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Asthma Biologics OHSU Drug Effectiveness Review Project Summary Report

Date of Review: July 2018

Date of Last Review: July 2016

Current Status of PDL Class:

See **Appendix 1**.

Research Questions:

1. What is the comparative efficacy for benralizumab, a recently approved biologic, compared to reslizumab and mepolizumab for the treatment of eosinophilic asthma?
2. What is the comparative tolerability and frequency of adverse events for benralizumab, reslizumab, and mepolizumab in the treatment of eosinophilic asthma?
3. What is the evidence on the benefits and harms of using omalizumab to treat patients with moderate-to-severe allergic asthma?
4. What is the evidence on the benefits and harms of using omalizumab to treat patients with chronic spontaneous urticaria (CSU)?
5. Are there subgroups of patients (e.g. groups defined by demographics, asthma severity, comorbidities) for which biologic medications used to treat asthma differ in efficacy, or frequency of adverse events?

Conclusions:

Interleukin-5 Antagonists in Eosinophilic Asthma (Benralizumab, Reslizumab, and Mepolizumab)

- High quality evidence demonstrates asthma exacerbations requiring oral corticosteroids were significantly less likely with benralizumab than placebo in patients with severe asthma (3 Randomized Controlled Trials (RCTs), rate ratio 0.62, 95% Confidence Interval (CI) 0.55 to 0.70).¹ In absolute terms, this difference was 0.37 fewer events per patient per year with benralizumab (95% CI 0.44 to 0.29), with an event rate of 0.98 in the placebo group.² Moderate quality evidence shows exacerbations requiring emergency department (ED) or hospital admission were significantly less likely with benralizumab than placebo in patients with severe asthma (2 RCTs, rate ratio 0.68, 95% CI 0.47 to 0.98).¹ The absolute difference for this outcome was 0.04 fewer events per patient per year with benralizumab (95% CI 0.06 to 0.002), with a rate of 0.11 in the placebo group.²
- Moderate quality evidence demonstrates the effectiveness of reslizumab in reducing asthma exacerbations requiring oral corticosteroids in adults with severe asthma when compared to placebo (2 RCTs, rate ratio 0.43, 95% CI 0.33 to 0.55).¹ The absolute difference was 0.93 fewer events per patient per year (range: 1.09 to 0.73 fewer) with a rate of 1.54 events per patient per year in the placebo group.² Moderate quality evidence demonstrates that asthma exacerbations requiring ED visits or hospitalizations are not significantly reduced when adults are treated with reslizumab (2 RCTs, rate ratio 0.67, 95% CI 0.39 to 1.17), with an absolute difference of 0.04 fewer events per patient per year (0.07 fewer to 0.02 more) and a rate of 0.12 in the placebo group.²

- High quality evidence shows clinically significant asthma exacerbations (those requiring oral corticosteroids) were significantly less likely in patients given mepolizumab than those given placebo (2 RCTs, rate ratio 0.45, 95% CI 0.36 to 0.55).¹ In absolute terms, for mepolizumab, there were 0.81 fewer events per patient per year (95% CI 0.66 fewer to 0.94 fewer); the rate in patients on placebo was 1.48 events per patient per year.² High quality evidence demonstrates patients treated with mepolizumab were significantly less likely to have exacerbations requiring ED treatment or hospital admission compared to patients who received placebo (rate ratio 0.36, 95% CI 0.20 to 0.66).¹ In absolute terms, there were 0.10 fewer events per patient per year (95% CI 0.05 to 0.12 fewer), with a rate in patients on placebo of 0.15 events per patient per year.²
- High quality evidence suggests the difference in Asthma Quality of Life Questionnaire (AQLQ) score was significantly greater with benralizumab treatment than with placebo (mean difference (MD) 0.23, 95% CI 0.11 to 0.35); however it was less than the minimum clinically significant difference of 0.5 or more change in score.² Moderate quality evidence suggests quality of life was statistically better with reslizumab, but the difference was not clinically significant (2 RCTs, MD 0.28, 95% CI 0.17 to 0.39).² High strength evidence shows mepolizumab improves quality of life both statistically and clinically (2 RCTs, MD -7.40, 95% CI -9.50 to -5.29).²
- Moderate quality evidence suggests lower rates of serious adverse events were observed with benralizumab compared to placebo in patients with asthma (5 RCTs, 11% vs. 14%, relative risk (RR) 0.78, 95% CI 0.64 to 0.96, I²=0%).² This is likely due to the inclusion of asthma exacerbations as serious adverse events, which were reduced with benralizumab.² Moderate quality evidence found no differences in adverse events outcomes (7.6% vs. 9.3%, RR 0.81, 95% CI 0.57 to 1.75) or withdrawals due to adverse events (3.0% vs. 4.4%, RR 0.67, 95% CI 0.37 to 1.20) with reslizumab compared to placebo patients with asthma.² Low quality evidence showed no difference in adverse effects between placebo and mepolizumab in patients with asthma (6.0% vs. 12%, RR 0.50, 95% CI 0.24 to 1.05).²
- As of December, 2017 mepolizumab received an expanded indication from FDA for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).³

IgE Antagonist in Allergic Asthma and Chronic Urticaria (Omalizumab)

- In children and adults with moderate-to-severe allergic asthma, moderate quality evidence demonstrates omalizumab reduces severe exacerbations requiring ED visits, office visits, or hospitalizations (16% vs. 26%, OR 0.55, 95% CI 0.42 to 0.60).⁴ Among the subgroup with moderate-to-severe asthma, the reduction was also significant (7 RCTs, odds ratio (OR) 0.50, 95% CI 0.42 to 0.60), while in the subgroup with severe asthma there was not a significant reduction (2 RCTs, OR 1.0, 95% CI 0.5 to 1.99).² An analysis of exacerbations requiring the use of oral corticosteroids found that omalizumab significantly reduced the rate of exacerbations in patients with moderate-to-severe asthma (2 RCTs, rate ratio 0.52, 95% CI 0.37 to 0.73).²
- Moderate quality evidence showed that omalizumab improved quality of life in patients with moderate-to-severe asthma, but the difference may not be clinically important (6 RCTs, MD 0.31, 95% CI 0.23 to 0.39).²
- Low to moderate quality evidence showed less adverse events with omalizumab compared to placebo in patients with moderate-to-severe asthma (4.5% vs. 6.4% OR 0.72, 95% CI 0.57 to 0.91).² Withdrawals due to adverse events were few, with no clear differences between groups.²
- Two observational studies evaluated harms of omalizumab therapy.^{5,6} For malignancies that occurred during the course of the study, crude rates of 16.0 per 1000 patient-years with omalizumab and 19.1 with placebo were identified.⁵ The crude (unadjusted for potential confounders) rate ratio was not statistically significant (0.84, 95% CI 0.62 to 1.13).⁵ However, there were several issues identified with the study design including biased selection criteria, biased exclusion criteria, and the high discontinuation rates leading to the conclusion that these study results should be interpreted with caution.⁷ In a second analysis cardiovascular (CV) and cerebrovascular events were evaluated.⁶ The incidence of any cardiovascular or cerebrovascular event was 13.4 per 1000 patient-years with omalizumab, compared with 8.1 for the control group.⁶ Differences in asthma severity between cohorts likely contributed to this imbalance, but some increase in CV risk associated with omalizumab administration cannot be excluded.⁶

- In patients with CSU, high quality evidence shows omalizumab significantly improves the chance for complete response as assessed by the urticaria activity score when compared to placebo (RR 4.55, 95% CI 3.33 to 6.23).⁸ Quality of life was statistically better with omalizumab compared to placebo, but the difference was not clinically significant (high quality evidence).²
- No differences in adverse events outcomes were observed when data was pooled from 4 RCTs of omalizumab used to treat patients with urticaria (RR 0.80, 95% CI 0.24 to 2.65).² Withdrawals due to adverse events were very low, 1% and 0.9% across the 4 RCTs with omalizumab and placebo, respectively.² The pooled relative risk is 1.03 (95% CI 0.24 to 4.41), with no heterogeneity (I² = 0%).²

Recommendations:

- Recent evidence summarized in the Drug Effectiveness Review Project report for the asthma biologic medications does not support specific changes to the current Preferred Drug List (PDL).
- Add benralizumab to prior authorization (PA) criteria for monoclonal antibodies for asthma.
- Revise monoclonal antibodies for asthma PA criteria to include expanded indication for mepolizumab in patients experiencing eosinophilic granulomatosis with polyangiitis (EGPA).
- Evaluate costs in executive session to evaluate preferred drug list (PDL) status for benralizumab.

Previous Conclusions:

- Moderate quality evidence over 32 weeks demonstrate mepolizumab 100 mg administered subcutaneously (SC) every 4 weeks reduces about one clinically significant asthma exacerbation (defined as an exacerbation that requires use of systemic corticosteroids, an ED visit, and/or hospitalization) in patients with severe eosinophilic asthma compared to placebo. Low quality evidence suggests mepolizumab 100 mg SC every 4 weeks may also reduce the rate of exacerbations that require hospitalization or ED visits compared with placebo by 0.12 events per year compared to placebo (0.08 vs. 0.20 events per year, respectively).
- Low quality evidence suggests mepolizumab may be associated with a statistically significant and clinically meaningful improvement in quality of life. The difference in total St. George's Respiratory Questionnaire scores from baseline between mepolizumab and placebo was -7.0 points (95% CI, -10.2 to -3.8). Low quality evidence also suggests mepolizumab may be associated with a statistically significant symptom improvement. The difference in total Asthma Control Questionnaire (ACQ) scores from baseline between mepolizumab and placebo was -0.44 points (95% CI, -0.61 to -0.23); however, this difference did not exceed the minimal clinically important difference of 0.5 points.
- There is insufficient evidence to differentiate differences in efficacy between mepolizumab and other monoclonal antibodies approved for severe asthma.
- Safety data from Phase 3 trials and 2 long-term safety studies for mepolizumab reveal no major safety concerns at 1 to 3.5 years of treatment. Adverse events of interest for mepolizumab are similar to other monoclonal antibodies and include allergic reactions, local injection site reactions, serious cardiac events, infections, malignancy, and immunogenicity.
- Moderate quality evidence over 52 weeks supports the efficacy of reslizumab 3 mg/kg intravenous infusion every 4 weeks in reducing the number of patients experiencing at least one asthma exacerbation in adults (≥18 years) with severe eosinophilic asthma compared to placebo (32% vs. 50%, respectively; RR 0.64; 95% CI 0.5 to 0.7) with an absolute risk reduction (ARR) of 18% and a number-needed-to-treat (NNT) of 5 over 52 weeks. Low quality evidence suggests reslizumab 3 mg/kg IV every 4 weeks does not reduce the rate of exacerbations that require hospitalization or ED 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, defined as a 0.5 point reduction or more in the Asthma Control Questionnaire (ACQ) and the Asthma Quality of Life Questionnaire (AQLQ).

- Reslizumab is associated with similar frequencies of serious adverse events as placebo, with the majority of events related to asthma exacerbations.
- Overall, there is moderate quality evidence that omalizumab is more effective than placebo in reducing exacerbations and hospitalizations as adjunctive therapy to standard therapy in IgE-mediated moderate to severe asthma. Effects were less profound when only participants with severe disease were included and evidence remains insufficient for the treatment of severe, oral corticosteroid dependent asthma.
- Although distinctly different, there is no evidence to support using omalizumab in combination with either reslizumab or mepolizumab.

Previous Recommendations:

- Maintain mepolizumab and reslizumab as a non-preferred drugs subject to Prior Authorization (PA) criteria

Current Policy and Utilization Trends:

The Oregon Health Plan (OHP) provides coverage through PA criteria for the 2 biologic agents (mepolizumab and reslizumab) approved to manage eosinophilic asthma refractory to other asthma therapies. The most recently approved biologic agent for management of severe asthma, benralizumab, will be evaluated in this review for addition to the PDL. An additional biologic agent (omalizumab), is also part of the monoclonal antibodies for asthma PA criteria and provides coverage for patients with severe allergic asthma. Omalizumab is also indicated for management of chronic urticaria; however, this diagnosis is not funded according to the Health Evidence Review Commission (HERC) prioritized list.

During the first quarter of 2018 the only asthma biologic agent prescribed in the fee-for-service (FFS) population was omalizumab with 9 claims. Omalizumab claims for coordinated care organizations (CCO) were slightly higher (14 claims) compared to the FFS claims and 8 CCO claims were processed for mepolizumab. The biologic agents accounted for 20% of the CCO costs associated with the miscellaneous pulmonary agents; however, claims for the 2 biologic agents were less than 1% of the total utilization for this class of drugs.

Background:

Asthma is a heterogeneous disease, characterized by chronic airway inflammation.⁹ According to the 2007 National Asthma Education and Prevention Program (NAEPP) guidelines, asthma severity is classified according to symptoms and level of treatment required to control exacerbations.¹⁰ Mild asthma (step 1 or 2) is well controlled with low dose inhaled corticosteroid (ICS) therapy.¹⁰ Moderate (Step 3), and severe (Steps 4 and 5) asthma may require more potent ICS and addition of other controller-drug treatments.¹⁰ The 2018 Global Initiative for Asthma (GINA) guidelines recommend a biologic agent for patients with severe asthma unresponsive to controller-drug treatments.⁹ Severe asthma is reported to account for about 5 to 10 percent of the total asthma population, but exact prevalence is unknown due to heterogeneity in presentation of severe asthma.¹¹ Although the prevalence of severe asthma is relatively low, it accounts for 50% of the health care costs associated with managing exacerbations.¹²

Recognition that asthma is not a single disease, but multiple, overlapping, phenotypes of disease has changed the way asthma is categorized, and treated.^{13,14} Phenotyping severe asthma based on demographic or clinical characteristics may help target treatments more effectively. Some asthma phenotypes include eosinophil predominant, neutrophil predominant, and allergic asthma.¹⁴ Recent literature has proposed endotypes to further categorize phenotypes of severe asthma.¹⁵ One endotype of eosinophilic asthma is Type 2 (T2)-high asthma indicating high levels of T-helper type 2 lymphocytes.¹⁶ Patients with T2-high asthma have high levels of bronchial tissue IL-5 mRNA, high sputum levels of eosinophils, greater numbers of mast cells, and overexpression of periostin.¹² T2-high asthma responds well to ICS therapy, and patients that fail to respond to ICS agents may benefit from biologic medications.¹⁷ The threshold for identifying elevated blood eosinophils that are a reliable marker for elevated sputum eosinophils ($\geq 3\%$) is not entirely clear, but studies of biologic agents have used eosinophil blood levels from ≥ 150 cells/ μL to ≥ 400 cells/ μL .¹⁷

Omalizumab is an anti-immunoglobulin E (IgE) monoclonal antibody that has been available for over a decade to manage severe allergic asthma and chronic urticaria. Three additional monoclonal antibodies; mepolizumab, reslizumab, and the newest formulation, benralizumab, mediate the effects of interleukin (IL)-5 and are effective in management of eosinophilic asthma as add on therapy. Activated eosinophils can increase airway smooth muscle contraction and mucous secretion. Reslizumab and mepolizumab are anti-IL-5 antibodies while benralizumab binds to the IL-5 receptor. Blocking IL-5 from binding to its receptor inhibits the growth, differentiation, activation, and survival of eosinophils.¹⁸ The monoclonal antibodies that mediate IL-5 activity are FDA-approved to treat severe asthma in patients with an eosinophilic phenotype of asthma. Safety and efficacy of these agents have not been assessed in head-to-head trials. Several monoclonal antibodies targeting different cytokines (IL-4 and IL-13) are currently being investigated for their safety and efficacy in treating severe asthma. These agents include dupilumab and lebrikizumab.

Although the biologic agents used to manage severe asthma are well-tolerated, serious adverse reactions have been reported. Omalizumab has a boxed warning due to reports of serious and life-threatening allergic reactions; therefore administration in a healthcare setting under direct medical supervision is required.¹⁹ Delayed anaphylaxis occurring 24 hours or later after omalizumab administration has also been reported.¹⁹ It is recommended to provide patients with epinephrine to manage delayed anaphylaxis if it occurs as an outpatient after omalizumab administration. Anaphylaxis has been reported in 0.3% of patients receiving reslizumab, so the drug carries an FDA boxed warning recommending observation after infusion.²⁰ Hypersensitivity reactions have been observed with mepolizumab and benralizumab; however neither drug has a boxed warning regarding anaphylaxis.^{3,21} Adverse effects reported with mepolizumab include headache, injection site reactions, back pain and fatigue.³ Herpes zoster infections have occurred in a small number of patients receiving mepolizumab, so vaccination is recommended if medically appropriate.³ In clinical trials, the rate of serious adverse events with benralizumab was similar to placebo (12%-14%), and the most common adverse events include worsening asthma, nasopharyngitis, and upper respiratory tract infections.²²

There are notable differences between each biologic agent approved to treat asthma primarily related to the age of administration, route of administration and dosing regimen. In clinical trials, the definition of severe eosinophilic asthma ranged from greater than or equal to 150 eosinophils/ μ L to greater than or equal to 400 eosinophils/ μ L depending on the drug being investigated. Currently, all the monoclonal antibodies used to manage asthma must be administered by a health care provider. **Table 1** summarizes significant prescribing information for the 4 biologic agents with FDA approval to treat severe asthma.

Table 1. Monoclonal Antibodies Approved to Manage Severe Asthma^{3,19-21}

Generic Name	Brand Name	FDA Approval Year	Target	FDA Approved Indication	Maintenance Dose and Administration Route	FDA Approved Administration Age	FDA Boxed Warning	Blood Eosinophil Levels in Clinical Trials in Primary Analysis Population
Benralizumab	Fasenra TM	2017	IL-5 Receptor	Severe asthma with an eosinophilic phenotype	30 mg SC every 8 weeks	≥ 12 yo	No	≥300 cells/ μ L
Reslizumab	Cinqair [®]	2016	IL-5	Severe asthma with an eosinophilic phenotype	3 mg/kg IV infusion every 4 weeks	≥ 18 yo	Yes: for possible anaphylaxis	≥ 400 cells/ μ L
Mepolizumab	Nucala [®]	2015	IL-5	-Severe asthma with an eosinophilic phenotype	-Asthma: 100 mg SC every 4 weeks	-Asthma: ≥ 12 yo -EGPA: ≥ 18 yo	No	≥ 150 cells/ μ L at screening or ≥ 300

				-EGPA in adults	-EGPA: 300 mg SC every 4 weeks			cells/ μ L in the previous year
Omalizumab	Xolair [®]	2003	IgE	-Moderate to severe persistent asthma -Antihistamine refractory CSU	-Asthma: 75 to 375 mg SC every 2 to 4 weeks. (Dosing is determined by weight and serum IgE levels for asthma) -CSU: 150 to 300 mg SC every 4 weeks	-Asthma: \geq 6 yo -CSU: \geq 12 yo	Yes: for possible anaphylaxis	Not Applicable

Abbreviations: CSU = Chronic Spontaneous Urticaria; EGPA = Eosinophilic Granulomatosis with Polyangiitis; FDA = Food and Drug Administration; IgE = immunoglobulin E; IL-5 = interleukin-5; IV = intravenous; SC = subcutaneous; YO = years old

Clinically relevant outcomes to assess treatments of severe asthma include reduction in asthma exacerbations that result in: 1) decreased ED visits or hospitalizations; 2) decreased chronic use of oral corticosteroids; 3) improved quality of life; and 4) improved symptom management. Three 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 Asthma Control Questionnaire (ACQ) is a 7-item questionnaire that assesses asthma symptoms and rescue inhaler use in the preceding week.²³ Scores range from 0 (totally controlled) to 6 (severely uncontrolled), with a change in score of 0.5 units the minimally clinical important difference.²⁴ An ACQ score consistently greater than 1.5 indicates poor symptom control.²⁴ The AQLQ is a 32-item quality-of-life instrument that assesses both physical and emotional impact of disease.²⁵ Scores range from 1 (severely impaired) to 7 (not impaired at all), with higher scores indicating better quality of life.²⁵ The minimally clinical important difference for this assessment is a difference of 0.5 for each item.²⁵ The St. George's Respiratory Questionnaire (SGRQ) is a 50-item quality-of-life tool for patients with obstructive airway disease.²⁶ The questionnaire is composed of 2 parts. Part 1 assesses symptoms and part 2 assesses limitation of activities and its social and psychological impact.²⁶ Scores range from 0 to 100, with higher scores indicating more limitations.²⁶ A change of 4 points is associated with slightly efficacious treatment, 8 points for moderately efficacious treatment, and 12 points for very efficacious treatment.²⁶

Chronic spontaneous urticaria (CSU) is defined as recurrent episodes of hives with or without angioedema, that last 6 weeks or more.²⁷ CSU affects 1% to 2% of the US population.²⁷ In most patients, there is no known allergic cause, although external factors such as stress, medications, or exercise can trigger the symptoms. The Urticaria Activity Score (UAS) is a broadly accepted tool used to assess CSU disease activity in clinical trials.²⁸ In the UAS-7, two symptoms (number of wheals and severity of itching), are documented by adult patients once a day for seven days in a row.²⁸ The answers related to each symptom are rated from 0 to 3 points, and the minimum and maximum daily score are 0 and 6 points, respectively, with higher values indicating stronger disease activity.²⁸ Treatment of CSU depends largely on 2nd generation H1-antihistamines, such as cetirizine or loratadine.²⁹ In several small trials leukotriene receptor antagonists (e.g. montelukast, zafirlukast) were successfully added to antihistamine therapy to assist with CSU symptom control.^{30,31} In patients with CSU refractory to antihistamines or leukotriene receptor antagonists, omalizumab has been successfully added to these therapies to alleviate symptoms.⁸

Methods:

The April 2018 report on biologic drugs to treat asthma and chronic urticaria by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center (EPC) at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.²

The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available in the agenda packet and on the DURM website.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

Summary Findings:

The literature search for the DERP report included published trials through December 2017 focused on biologic drugs for asthma and chronic urticaria. The search included adults or children with persistent or chronic asthma and adults with CSU in outpatient settings. Study designs included in the report included randomized clinical trials (RCTs) of at least 12 weeks duration, systematic reviews (SRs) and observational trials of at least 6 months duration to evaluate serious adverse events. The drug class report includes 15 RCTs, 2 observational studies, and 5 SRs, including 12,683 patients.² The majority of studies were fair to good quality.² Evidence for use of the IL-5 inhibitors (benralizumab, reslizumab, and mepolizumab) in patients with eosinophilic asthma was identified in 1 SR and an additional 1 trial each of benralizumab, mepolizumab, and reslizumab. Evidence for omalizumab in patients with allergic asthma was published in 3 SRs, 6 additional RCTs, and 2 observational studies. Omalizumab in chronic spontaneous urticaria was evaluated in one 1 SR and 2 additional RCTs. The results are organized by drug class, and then study population.

Interleukin-5 Inhibitors in Eosinophilic Asthma

Benralizumab in Moderate to Severe Asthma

A Cochrane review of IL-5 inhibitors in adults and children with moderate to severe asthma included 4 good-quality, placebo-controlled trials for benralizumab (N=2,648).¹ In these trials, benralizumab 20 mg or 30 mg was administered every 4 or every 8 weeks with 48 to 56 weeks of follow-up.¹ The FDA-approved benralizumab dose is 30 mg every 4 weeks for the first 3 doses, followed by 30 mg every 8 weeks.²¹ The Cochrane SR defined clinically significant asthma exacerbations as those requiring oral corticosteroids for 3 or more days.¹ Exacerbations were significantly less likely with benralizumab than placebo (3 RCTs, N=2456; rate ratio 0.62, 95% CI 0.55 to 0.70).² In absolute terms, the difference was 0.37 fewer events per patient per year with benralizumab (95% CI 0.44 to 0.29), with an event rate of 0.98 in the placebo group.² Significant differences in exacerbation rates between benralizumab and placebo were seen both in patients with eosinophilic (≥ 300 cells/ μ L; rate ratio 0.59, 95% CI 0.51 to 0.68) and non-eosinophilic phenotypes (rate ratio 0.69, 95% CI 0.56 to 0.85).² Exacerbations requiring ED or hospital admission were significantly less likely with benralizumab than placebo (2 RCTs, N=1537; rate ratio 0.68, 95% CI 0.47 to 0.98) in patients with eosinophilia (≥ 300 cells/ μ L). The absolute difference was 0.04 fewer events per patient per year with benralizumab (95% CI 0.06 to 0.002), with a rate of 0.11 in the placebo group.²

Three high quality trials (N=1541) of patients with eosinophilic asthma measured quality of life using the 7-point AQLQ(S) + 12, which is the Standardized Asthma Quality of Life Questionnaire for subjects 12 years and older.¹ The difference in AQLQ(S) + 12 score was greater with benralizumab treatment than with placebo (MD 0.23, 95% CI 0.11 to 0.35).² Although this difference was statistically significant, it was less than the minimum clinically significant difference of 0.5 or more change in score.²

An additional RCT, the ZONDA trial, was published after the Cochrane review was completed.³² This high quality trial (N=220) of adults with severe asthma randomized patients to benralizumab 30 mg or placebo administered every 4 weeks for 28 weeks, or every 4 weeks for the first 12 weeks, then every 8 weeks for the remaining 16 weeks of the trial.² The primary outcome in this trial was the percent reduction in oral corticosteroid dose from baseline to week 28.³² The

median reduction of corticosteroid dose in the placebo arm was 25%, while in each benralizumab arm the median reduction in dose was 75% ($p < 0.001$).³² Among the secondary outcomes, benralizumab administered every 4 weeks resulted in an annual exacerbation rate that was 55% lower than the rate with placebo (marginal rate 0.83 vs. 1.83, $p = 0.003$), and benralizumab administered every 8 weeks resulted in an annual exacerbation rate that was 70% lower than the rate with placebo (marginal rate 0.54 vs. 1.83, $p < 0.001$).³² Quality of life as assessed by the AQLQ(S) + 12 score improved for patients treated with benralizumab compared with those given placebo, with the difference significant for treatment every 8 weeks (MD 0.45, 95% CI 0.14 to 0.76) although not every 4 weeks (MD 0.23, 95% CI 0.08 to 0.53).²

Serious adverse effect data was pooled by the DERP authors using results from the 4 trials in the Cochrane meta-analysis and the additional data from the ZONDA trial. Serious adverse effects were lower with benralizumab compared to placebo (5 RCTs, 11% vs. 14%, RR 0.78, 95% CI 0.64 to 0.96, $I^2 = 0\%$).² This is likely due to the inclusion of asthma exacerbations as serious adverse events, which were reduced with benralizumab.² Three good quality RCTs reported withdrawals due to adverse events. This data was pooled with the ZONDA trial and no significant difference in withdrawals due to adverse events was observed with benralizumab compared to placebo (4 RCTs, 2.2% vs. 1.0%, RR 1.84, 95% CI 0.92 to 3.68).² Differences in injection site reactions were reported in sub-group analysis of 2 trials.² When the DERP authors pooled this data, no statistically significant difference in skin reactions for patients treated every 8 weeks with benralizumab compared to placebo was observed (2.4% vs. 1.6%, relative risk [RR] 1.44, 95% CI 0.69 to 3.00).²

Reslizumab in Moderate to Severe Asthma

The previously discussed Cochrane IL-5 inhibitor review included 4 placebo-controlled RCTs of reslizumab in adults with moderate to severe asthma.¹ Three of the RCTs required patients have blood eosinophils of greater than or equal to 400 cells/ μL ($N = 1164$), while the fourth study was of patients with non-eosinophilic asthma.² Patients in these studies were using medium doses of inhaled corticosteroids, and had a history of at least 1 clinically relevant asthma exacerbation in the past year.² Reslizumab was administered at 3 mg/kg intravenously every 4 weeks for 4 doses (2 RCTs) or for 13 doses (2 RCTs).² Two of the studies were high quality, and the others were moderate quality.²

In the 4 RCTs analyzed in the Cochrane SR, asthma exacerbations were reported as those requiring oral corticosteroids or those requiring an ED visit or admission to hospital.¹ Using the more conservative definition (requiring oral steroids), reslizumab significantly reduced the risk of exacerbation compared with placebo (2 RCTs, rate ratio 0.43, 95% CI 0.33 to 0.55).¹ The absolute difference was 0.93 fewer events per patient per year (range: 1.09 to 0.73 fewer) with a rate of 1.54 events per patient per year in the placebo group.² Based on the more serious definition of an exacerbation requiring an ED visit or hospital admission, reslizumab did not reduce the risk compared with placebo (2 RCTs, rate ratio 0.67, 95% CI 0.39 to 1.17), with an absolute difference of 0.04 fewer events per patient per year (0.07 fewer to 0.02 more) and a rate of 0.12 in the placebo group.² Quality of life as assessed by AQLQ scores was statistically better with reslizumab than with placebo (2 RCTs, MD 0.28, 95% CI 0.17 to 0.39). However, as the difference did not meet the established effect size of 0.5, it is unclear if this difference is clinically meaningful.²

An additional fair-quality trial included in the DERP report did not meet Cochrane review inclusion criteria of trial duration at least 16 weeks. This 12-week RCT enrolled adults with poorly controlled, moderate-to-severe asthma with sputum eosinophils greater than or equal to 3% ($n = 106$).³³ The Cochrane review notes that studies evaluating blood and sputum eosinophil levels have found that blood eosinophil levels of greater than or equal to 400 cells/ μL correlate well with sputum levels greater than or equal to 3%.¹ Subjects received reslizumab 3 mg/kg at baseline and every 4 weeks for a total of 4 doses or infusion of placebo.³³ The primary efficacy measure was the difference between the reslizumab and placebo groups in the change in the 7 question ACQ score from baseline to end of therapy.³³ A change of least 0.5 in the ACQ score is considered clinically significant.²³ Mean changes from baseline to end of therapy in ACQ score were -0.7 in the reslizumab group and -0.3 in the placebo group did not reach statistical significance (MD -0.38, 95% CI -0.76 to 0.01, $p = 0.054$).³³ Overall, 59% of patients in

the reslizumab group and 40% of patients in the placebo group achieved an improvement of at least 0.5 in ACQ score (OR 2.06, 95% CI 0.88 to 4.86, $p=0.0973$).³³ The 12-week study used a broad definition of exacerbations, which included a greater than 20% decrease in FEV₁, or ED visit or 3 days of oral corticosteroid treatment.³³ The results for reducing exacerbations did not reach statistical significance, but the absolute difference was large, 8% versus 19% ($p=0.083$).²

DERP analysis of adverse event outcomes was based on pooled data from 3 RCTs (N=1059).² There were no differences between reslizumab and placebo in serious adverse events (7.6% vs. 9.3%, RR 0.81, 95% CI 0.57 to 1.75).² There were also no differences between reslizumab and placebo in withdrawals due to adverse events (3.0% vs. 4.4%, RR 0.67, 95% CI 0.37 to 1.20).²

Mepolizumab in Severe Asthma

The Cochrane review of IL-5 inhibitors included placebo-controlled trials of both intravenous and subcutaneous mepolizumab.¹ Only the subcutaneous formulation is approved in the United States, so DERP authors excluded data from trials of intravenous mepolizumab. The Cochrane review included data from 2 good-quality trials of subcutaneous mepolizumab (N=1,127) in patients with severe eosinophilic asthma.² Clinically significant asthma exacerbations (those requiring oral corticosteroids) were significantly less likely in patients given mepolizumab than those given placebo (2 RCTs, N=936; rate ratio 0.45, 95% CI 0.36 to 0.55).² In absolute terms, for mepolizumab, there were 0.81 fewer events per patient per year (95% CI 0.66 fewer to 0.94 fewer); the rate in patients on placebo was 1.48 events per patient per year.²

Based on these 2 trials, those treated with mepolizumab were significantly less likely to have exacerbations requiring ED treatment or hospital admission (rate ratio 0.36, 95% CI 0.20 to 0.66).¹ In absolute terms, there were 0.10 fewer events per patient per year (95% CI 0.05 fewer to 0.12 fewer), with a rate in patients on placebo of 0.15 events per patient per year.² Quality of life was assessed using the SGRQ in 2 trials. A change of 4 or more points on this questionnaire is considered clinically significant.¹ In the Cochrane analysis quality of life improved more for patients treated with mepolizumab than for those given placebo (MD -7.40, 95% CI -9.50 to -5.29).¹

The Cochrane review excluded results from a third RCT, the SIRIUS trial, because its primary outcome was reduction in glucocorticoid use. However the DERP authors included results from this trial in their report.² The SIRIUS trial was a high quality randomized, double-blind trial involving 135 patients with severe eosinophilic asthma.² Mepolizumab 100 mg administered subcutaneously every 4 weeks for 20 weeks was compared to placebo.³⁴ The primary outcome was the degree of reduction in the glucocorticoid dose (90 to 100% reduction, 75 to less than 90% reduction, 50 to less than 75% reduction, more than 0 to less than 50% reduction, or no decrease in oral glucocorticoid dose, a lack of asthma control during weeks 20 to 24, or withdrawal from treatment).³⁴ Other outcomes included the rate of asthma exacerbations, asthma control, and safety. The likelihood of a reduction in the glucocorticoid-dose stratum was greater in the mepolizumab group than in the placebo group (OR 2.39, 95% CI 1.25 to 4.56; $p=0.008$).³⁴ The median percentage reduction from baseline in the glucocorticoid dose was 50% in the mepolizumab group, as compared with no reduction in the placebo group ($p=0.007$).³⁴ Despite receiving a reduced glucocorticoid dose, patients in the mepolizumab group, as compared with those in the placebo group, had a relative reduction of 32% in the annualized rate of exacerbations (1.44 vs. 2.12, $p=0.04$) and a reduction of 0.52 points with respect to asthma symptoms ($p=0.004$, 95% CI -0.87 to -0.17), as measured on the ACQ.³⁴ Quality of life improved more for patients treated with mepolizumab than for those given placebo (MD -5.8, 95% CI -10.6 to -1.0).³⁴

In the DERP analysis of 3 RCTs evaluating subcutaneous mepolizumab, serious adverse events were not significantly different compared to placebo (6.0% vs. 12%, RR 0.50, 95% CI 0.24 to 1.05).² There was moderate statistical heterogeneity in this pooled analysis ($I^2=57%$), due to variation in the magnitude of effect across the trial arms.² Because of this, DERP confidence in these findings is low; it could change with additional evidence.² Few patients withdrew due to adverse

events in the 2 trials in the Cochrane review or the SIRIUS trial (16 of 1,071 patients across the 3 trials); however, evidence was insufficient to compare rates between mepolizumab and placebo (1.1% vs. 1.9%, RR 0.63, 95% CI 0.22 to 1.77).²

IgE Antagonist in Allergic Asthma and Chronic Urticaria

Omalizumab in Allergic Asthma

A good-quality Cochrane systematic review of omalizumab in patients with moderate to severe allergic asthma included a total of 25 RCTs.⁴ Ten of the trials (N=3261) evaluated subcutaneous omalizumab every 2 to 4 weeks in patients also receiving stable doses of inhaled corticosteroids, while 5 (N=1634) had a 12- to 28-week period of stable oral or inhaled corticosteroid dose, followed by a period of attempted steroid-dose reduction.² Dosing varied, ranging from 75 mg every 2 weeks to 375 every 4 weeks or was determined by weight and IgE-level.² The studies ranged from 16 to 60 weeks in duration, included both adults and children, and most studies were fair quality.² The review analyzed the studies according to whether they evaluated only a stable steroid dose, or if they evaluated stable-dose followed by dose-reduction of steroids, and according to severity of asthma (moderate-to-severe or severe only).² The omalizumab studies reported medically serious exacerbations; those requiring a hospitalization, an ED visit, or an office visit.² Based on 10 moderate quality RCTs (N=3261, all continuing inhaled corticosteroids), omalizumab resulted in a significant reduction in exacerbations when used every 2 to 4 weeks for 16 to 60 weeks in patients with allergic asthma when compared to placebo (16% vs. 26%, OR 0.55, 95% CI 0.42 to 0.60).⁴ Among the subgroup with moderate-to-severe asthma, the reduction was also significant (7 RCTs, OR 0.50, 95% CI 0.42 to 0.60), while in the subgroup with severe asthma there was not a significant reduction (2 RCTs, OR 1.0, 95% CI 0.5 to 1.99).²

An analysis of exacerbations requiring the use of oral corticosteroids found that omalizumab significantly reduced the rate of exacerbations in patients with moderate-to-severe asthma (2 RCTs, rate ratio 0.52, 95% CI 0.37 to 0.73).⁴ In a single study of patients with severe asthma, the rate was significantly reduced in patients receiving inhaled corticosteroids and long-acting beta agonists as background therapy (rate ratio 0.66, 95% CI 0.45 to 0.97), but not significant in those receiving both oral and inhaled corticosteroids as background therapy (rate ratio 0.95, 95% CI 0.63 to 1.43).²

Limiting the analysis to studies of 52 weeks or longer, another fair-quality systematic review also found a reduction in serious asthma exacerbations (21% with omalizumab vs. 38% with placebo, RR 0.63, 95% CI 0.55 to 0.71).³⁵ Limiting the analysis to children (ages 6 to 20), the incidence of exacerbations was higher than in the overall population, but the reduction with omalizumab was also significant.³⁶ Twenty-seven percent of children taking omalizumab had an exacerbation, compared with 41% taking placebo (3 RCTs, RR 0.69, 95% CI 0.59 to 0.80).³⁶

Quality of life was measured using the AQLQ, and was found to be significantly improved with omalizumab in patients with moderate-to-severe allergic asthma (6 RCTs, MD 0.31, 95% CI 0.23 to 0.39), however this difference was small and was not found to meet the pre-specified clinically important effect size of 0.5 improvement.² DERP identified an additional 8 studies not included in the Cochrane review. Two RCTs evaluated quality of life in moderate to severe asthma patients treated with omalizumab in Brazil³⁷ and China³⁸ however, the Chinese study was of poor quality for the measurement of quality of life and was used only to evaluate harms of omalizumab.² The smaller Brazilian study (N=116) of patients with severe allergic asthma reported differences in AQLQ scores of 0.8 at 12 weeks, and 1.4 at 20 weeks (both p<0.001).³⁷ This difference does meet the clinically relevant threshold of a 0.5-point or greater improvement.² The study from Brazil also reported that significantly more patients had clinically relevant improvement on the AQLQ (≥0.5 points) with omalizumab versus placebo at 20 weeks (71.6% vs. 22.2%, p<0.001).³⁷

All of the RCTs reported serious adverse events including asthma exacerbations.² There were significant differences, favoring omalizumab over placebo. Overall, in the population with moderate-to-severe asthma, 4.5% had a serious adverse event with omalizumab, compared to 6.4% with placebo (OR 0.72, 95% CI 0.57

to 0.91).² Limiting the analysis only to longer-term studies (greater than 52 weeks), the incidences were slightly lower, but still favored omalizumab compared to placebo, (3.7% vs. 6.7%, RR 0.55, 95% CI 0.37 to 0.82).² In children, these incidences were 5.2% and 6.5% and the difference was not significant (RR 0.91, 95% CI 0.58 to 1.42), likely due to fewer patients.² Withdrawals due to adverse events were few, with no clear differences between groups.²

Two observational studies evaluated harms of omalizumab therapy (N=10,225).^{5,6} The EXCELS study was a prospective cohort study (N=5041) conducted between 2006 and 2011 to assess long term safety of omalizumab, and was funded by Genentech and Novartis.⁵ An imbalance in malignancy rates in patients who received omalizumab in clinical trials was the impetus for this study as the pooled trial data revealed malignancy rates of 0.5% (omalizumab) versus 0.2% (control).⁵ The omalizumab prescribing information includes malignancy as a potential risk.¹⁹ Patients with moderate-to-severe allergic asthma were followed for up to 5 years, with a mean of 3.7 for omalizumab and 3.5 for the control group (asthma patients that did not receive omalizumab).⁵ The first analysis reported on malignancies that occurred during the course of the study, finding crude rates of 16.0 per 1000 patient-years with omalizumab and 19.1 with placebo, with no statistical difference based on unadjusted analysis.⁵ The crude (unadjusted for potential confounders) rate ratio was not statistically significant (0.84, 95% CI 0.62 to 1.13).⁵ The authors of the study concluded omalizumab is not associated with an increased risk of malignancy.⁵ However, there were several issues identified with the study design including biased selection criteria, biased exclusion criteria, and the high discontinuation rates leading to the conclusion that these study results should be interpreted with caution.⁷ At this time, there is insufficient evidence to draw conclusions about the risks of malignancy associated with omalizumab therapy.

In a second analysis from the EXCELS study, cardiovascular and cerebrovascular events were evaluated, in particular arterial thromboembolic events (ATEs).⁶ This analysis was prompted by early reports suggesting increased CV and cerebrovascular events were associated with omalizumab administration. Similar to the malignancy analysis, most events were reported only as crude incidence rates.² The incidence of any CV or cerebrovascular event was 13.4 per 1000 patient-years with omalizumab, compared with 8.1 for the control group.⁶ Within the individual events reported, myocardial infarction and unstable angina had the largest difference between groups. The analysis of ATEs reported as serious adverse events during the study found a non-significant increase (adjusted hazard ratio 1.32, 95% CI 0.91 to 1.91).⁶ Differences in asthma severity between cohorts likely contributed to this imbalance, but some increase in CV risk associated with omalizumab therapy cannot be excluded.⁶ At this time, there is insufficient evidence to associated omalizumab administration with adverse CV effects.

Omalizumab in Chronic Urticaria

DERP authors identified 1 good-quality SR of 7 RCTs (N=1312) of omalizumab in patients with CSU.⁸ In the 7 trials, omalizumab was dosed at 75 to 600 mg every 2 to 4 weeks; patients included both adults and children, and were refractory to typical treatments for CSU (primarily antihistamines).² All of the included studies reported complete response, defined as UAS-7 score scale of 0.² In the analysis of 7 RCTs, 28% of omalizumab patients achieved complete response, versus 6% with placebo (RR 4.55, 95% CI 3.33 to 6.23).⁸ In a moderate quality RCT of Japanese and Korean CSU patients the response with omalizumab 300 mg was larger than the effect observed with 150 mg.³⁹ With 300 mg dosing, the rates were 35.6% versus 4.1% with placebo (OR 15.30, 95% CI 4.27 to 54.90), and with 150 mg they were 18.6% versus 4.1% with placebo (OR 5.36, 95% CI 1.43 to 20.08).³⁹

Quality of life was measured by the Dermatology Life Quality Index (DLQI, range 0 to 30, lower scores are better) in 4 trials.² Quality of life was statistically improved, but the difference did not reach clinical importance. It has been suggested that a difference of at least 4 or 5 points is required for clinical importance on this scale.⁴⁰ The mean change from baseline was -9.2 versus -5.6 in the omalizumab 300 mg groups compared with placebo.² The DERP pooled estimate of effect (difference in the mean change from baseline) was -3.38 (95% CI -4.42 to -2.34), with no heterogeneity (I² = 0%).²

Four RCTs reported serious adverse events, with 4.8% (omalizumab) versus 4.4% (placebo) of patients experiencing a serious adverse event.⁸ The DERP pooled analysis of these trials results in a relative risk of 0.80 (95% CI 0.24 to 2.65), indicating no difference in the incidence of serious adverse events between omalizumab 300 mg and placebo.² Withdrawals due to adverse events were very low, 1% and 0.9% across the 4 RCTs with omalizumab and placebo, respectively.² The pooled relative risk is 1.03 (95% CI 0.24 to 4.41), with no heterogeneity (I² = 0%).²

New Indication:

As of December, 2017 mepolizumab received an expanded indication from FDA for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).³ EGPA, formerly called Churg-Strauss Syndrome, is a rare vasculitis with persistent eosinophilia greater than 10% of the total white blood cell count (e.g., > 1500 cells/ μ L) that occurs primarily in patients with asthma.⁴¹ Systemic corticosteroids are considered first line therapy followed by immunosuppressants in cases refractory to steroids. A multi-center clinical trial conducted in 136 subjects with relapsing and/or refractory EGPA randomized patients to either placebo or mepolizumab 300 mg subcutaneously every 4 weeks for 52 weeks.⁴² Mepolizumab dosing used in this trial was higher than the dose approved by FDA for treatment of severe asthma. The two primary end points were the accrued weeks of remission over a 52-week period, and the proportion of participants in remission at both week 36 and week 48.⁴² Mepolizumab treatment led to significantly more accrued weeks of remission than placebo (28% vs. 3% of the participants had \geq 24 weeks of accrued remission; OR 5.91; 95% CI 2.68 to 13.03; P<0.001) and a higher percentage of participants in remission at both week 36 and week 48 (32% vs. 3%; OR 16.74; 95% CI, 3.61 to 77.56; P<0.001).⁴² Of note, remission did not occur in 47% of the participants in the mepolizumab group versus 81% of those in the placebo group.⁴² In the 52-week trial, the percentage of subjects who experienced systemic reactions was 1% (placebo) compared to 6% (mepolizumab).³

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Appendix 1: Current Preferred Drug List

Route	Form	Brand	Generic	PDL
SUB-Q	VIAL	NUCALA	MEPOLIZUMAB	N
INTRAVEN	VIAL	CINQAIR	RESLIZUMAB	N
SUB-Q	SYRINGE	FASENRA	BENRALIZUMAB	N
SUB-Q	VIAL	XOLAIR	OMALIZUMAB	N

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 an Emergency Department visit or hospitalization.
- Restrict use for conditions not funded by the OHP (e.g., chronic urticaria).

Length of Authorization:

- Up to 12 months

Requires PA:

- Omalizumab
- Mepolizumab
- Reslizumab
- [Benralizumab](#)

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 continuation of therapy previously approved by the FFS program?	Yes: Go to Renewal Criteria	No: Go to #3
3. Is the request for omalizumab, mepolizumab, reslizumab, or benralizumab?	Yes: Go to # 5	No: Go to # 4
4. Is the request for another monoclonal antibody for severe asthma and does the indication match the FDA-approved indication.	Yes: Approve for 6 months	No: Go to # 5
3-5. Is the claim for reslizumab in a patient under 18 years of age?	Yes: Pass to RPh. Deny; medical appropriateness.	No: Go to #6
4-6. Is the claim for mepolizumab or benralizumab in a patient under 12 years of age?	Yes: Pass to RPh. Deny; medical appropriateness	No: Go to # 7 5
7. Is the claim for omalizuamb in a patient under 6 years of age?	Yes: Pass to RPh. Deny; medical appropriateness	No: Go to #8
8. Is the claim for mepolizumab in an adult patient diagnosed with eosinophilic granulomatosis with polyangiitis (EGPA) for at least 6 months that is refractory to at least 4 weeks of oral corticosteroid therapy (equivalent to oral prednisone or prednisolone 7.5 to 50 mg per day)?	Yes: Approve 300 mg (3 x 100mg syringes) every 4 weeks x 1 year	No: Go to #9
5-9. Is the diagnosis an OHP-funded diagnosis? <u>Note:</u> chronic urticaria is not an OHP-funded condition	Yes: Go to # 10 6	No: Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
6-10. Is the prescriber a pulmonologist or an allergist who specializes in management of severe asthma?	Yes: Go to # 117	No: Pass to RPh. Deny; medical appropriateness.
11. Has the patient required at least 2 hospitalizations or ED visits in the past 12 months while receiving a maximally-dosed inhaled corticosteroid (Table 1) AND 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, aminophylline, theophylline)? <u>Has the patient experienced greater than 2 exacerbations in the previous 12 months requiring additional medical treatment (oral corticosteroids, ER visit or hospitalization) while receiving a maximally-dose inhaled corticosteroid (Table 1) AND 2 additional controlled drugs (i.e. long-acting inhaled beta-agonist, montelukast, zafirlukast, or theophylline)?</u>	Yes: Go to # 128 Document number of hospitalizations, or ED visits, <u>or additional oral corticosteroid doses</u> for asthma exacerbation in past 12 months: _____. This is the baseline value to compare to in renewal criteria.	No: Pass to RPh. Deny; medical appropriateness.
7-12. Has the patient been adherent to current asthma therapy in the past 12 months?	Yes: Go to # 139	No: Pass to RPh. Deny; medical appropriateness.
8-13. Is the patient currently receiving another monoclonal antibody for asthma (e.g., omalizumab, mepolizumab, <u>benralizumab</u> or reslizumab)?	Yes: Pass to RPh. Deny; medical appropriateness.	No: Go to # 140
9-14. If the claim is for omalizumab, can the prescriber provide documentation of allergic IgE-mediated asthma diagnosis, confirmed by a positive skin test or in vitro reactivity to perennial allergen?	Yes: Approve once every 2-4 weeks for up to 12 months. Document test and result:_____	No: Go to # 154

Approval Criteria

~~40-15.~~ If the claim is for mepolizumab, [benralizumab](#) or reslizumab, can the prescriber provide documentation of [severe](#) eosinophilic ~~asthma~~[phenotype](#), confirmed by blood eosinophil count ≥ 300 cells/ μ L in the past 12 months?

Yes: Approve once every 4 [to 8](#) weeks for up to 12 months.

[Note: Initial benralizumab dose is 30 mg every 4 weeks x 3 doses followed by 30 mg every 8 weeks](#)

Document eosinophil count (date): _____

No: Pass to RPh. Deny; medical appropriateness.

Renewal Criteria

[1.](#) Is the request to renew mepolizumab for EGPA?

Yes: Go to [#2](#)

No: Go to [#3](#)

[2.](#) Have the patient's symptoms improved with mepolizumab therapy?

Yes: Approve for 12 months

No: Pass to RPh. Deny; [medical appropriateness.](#)

~~4-3.~~ Is the patient currently taking a maximally-dosed inhaled corticosteroid and 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, [aminophylline](#) theophylline)?

Yes: Go to [#42](#)

No: Pass to RPh. Deny; medical appropriateness.

Renewal Criteria

2.4. Has the number of ED visits, ~~or~~ hospitalizations, or additional oral corticosteroid doses in the last 12 months been reduced from baseline, or has the patient reduced their systemic corticosteroid dose by $\geq 50\%$ compared to baseline?

Yes: Approve for up to 12 months.

No: Pass to RPh. Deny; medical appropriateness.

P&T Review: 7/18 (DM); 7/16
Implementation: TBD, 8/16