacerbation in year prior Key Exclusion Criteria: Any clinically meaningful comorbidity, other lung disease, current smoker, any inadequately controlled medical factors (diabetes, GERD), pregnant or nursing females, HIV, drug and alcohol abuse.	ITT: 1. 245 2. 244 Attrition: 1. 0 2. 0	Primary Endpoint: Rate of asthma exacerbations per patient per year* 1. 0.90 2. 1.80 RR 0.50 (95% CI 0.37 to 0.67) Patients with ≥ 1 CAE 1. 92 (38%) 2. 132 (54%) RR 0.69 (95% CI 0.56 go 0.85) Secondary Endpoints: Proportion of patients achieving a 0.5 point reduction in ACQ score from baseline: 1. 184 (76%) 2. 152 (63%) OR 0.5; 95% CI 0.3 to 0.8 Proportion of patients achieving a 0.5 point reduction in AQLQ score from baseline: 1. 75% 2. 65% OR 0.6; 95% CI 0.4 to 0.9) Rate of CAE requiring hospitalization or ER treatment per patient per year: 1. 0.14 2. 0.21 RR 0.66 (95% CI 0.32 to 1.36) P=0.26	NA 16/6 13/7 10/10 NS	Outcome: D/C due to AE: 1. 4 (1.6%) 2. 8 (3.3%) SAE (includes asthma-related AE): 1. 10% 2. 14%	NS NS	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized 1:1 by computerized central randomization and interactive response technology. Performance Bias: (low) patients and investigators remained masked. RES and PBO identical volume and in appearance. Detection Bias: (unclear) Funder's clinical staff masked until analysis; unclear of outcome assessors blinded. Attrition Bias: (low) overall attrition low and similar across groups based on mITT analysis; imputation of missing data unclear for several dropouts. Appropriate statistical tests used. Reporting Bias: (unclear) Funded by Teva. Teva employees were involved in all steps of study design and data analysis and had access to all study data and were involved in writing and publishing of the manuscript. **Applicability**: Patient: extensive and elusive exclusion criteria limits applicability of study results. Intervention: FDA suggested that multiple doses of RES studied in phase 3 trials. Unclear on optimal dose due to lack of dose response data. Comparator: PBO allows investigators to assess efficacy of RES, but a direct comparison with other monoclonal antibodies for severe asthma would be helpful to understand place in therapy Outcomes: clinically significant asthma exacerbation defined as a composite of many outcomes but it is unclear what criteria primarily drove the reduction in exacerbations; no clear dose-response observed across doses. Short study duration. Setting:128 centers in Asia, Australia, North America, South America, South Africa, and Europe. Only 15% in the US.

2. Castro, et al.[24] (Study 2) MC, DB, PC, RCT Phase 3 Study 3083	1. RES 3 mg/kg IV Q 4 weeks 2. Placebo	Demographics: Mean age: 48 y Females: 63% White: 73% Chronic OCS: 12% LABA use: 82% Mean ACQ: 2.59 Key Inclusion Criteria: Age 12-75 years blood eosinophil≥ 400 cells/ µL; ACQ-7 score ≥1.5, at least medium dose ICS, ≥1 exacerbation in year prior Key Exclusion Criteria: Any clinically meaningful comorbidity, other lung disease, current smoker, any inadequately controlled medical factors (diabetes, GERD), pregnant or nursing females, HIV, drug and alcohol abuse.	ITT: 1. 232 2. 232 Attrition: 1. 0 2. 0	Primary Endpoint: Rate of asthma exacerbations per patient per year* 1. 0.86 2. 2.11 RR 0.41 (95% CI 0.28 to 0.59) Patients with ≥ 1 CAE 1. 59 (25%) 2. 105 (45%) RR 0.56 (95% CI 0.4 to 0.74) Secondary Endpoints: Proportion of patients achieving a 0.5 point reduction in ACQ score from baseline: 1. 178 (77%) 2. 140 (61%) OR 0.4; 95% CI 0.2 to 0.6 Proportion of patients achieving a 0.5 point reduction in AQLQ score from baseline: 1. 74% 2. 64% OR 0.6; 95% CI 0.4 to 1.0) Rate of CAE requiring hospitalization or ER treatment per patient per year: 1. 0.03 2. 0.05 RR 0.69 (95% CI 0.29 to 1.65) P=0.4	NA 20/5 16/6 NS NS	Outcome: D/C due to AE: 1. 8 (3.4%) 2. 9 (3.9%) SAE (includes asthma-related AE): 1. 8% 2. 10%	NS NS	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized 1:1 by computerized central randomization and interactive response technology. Performance Bias: (low) patients and investigators remained masked. RES and PBO identical volume and in appearance. Detection Bias: (unclear) Funder's clinical staff masked until analysis; unclear of outcome assessors blinded. Attrition Bias: (low) overall attrition low and similar across groups based on mITT analysis; imputation of missing data unclear for several dropouts. Appropriate statistical tests used. Reporting Bias: (unclear) Funded by Teva. Teva employees were involved in all steps of study design and data analysis and had access to all study data and were involved in writing and publishing of the manuscript. **Applicability**: Patient: extensive and elusive exclusion criteria limits applicability of study results. Intervention: FDA suggested that multiple doses of RES studied in phase 3 trials. Unclear on optimal dose due to lack of dose response data. Comparator: PBO allows investigators to assess efficacy of RES, but a direct comparison with other monoclonal antibodies for severe asthma would be helpful to understand place in therapy Outcomes: clinically significant asthma exacerbation defined as a composite of many outcomes but it is unclear what criteria primarily drove the reduction in exacerbations; no clear dose-response observed across doses. Short study duration. Setting: 128 centers in Asia, Australia, North America, South America, South Africa, and Europe. Only 7% in the US.

Abbreviations [alphabetical order]: ACQ = 5-item Asthma Control Questionnaire (scale 0-6); AQLQ = 32-item Asthma Quality of Life Questionnaire (scale 1-7); ARI = absolute risk increase; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; h/o = history of; ICS = inhaled corticosteroid; ITT = intention to treat; IV = intravenous; LABA = Long Acting Beta Agonist; MC = multi-centered; MD = mean difference; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not statistically significant; OCS = oral corticosteroid; OR = odds

ratio; PC = placebo-controlled; PBO = placebo; PG = parallel group; PP = per protocol; RR = relative risk; RES = reslizumab; RRR = relative risk reduction; SAE = serious adverse event; y = years; µL = microliters.

*Worsening of asthma that resulted in use of systemic corticosteroids in patients not already receiving treatment, or a two-times increase in the dose of either ICS or OCS for 3 or more days, or the need for emergency department or hospital admission or unscheduled physician's office visit.

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Appendix 1: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CINQAIR safely and effectively. See full prescribing information for CINQAIR.

CINQAIR® (reslizumab) injection, for intravenous use
Initial U.S. Approval: 2016

WARNING: ANAPHYLAXIS
See full prescribing information for complete boxed warning.

- **Anaphylaxis occurred with CINQAIR infusion in 0.3% of patients in placebo-controlled studies (5.1)**
- **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 (5.1)**
- **Discontinue CINQAIR immediately if the patient experiences anaphylaxis (5.1)**

----------**INDICATIONS AND USAGE**----------
CINQAIR is an interleukin-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).

Limitations of Use: CINQAIR is **not** indicated for:
- treatment of other eosinophilic conditions (1)
- relief of acute bronchospasm or status asthmaticus (1)

----------**DOSAGE AND ADMINISTRATION**----------
- CINQAIR is for intravenous infusion only. Do not administer as an intravenous push or bolus (2.1)
- CINQAIR should be administered in a healthcare setting by a healthcare professional prepared to manage anaphylaxis (2.2)
- Recommended dosage regimen is 3 mg/kg once every 4 weeks by intravenous infusion over 20-50 minutes (2.1)

----------**DOSAGE FORMS AND STRENGTHS**----------
Injection: 100 mg/10 mL (10 mg/mL) solution in single-use vials (3)

----------**CONTRAINDICATIONS**----------
Known hypersensitivity to reslizumab or any of its excipients (4)

----------**WARNINGS AND PRECAUTIONS**----------
- Malignancy: Malignancies were observed in clinical studies. (5.3)
- Reduction in Corticosteroid Dosage: Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with CINQAIR. Decrease corticosteroids gradually, if appropriate. (5.4)
- 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. (5.5)

----------**ADVERSE REACTIONS**----------
The most common adverse reaction (incidence greater than or equal to 2%) includes oropharyngeal pain. (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 03/2016

Monoclonal Antibodies for Severe Asthma

Goal(s):

- Restrict use of monoclonal antibodies to patients with severe asthma requiring chronic systemic corticosteroid use or with history of asthma exacerbations in the past year that required and Emergency Department visit or hospitalization.

Length of Authorization:

Up to 12 months

Requires PA:

- Mepolizumab
- Reslizumab

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Maximum Adult Doses for Inhaled Corticosteroids.

High Dose Corticosteroids:	**Maximum Dose**
Qvar (beclomethasone)	320 mcg BID
Pulmicort Flexhaler (budesonide)	720 mcg BID
Alvesco (ciclesonide)	320 mcg BID
Aerospan (flunisolide)	320 mcg BID
Arnuity Ellipta (fluticasone furoate)	200 mcg daily
Flovent HFA (fluticasone propionate)	880 mcg BID
Flovent Diskus (fluticasone propionate)	1000 mcg BID
Asmanex Twisthaler (mometasone)	440 mcg BID
Asmanex HFA (mometasone)	400 mcg BID
High Dose Corticosteroid / Long-acting Beta-agonists	**Maximum Dose**
Symbicort (budesonide/formoterol)	320/9 mcg BID
Advair Diskus (fluticasone/salmeterol)	500/50 mcg BID
Advair HFA (fluticasone/salmeterol)	460/42 mcg BID
Breo Ellipta (fluticasone/vilanterol)	200/25 mcg daily
Dulera (mometasone/formoterol)	400/10 mcg BID

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for renewal of current therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the diagnosis an OHP-funded diagnosis?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is the prescriber a pulmonologist or an allergist who specializes in management of severe asthma?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the patient currently taking a maximally-dosed inhaled corticosteroid and a second controller drug (i.e., long-acting inhaled beta-agonist, theophylline, montelukast, zafirlukast)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the patient required at least 2 hospitalizations or ED visits in the past 12 months while receiving a maximally-dosed inhaled corticosteroid and a second controller agent?	**Yes:** Go to #8	**No:** Go to #7
7. Is the patient currently receiving chronic systemic corticosteroids to prevent asthma exacerbations?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.
8. Is the claim for reslizumab in a patient under 18 years of age?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #9
9. Does the patient have an eosinophilic phenotype, defined as document blood eosinophil count ≥300 cells/μL in the past 12 months?	**Yes:** For mepolizumab, approve 100 mg every 4 weeks for up to 12 months. For reslizumab, approve 3 mg/kg every 4 weeks for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the patient currently taking a maximally-dosed inhaled corticosteroid and a second controller drug (i.e., long-acting inhaled beta-agonist, theophylline, montelukast, zafirlukast)?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness.
2. Has there been a reduction in the number of ED visits or hospitalizations in the last 12 months, or has the patient reduced their systemic corticosteroid dose by ≥50%	**Yes:** For mepolizumab, approve 100 mg every 4 weeks for up to 12 months. For reslizumab, approve 3 mg/kg every 4 weeks for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *7/16*
Implementation: *TBD*