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Drug Class Update: Asthma and COPD Maintenance Medications

Date of Review: October 2020

Date of Last Review:
Inhalers (May 2019)
Asthma Biologics (July 2018)
Oral Agents (Sept 2015)

Literature Search:
Inhalers 05/01/19 – 07/08/20
Asthma Biologics 04/01/18 – 08/07/20
Oral Agents 10/01/15 -- 07/08/20

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
Asthma and chronic obstructive pulmonary disease (COPD) maintenance medications are being reviewed to evaluate need to change policy based on evidence published since the last class updates.

Research Questions:
1. What is the comparative evidence of efficacy for asthma and COPD maintenance medications for important outcomes such as symptoms, lung function, hospitalizations and mortality?
2. What is the evidence for harms associated with asthma and COPD maintenance medications?
3. Are there subgroups of patients based on demographics (age, racial groups, gender), comorbidities (drug-disease interactions), or other medications (drug-drug interactions) for which treatments for asthma or COPD differ in efficacy/effectiveness or frequency of adverse events?

Conclusions:
ASTHMA
- A Cochrane review evaluated the safety of formoterol compared to formoterol combined with an inhaled corticosteroid (ICS) in adult, children and adolescent patients with asthma.[1] All-cause mortality occurred in 17 of 18,645 adults who were using formoterol with an ICS compared to 13 patients taking an ICS alone, which equated to 1 patient per 1000 patients for each group over a 26-week time period, based on moderate strength of evidence. No deaths were reported for children or adolescents. Non-fatal severe adverse events were similar between groups for adults, children and adolescents.

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- A 2020 National Institute for Health and Care Excellence (NICE) guidance found low quality evidence of no significant reduction in asthma exacerbations upon increasing ICS doses in children and young people via self-directed management at the onset of an asthma exacerbation compared to keeping the usual maintenance ICS dose as part of a self-directed management plan.[2]
- A 2019 NICE update provided guidance on the use of the biologic treatment, benralizumab, for the treatment of severe eosinophilic asthma. Benralizumab is recommended for adult patients with inadequately controlled asthma despite optimization of maintenance therapy with high-dose corticosteroids and LABAs who also have blood eosinophil counts of 300 cells/µL or more and 4 or more exacerbations needing systemic corticosteroids in the previous 12 months or those who have continuous oral corticosteroid use equivalent to prednisone 5 mg/day over the previous 6 months or blood eosinophil count has been recorded as 400 cells/µL or more with at least 3 exacerbations needing systemic corticosteroids in the past 12 months.
- European Respiratory Society and the American Thoracic Society (ERS/ATS) 2019 recommendations for the treatment of severe asthma are consistent with current policy for monoclonal antibodies.

COPD

- A Cochrane systematic review provided evidence that phosphodiesterase-4 (PDE4) inhibitors improved lung function and reduction in COPD exacerbations but had no effect on symptoms and quality of life (moderate to high quality of evidence). PDE4 inhibitors modestly improved forced expiratory volume in one second (FEV_1) compared to placebo in patients with moderate to very severe COPD by a mean difference (MD) of 70.7 mL, which is lower than the clinically meaningful change of 100 mL.[3] St. George's Respiratory Questionnaire (SGRQ) scores were also more improved with PDE4 inhibitors compared to placebo by a MD of 3.27 points, which is lower than the minimal clinically important difference (MCID) of 4 points.[3] Mortality was not different between groups.
- An Agency for Healthcare Research and Quality (AHRQ) review of adult patients with COPD found insufficient evidence for the use of ICS (with or without terbutaline or formoterol) on hospitalizations, intubations and mortality.[4] There was low quality evidence from one trial that ICS improved FEV_1 percent predicted by 10.10% more than placebo which almost meets the threshold for MCID for change.
- A 2017 review by NICE provided guidance on the use of roflumilast in adult patients with COPD which is consistent with current policy.[5]

Recommendations:

- Update roflumilast prior authorization (PA) criteria with clinical definition of severe and very severe COPD (Appendix 5).
- Clarify age recommendations for use of monoclonal antibodies.
- New clinical evidence does not warrant changes to the preferred drug list (PDL).
- After executive session Tudorza was made non-preferred and the following were made preferred; AirDuo Respiclick, Anoro Ellipta and Stiolto Respimat.

Summary of Prior Reviews and Current Policy

Asthma and COPD

- Maintenance therapies for the treatment of asthma and COPD were last reviewed in 2015. There was no compelling efficacy or safety evidence to justify changes to the PDL.
- A new PDL class for combination long-acting muscarinic antagonists (LAMA) and long-acting beta-agonists (LABA) products was created.
- The PA criteria for maintenance inhalers was reorganized with the following changes:
    - All non-preferred LABA, ICS, LABA/ICS, and LAMA/LABA inhalers require PA to ensure appropriate step therapy.
    - Prior authorization was removed for leukotriene inhibitors. Non-preferred leukotriene receptor antagonist (LTRA) currently use the generic non-preferred PDL PA.

Asthma Monoclonal Antibodies

- A recent review of asthma biologics in 2018 found no clinical evidence to support changes to the PDL. There are 5 monoclonal antibodies for asthma all of which require PA which limits coverage to refractory asthma and attempts to mitigate risk of severe adverse reactions (e.g., anaphylaxis). Mepolizumab, reslizumab, dupilumab and benralizumab are reserved for use in patients with severe asthma with the eosinophilic phenotype. Omalizumab is indicated for allergic asthma and chronic uticaria; however, chronic uticaria is not a funded diagnosis on the Oregon Health Evidence Review Commission (HERC) prioritized list.
- Current criteria require that auto-injectable epinephrine be co-prescribed with all asthma biologics due to the risk of delayed anaphylaxis.
- There are no preferred monoclonal antibodies for asthma.

Utilization

- Adherence to preferred therapies is high for inhaled and oral therapies for asthma and COPD; however, cost for the classes account for a significant expenditure to the OHP. Claims for miscellaneous pulmonary drugs (e.g., asthma biologics, leukotriene antagonists, and PDE4 inhibitors) are few, with the majority of claims being for the preferred product montelukast.

Background:

ASTHMA

Asthma is a chronic inflammatory condition of the lungs resulting in airway obstruction, bronchial hyperresponsiveness and airway edema. Genetics and environmental factors are thought to contribute to asthma development. Centers for Disease Control and Prevention data from 2018 reports the burden of asthma in Oregon to be over 11%.[6] Nationwide total asthma costs were projected to be over $20 billion in 2010.[7]

Asthma is characterized by symptoms of wheezing, cough, dyspnea and chest tightness. Diagnosis is confirmed by spirometry (FEV_1 > 200 mL or ≥ 12% from baseline after short-acting beta agonist [SABA] use), airway obstruction that is at least partially reversible and exclusion of other potential diagnoses. Asthma is characterized as being intermittent or persistent (further divided into mild, moderate or severe).[8] The underlying pathophysiology of asthma is multi-factorial and include several phenotypes: eosinophil predominant, neutrophil predominant and allergic asthma. In particular those patients with eosinophil asthma Type 2 (T2)-high, which indicates high levels of T-helper type 2 lymphocytes, respond well to ICS therapy and biologic therapy if asthma remains uncontrolled.[9] Patients with eosinophil asthma also have high levels of sputum eosinophils, and while a correlation of blood eosinophil levels to sputum eosinophils is not well defined, guidelines define the threshold as blood

eosinophils of ≥150 cells/µL.[10] Studies of biologic therapies have evaluated use in patients with eosinophil levels of greater than 150 cells/µL to more than 400 cells/µL.

Asthma treatment can be divided into two categories, quick-relief medication and long-term control medications. The Expert Panel Report 3 (EPR3) recommends asthma treatment be approached in a stepwise manner based on the severity of asthma symptoms.[8] Patients with persistent asthma require long-term control medications to contain the underlying inflammation associated with asthma. ICSs are the preferred maintenance therapy for all patients with persistent asthma. If additional therapy is required to control asthma symptoms, LABAs are recommended in combination with ICS.[8] Other maintenance therapy options include leukotriene inhibitors, methylxanthines, cromolyn sodium and nedocromil. SABAs, anticholinergics and systemic corticosteroids are recommended for acute symptom management. Biological asthma treatments are recommended for those patients with severe asthma that is unresponsive to controller-drug therapy.[9] Biologic asthma therapy includes an anti-immunoglobulin E (IgE) monoclonal antibody (omalizumab), an interleukin 13 and 4 receptor inhibitor (dupilumab), and 3 different anti-interleukin (IL)-5 antibodies (benralizumab, reslizumab and mepolizumab).

Outcome measures used in asthma trials are FEV_1, asthma exacerbations, hospitalization, emergency room visits, and need for oral corticosteroids. Change from baseline in FEV_1 is a common surrogate endpoint used since it is highly reproducible. Research in COPD patients suggest that minimally important FEV_1 changes range from 100-140 mL.[11] Moderate-quality evidence suggests that targeting interventions for asthma based on sputum eosinophil levels compared to clinical symptoms may reduce the number and severity of asthma attacks in adults; however, additional research is needed.[12]

COPD

COPD is a chronic respiratory disorder characterized by reduced expiratory flow due to irreversible airway inflammation. Airway narrowing, hyperinflation and impaired gas exchange are pathological changes associated with COPD. The most common cause of COPD is airway irritation, usually from cigarette smoking. In rare cases alpha-1 antitrypsin (AAT) deficiency has been implicated in the development of early onset COPD. It is estimated almost 6% of Oregonians were diagnosed with COPD in 2011.[13] Forty-one percent of these individuals were on at least one daily treatment for COPD.[13]

Chronic cough or sputum production and dyspnea are common symptoms of COPD. The diagnosis and management of COPD is based on spirometry (post-bronchodilator ratio of $FEV_1/FVC < 0.70$), symptom severity, risk of exacerbations and comorbidities.[1] COPD is classified into four stages based on spirometric measurements of FEV_1/FVC: grade 1 (mild), grade 2 (moderate), grade 3 (severe), and grade 4 (very severe). The Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (GOLD) guidelines recommend therapeutic approaches based on disease burden as well as FEV_1, which classifies patients into groups A-D (low to high risk of symptoms and exacerbations).[1] This type of classification system shifts the focus from including just FEV_1 measurements, as these are not always indicative of COPD status.

Common treatment options for patients with COPD are bronchodilators (SABAs, SAMAs, LABAs and LAMAs), corticosteroids and methylxanthines. Bronchodilators (short and long-acting) have demonstrated improvements in FEV_1 and symptom improvement. Long-acting bronchodilators (LAMAs and LABAs) improve lung function, dyspnea, health status and reduce exacerbation rates.[9] Inhaled corticosteroids/LABAs have been shown to improve health status, reduce exacerbations and improve lung function compared to monotherapy. Conclusive evidence of benefit has not been demonstrated with ICS alone in patients with COPD. Phosphodiesterase-4 inhibitors have a role in COPD management by minimizing airway narrowing and damage due to inflammation. Phosphodiesterase-4 inhibitors are used as add-on therapy for patients with COPD who have persistent symptoms or exacerbations despite optimal treatment with other COPD therapies. There is a lack of conclusive benefit of improved survival rates with any of the inhaled respiratory medications used in the management of COPD and no medications have shown a preventative effect in the decline of lung function.[9]

Goals of therapy for COPD management are to improve symptoms and reduce frequency of exacerbations. Important outcomes to access the effectiveness of therapies include: lung function, quality of life (QoL), dyspnea, exacerbation rate and/or severity, mortality and adverse events. FEV_1 is the most common surrogate outcome used in studies to determine therapy effectiveness. The MCID in FEV_1 values for COPD changes have not been clearly defined but Cochrane reviews recommend a change of 100 mL.[1] Other sources suggest a change in percent predicted FEV_1 of 10.38% or more is considered a MCID.[14] The SGRQ is used to determine the effects of COPD on quality of life with scores ranging from 0-100, higher scores indicate more limitations. The MCID for the SGRQ is a change of 4 units.[3]

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

ASTHMA

Cochrane – Inhaled Steroids With and Without Regular Formoterol for Asthma: Serious Adverse Events

A recent Cochrane review analyzed safety data associated with the use of ICS compared to ICS and formoterol in adults and children with asthma.[1] The review is in response to safety concerns with an increased mortality risk with LABAs and if this risk is attenuated with the addition of an ICS. Thirty-nine studies were identified in a search through February 2019. This is an update from a previous review published in 2012. ICS therapies included in the review were: beclomethasone (200 to 800 mcg), budesonide (200 to 1600 mcg), fluticasone (200 to 250 mcg), and mometasone (200 to 800 mcg).[1] Formoterol was studied at doses of 12 to 48 mcg. Most of the combination beta-2 agonist and ICS regimens were provided in a fixed dose combination inhaler. Studies in adults were a weighted mean duration of 26 weeks and those in children and adolescents were 12.5 weeks. Most domains had a low risk of bias with the exception of detection bias due to lack of independent assessment.

Asthma related deaths were low in all populations studied. There were no children or adolescents (n=4035) that died from asthma. However, 3 adult patients (n=12,777) who were taking an ICS and formoterol died of asthma.

- All-cause mortality occurred in 17 of 18,645 adults who were using formoterol with an ICS compared to 13 patients taking an ICS alone (Odds ratio [OR] 1.25; 95% confidence interval [CI], 0.61 to 2.56) or one death for every 1000 adults who were treated for 26 weeks which was the same for both groups (moderate strength of evidence).[1]
- All-cause, non-fatal serious adverse events (life-threatening, hospitalization or prolonging of existing hospitalization, causing persistent or significant disability, or congenital abnormality or defect) were the same in both groups, 2.1% (OR 1.00; 0.87 to 1.16) (high strength of evidence).[1]
- Asthma-related, non-fatal serious adverse events at 26 weeks occurred in 6 of 1000 patients for those treated with an ICS compared to 5 per 1000 patients treated with ICS/formoterol (OR 0.86; 95% CI, 0.64 to 1.14) (moderate strength of evidence).[1]
- All-cause non-fatal serious adverse events occurred in 8 per 1000 children and adults taking ICS alone compared to 11 per 1000 taking formoterol with an ICS (OR 1.33; 95% CI, 0.71 to 2.49) with follow-up of 12.5 weeks (moderate strength of evidence).[1]

In conclusion, there was no conclusive evidence suggesting an increase safety risk with the use of combination formoterol and ICS compared to ICS alone; however, the potential for an increased risk with formoterol cannot be ruled out due to the low incidence of deaths.[1]

COPD

<u>Cochrane – Phosphodiesterase-4 inhibitors for Chronic Obstructive Pulmonary Disease</u>

A Cochrane review analyzed the data on treating COPD with PDE4 inhibitors (roflumilast, cilomilast [not available in the US] and tetomilast [not available in the US].[3] Literature was searched through March 2020, which identified 42 randomized clinical trials for inclusion; 28 roflumilast trials (500 µg was evaluated in all trials with the exception of one roflumilast 250 µg trial), 14 cilomilast trials and 1 trial for tetomilast. Trial duration was 6 weeks to 1 year.[3] Mean participant age was 64 years and patients had moderate to very severe COPD. Important endpoints were changes in lung function (FEV_1) and QoL. Allocation bias was present in half of the roflumilast trials, but otherwise risk of bias was generally low for performance, detection, attrition and reporting bias.

Improvements in lung function as measured by FEV_1 were higher with PDE4 inhibitors compared to placebo, MD of 49.33 mL (95% CI, 44.17 to 54.49 mL) compared to placebo, with a mean follow up of 40 weeks (moderate quality of evidence).[3] FEV changes were a mean difference of 86.98 mL higher for PDE4 inhibitors compared placebo (95% CI, 74.65 to 99.31), based on high quality of evidence of trials lasting a weighted mean of 45 weeks. There is moderate quality of evidence that PDE4 inhibitors were more effective at improving SGRQ scores but only by 3.27 units which is less than the MCID.[3] There were more patients with 1 or more exacerbations in those treated with placebo compared to PDE4 inhibitors, 33 per 100 patients versus 27 per 100 patients (OR 0.78; 95% CI, 0.73 to 0.84) based on high quality evidence.[3]

Gastrointestinal adverse reactions (e.g., diarrhea) were more common in patients treated with PDE4 inhibitors compared to placebo (OR 3.10; 95% CI, 2.74 to 3.50) based on high quality of evidence. Roflumilast 500 µg increased risk of psychiatric adverse events compared to placebo by an additional 4 patients per 100 treated, 7 per 100 patients versus 3 per 100 patients (moderate quality of evidence).[3] No difference in morality was demonstrated between PDE4 inhibitors and placebo based on moderate quality of evidence (OR 0.98; 95% CI, 0.77 to 1.24).

<u>AHRQ – Pharmacological and Nonpharmacological Therapies in Adult Patients with Exacerbation of COPD</u>

AHRQ conducted a systematic review of therapies to manage adult patients with COPD experiencing an exacerbation.[4] Evidence was searched through January 2020. There were 98 randomized trials, totaling 13,401 patients meeting criteria for inclusion.[4] Effectiveness of interventions were measured by health outcomes including mortality, exacerbation resolution, hospital readmission, repeat exacerbations and need for intubation. Studies on the use of maintenance medications for an acute exacerbation of COPD looked at surrogate outcomes (changes in FEV_1). Overall, there was insufficient evidence on hospitalizations, intubations and mortality.

Four studies evaluated the effects of ICS in patients with mild, moderate and severe COPD. Patients (n=106) with moderate to severe COPD taking inhaled budesonide demonstrated higher FEV_1 percent predicted (FEV_1PP) increases compared to placebo (weighted mean difference [WMD] 10.10%; 95% CI, 4.23 to 15.97%).[4] No difference was found between ICS and placebo in dyspnea, 30-day hospital admission, and need for intubation. Combination budesonide and terbutaline increased FEV_1PP compared to placebo in 40 patients (WMD 8.30%; 95% CI, 2.92 to 13.68%).[4] There were no significant differences in adverse events between active treatment and placebo in all studies. Combination ICS and LABA (budesonide and formoterol) compared to placebo had no significant effect on FEV_1 in 30 patients with mild COPD.[4]

Evidence is insufficient to support the use of inhaled corticosteroids in acute exacerbations of COPD for outcomes of mortality, dyspnea, need for intubation and hospital admission.

After review, 4 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[15–19]

New Guidelines:

High Quality Guidelines:

NICE – Asthma Diagnosis, Monitoring and Chronic Management

A February 2020 update was done by NICE to determine if increasing ICS treatment in children and young people (ages less than 18years) via self-management is an effective way to manage asthma at the onset of an exacerbation.[2] Children and young people who use ICS preventative therapy and have a personalized action plan were included in the evidence review. Adults who use ICS therapy and have action plans to manage exacerbation were also included due to a paucity of evidence in children and young people. Five studies were identified for inclusion. The primary outcome of interest was the number of subsequent asthma exacerbations.

The quality of evidence was low with only one study in children and young people. The number of adolescents included in the adult studies was too small to extrapolate evidence to children and young people. NICE recommends that the ICS dose not be increased according to a self-directed action plan in children and young people at the onset of an exacerbation due to the lack of high quality evidence.[2]

NICE – Benralizumab for Treating Severe Eosinophilic Asthma

A 2019 NICE update provided guidance on the use of the biologic treatment, benralizumab, for the treatment of severe eosinophilic asthma.[20] NICE recommends the use of benralizumab for patients meeting the following criteria:

- Adult patients with inadequately controlled asthma despite optimization of maintenance therapy with high-dose corticosteroids and LABAs[20] **AND**
- Blood eosinophil counts of 300 cells/µL or more and 4 or more exacerbations needing systemic corticosteroids in the previous 12 months or continuous oral corticosteroid use equivalent to prednisone 5 mg/day over the previous 6 months[20] **OR**
- Blood eosinophil count has been recorded as 400 cells/µL or more with at least 3 exacerbations needing systemic corticosteroids in the past 12 months[20]

NICE recommends that patients meeting the criteria for benralizumab use be referred to a specialist for management. NICE recommends that benralizumab therapy be reevaluated every 12 months to ensure that there has been a reduction in the number of severe exacerbations needing systemic corticosteroids or clinically significant reduction in continuous oral corticosteroid without exacerbations of symptoms. [20]

The evidence supporting the recommendations for benralizumab come from 2 randomized-controlled trials. Pooled results from 2 trials demonstrated a reduction in the annual rate of exacerbations by 43% with benralizumab compared to placebo (relative risk [RR] 0.57; 95% CI, 0.47 to 0.69; $p<0.0001$).[20] Efficacy was greatest in patients with blood eosinophil counts greater than 300 cells/µL or in those with 3 or more exacerbations. Trial data found a reduction in the median final oral corticosteroid dose by 75% with benralizumab compared to a placebo reduction of 25%. There is insufficient head-to-head evidence to compare the efficacy of benralizumab to either reslizumab or mepolizumab.

NICE - Roflumilast for Treating Chronic Obstructive Pulmonary Disease

A 2017 NICE guidance outlined treatment recommendations for the use of roflumilast for patients with COPD.[5] Recommendations for the use of roflumilast are based on evidence used for roflumilast approval in 2011.

NICE Recommendations for Roflumilast use in Patients with COPD:

- Adult patients having severe COPD with bronchitis
- COPD has been classified as severe based on FEV_1 of less than 50% of predicted normal after bronchodilator use

And

- Patient has had 2 or more exacerbations in the previous 12 months despite triple inhaled therapy with LAMA/LABA/ICS
- Treatment is initiated by a specialist in respiratory medicine

Roflumilast is generally well tolerated. Most common reasons for discontinuations were weight loss and gastrointestinal side effects.

<u>European Respiratory Society and the American Thoracic Society (ERS/ATS) – Management of Severe Asthma</u>

A 2019 guidance on the management of severe asthma was authored by the ERS/ATS. Guideline methodology was generally of high quality based on the AGREE evaluation tool; however, most authors reported conflicts of interest.[21] A literature search was conducted through September 2018. Twelve trials were included which evaluated the use of monoclonal anti-interleukin (IL)-5 antibodies (mepolizumab, reslizumab and benralizumab) in adults and children with severe asthma.

All monoclonal anti-IL-5 antibody products reduce exacerbations and hospitalizations in patients with severe eosinophilic asthma. Mepolizumab and benralizumab reduced the oral corticosteroid dose in corticosteroid-dependent asthma. For the outcomes of asthma control, QoL and FEV_1, there was only modest benefit which did not meet MCID.

Table 1. ERS/ATS Management of Severe Asthma Recommendations[21]

Recommendation
1. Anti-IL-5 should be offered to patients as add-on therapy for adult patients with severe uncontrolled asthma with an eosinophilic phenotype and for those patients with severe oral corticosteroid dependent asthma (low quality of evidence)
2. A blood eosinophil count of $\geq$ 150 μL^{-1} can be used as a marker for anti-IL-5 initiation in adult patients with severe asthma and prior asthma exacerbations (low quality of evidence)
3. In adults and adolescents with severe asthma considering omalizumab the following should be considered: - Blood eosinophil count of $\geq$ 260 μL^{-1} to identify adolescents (>12 years) and adults with severe allergic asthma who would likely to benefit from therapy (low quality of evidence) - F_{ENO} cut off of $\geq$ 19.5 ppb to identify adolescents and adults with severe allergic asthma who would likely benefit from anti-IgE treatment (low quality of evidence)
4. For children, adolescents and adults with severe asthma uncontrolled with therapies outlined below in GINA step 4-5 or NAEPP guidelines as step 5 therapies, tiotropium is recommended (moderate quality of evidence)

Abbreviations: F_{ENO}- exhaled nitric oxide fraction; GINA – Global Initiative for Asthma; IL – interleukin; ppb = parts per billion; NAEPP – National Asthma Education and Prevention Program

Additional Guidelines for Clinical Context:

GINA – Global Strategy for Asthma Management and Prevention

GINA updates their recommendations on an annual basis to guide diagnosis and management of asthma in adults and adolescents.[9] Guidelines are based on a systematic search of the literature and publications are reviewed for acceptance by at least two committee members that are without conflicts of interest. Evidence is graded based on criteria developed by the National Heart Lung and Blood Institute which ranks the level of evidence from A to D, with A level evidence defined as: well-designed randomized controlled trials, meta-analyses or post-hoc or observational data.[9] There is no risk of bias assessment used as inclusion criteria for publications used for guideline development. Other limitations to the guideline include the absence of the following: target users, objective of the guidelines, specifics on evidence selection, diversity in representation from professional groups, patient and public input, external review by experts in the field, and discussion on resource implications/barriers of recommendations.[9] Therefore, guideline recommendations for pharmaceutical management will be provided for clinical context but not relied upon for decisions regarding the PDL.

Recommendations provided by GINA are based on asthma symptom severity ranging from steps 1 to step 5 as outlined below.[9] Medication recommendations based on corresponding steps are displayed in **Table 2**. A major update to the guidelines is the recommendation that adults and adolescents with asthma should no longer be treated with a SABA alone (**Tables 2 and 3**).[9] Daily or as-needed (ICS-formoterol) controller treatment should contain an ICS and replace SABA monotherapy. For step 1 and 2, as-needed low dose ICS-formoterol is recommended as the preferred reliever therapy. As-needed low dose ICS-formoterol for patients prescribed maintenance and reliever therapy is recommended for steps 3-5 (if patients prescribed budesonide-formoterol or beclometasone dipropionate (BDP)-formoterol for maintenance and reliever therapy).[9] As-needed SABA is an alternative option for all asthma steps. Patients with difficult to treat asthma (uncontrolled step 4 or step 5 asthma despite optimal therapy) should add treatment such as tiotropium, LTRA, and low dose macrolides and biologic agents for severe allergic or severe Type 2 asthma.

Asthma Severity Directing Therapy

Mild Asthma	*Step 1* – Symptoms less than twice a month
	Step 2 – Symptoms twice a month or more, but less than daily
Moderate Asthma	*Step 3* – Symptoms most days or waking with asthma once a week or more
Severe Asthma	*Step 4* – Symptoms most days or waking with asthma once a week or more or low lung function
	Step 5 – Severely uncontrolled asthma

Table 2. 2020 GINA Recommendations for Initial Controller Medications in Adults and Adolescents with Asthma*[9]

STEP	Treatment Recommendation	Level of Evidence

STEP 1	- As-needed low dose ICS-formoterol *or* - Low dose ICS whenever a SABA is taken	B B
STEP 2	- Daily low dose ICS *or* - As-needed low dose ICS-formoterol	A A
STEP 3	- Lose dose ICS-LABA *or* - Medium dose ICS or - Low dose ICS + LTRA	A B A
STEP 4	- Medium dose ICS-LABA *or* - High dose ICS, add on tiotropium or add-on LTRA	D A
STEP 5	- High dose ICS-LABA - Refer for phenotypic assessment +/- add-on therapy (tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R) *or* - Add low dose OCS but consider side effects	A Not reported Not reported
Key: * Preferred controller option listed first Abbreviations: ICS – inhaled corticosteroid; LABA – long-acting beta agonist; LTRA – leukotriene receptor antagonist; OCS – oral corticosteroid; SABA – short-acting beta agonist		

Table 3. 2020 GINA Recommendations for Initial Controller Medications in Children 6-11 with Asthma*[9]

STEP	Treatment Recommendation	Level of Evidence
STEP 1	- As-needed SABA - Low dose ICS when SABA taken *or* - Daily low dose ICS	Not reported
STEP 2	- Daily low dose ICS *or* - Daily LTRA or low dose ICS when SABA is taken	A B
STEP 3	- Lose dose ICS-LABA or medium dose ICS *or* - Low dose ICS + LTRA	A
STEP 4	- Medium dose ICS-LABA *and* - Referral to expert or - High dose ICS-LABA or add on tiotropium or add on LTRA	Not reported Not reported
STEP 5	- Refer for phenotypic assessment +/- add-on therapy (e.g. anti-IgE) *or*	Not reported

	- Add-on anti-IL5 or add-on low dose OCS, but consider side effects	
Key: * Preferred controller option listed first Abbreviations: ICS – inhaled corticosteroid; LABA – long-acting beta agonist; LTRA – leukotriene receptor antagonist; OCS – oral corticosteroid; SABA – short-acting beta agonist		

GOLD – Global Initiative for Chronic Obstructive Lung Disease

A 2020 guidance on the management of COPD was published by GOLD.[22] Methodology is the same as for the GINA guidelines (above) with the associated limitations as well. Bronchodilators and anti-inflammatory therapies are the cornerstone of COPD management. Recommendations are similar for the 2019 and 2020 COPD classification (**Table 4**) and initial management of COPD (**Figure 1**). A refined ABCD assessment tool was published in the 2020 guidance that recommends a three step process for COPD classification. The first step is a spirometrically confirmed diagnosis of COPD as indicated by a post-bronchodilator FEV_1/FVC <0.7. Assessment of airflow limitation should follow as described in **Table 4**. Lastly, assessment of symptoms/risk of exacerbations should be based off of **Figure 1** to determine the group that the patient would best fit (A, B, C, or D) which also will guide therapy selection. Group classification also requires the administration of modified Medical Research Council dyspnea questionnaire (mMRC) or COPD assessment test (CAT^m) to determine dyspnea symptoms. There is no high quality evidence to support the initial treatment selection for COPD; however, lower quality evidence suggests initiation of ICS/LABA is more effective than treatments with LAMA in patients with previous exacerbations and high levels of blood eosinophils (>300 cells/µL).[22]

Table 4. Classification of COPD Based on GOLD Guidelines*[20]

Classification	Severity	Post-Bronchodilator FEV_1 (% predicted)
GOLD 1	Mild	≥ 80
GOLD 2	Moderate	50 -79
GOLD 3	Severe	30-49
GOLD 4	Very severe	< 30

* For patients with a FEV1/FVC < 0.70

Figure 1. Initial Pharmacological Management of COPD[22]

≥ 2 moderate exacerbations or ≥ 1 leading to a hospitalization	**Group C** LAMA	**Group D** LAMA or LAMA + LABA* or ICS + LABA** * Consider if highly symptomatic (e.g., CAT > 20) ** Consider if EOS ≥ 300
0 or 1 moderate exacerbations (not leading to hospital admission)	**Group A** A Bronchodilator (short or long-acting)	**Group B** A Long Acting Bronchodilator (LABA or LAMA)
	mMRC 0-1 CAT <10	mMRC ≥ 2 CAT ≥ 10

Abbreviations: EOS = blood eosinophil count in cells per microliter; mMRC = modified Medical Research Council dyspnea questionnaire; CAT = COPD assessment test

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. 2020 Report. Available at: [14]. Accessed July 15, 2020.

Pharmacotherapy management of dyspnea and exacerbations should be directed by a review of the symptoms, assessment of current therapy (technique and adherence) and adjustment of therapy with escalation or de-escalation. Patients with persistent dyspnea on long acting bronchodilator monotherapy should be considered for dual therapy with a second long-acting bronchodilator.[22] Patients on ICS/LABA therapy can be considered for triple therapy with the addition of a LAMA. For patients who experience exacerbations on long acting bronchodilator therapy, transitioning to a LABA/LAMA or LABA/ICS is recommended.[22] Patients with a history of asthma and/or a peripheral blood level of 300 or more eosinophils per microliters are more likely to respond to LABA/ICS.[22] Patients with exacerbations on LABA/LAMA should be treated with roflumilast or azithromycin if blood eosinophils are less than 100 cells per microliter, or triple therapy with LABA/LAMA/ICS if blood eosinophil

levels are 100 cells per microliter or greater. Patients on triple therapy who continue to have exacerbations can be considered for roflumilast, macrolide therapy or discontinuation of ICS (due to risk of pneumonia or based on lack of efficacy).[22]

After review, one guideline was excluded due to poor quality.[23]

New Formulations and Indications:

Mepolizumab (NUCALA) – Mepolizumab was approved for use in pediatric patients, ages 6 years and older, for the treatment of severe asthma with an eosinophilic phenotype.[24] The efficacy of mepolizumab was extrapolated from data in adults in addition to pharmacokinetic data to support approval.

Budesonide/glycopyrrolate/formoterol (BREZTRI AEROSPHERE) – Budesonide 160 mcg/glycopyrrolate 9 mcg/formoterol fumarate 4.8 mcg (BGF) triple drug inhalation therapy (ICS/anticholinergic/LABA), indicated for maintenance therapy in patients with COPD, was approved in late July 2020.[25] BGF was studied in two phase 3, multicenter, parallel-group trials in patients with moderate to severe COPD, which are described in **Table 6**.[26,27] BGF was found to reduce COPD exacerbations and improve FEV1 outcomes compared to budesonide/formoterol fumarate and glycopyrrolate/formoterol fumarate; however, differences were small with unknown clinical significance.

Most common adverse reaction are upper respiratory tract infection, pneumonia, back pain, oral candidiasis, influenza, muscle spasm, urinary tract infection, cough, sinusitis, and diarrhea.[25]

New FDA Safety Alerts:

Table 5. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Montelukast[28]	Singulair	April 2020	Boxed Warning	Serious neuropsychiatric events have been reported. Monitor for neuropsychiatric symptoms in patients taking montelukast and discontinue if symptoms occur. Only use montelukast in patients with allergic rhinitis who have an inadequate response or intolerance to alternative therapies.
Roflumilast[29]	Daliresp	August 2017	Warnings and Precautions	Psychiatric events including suicidality have been reported. Patients should be aware of worsening insomnia, anxiety, depression, suicidal thoughts or other mood changes.

Randomized Controlled Trials:

A total of 130 citations were manually reviewed from the initial literature search. After further review, 124 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining three publications are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 6. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Interpretation
Rabe, et al[26] (ETHOS) 52-week, phase 3, DB, MC, PG, RCT	1) Budesonide 320 µg/ Glycopyrrolate 18 µg/ Formoterol fumarate 9.6 µg inhaled twice daily Vs. 2) Budesonide 160 µg/ Glycopyrrolate 18 µg/ Formoterol fumarate 9.6 µg inhaled twice daily Vs. 3) Glycopyrrolate 18 µg/ Formoterol fumarate 9.6 µg inhaled twice daily Vs. 4) Budesonide 320 µg/ Formoterol fumarate 9.6 µg inhaled twice daily	Patients with moderate to very severe COPD and at least one exacerbation in the last year (n=8509)	The annual rate (estimated mean number per patient per year) of moderate or severe COPD exacerbations	1) 1.08 2) 1.07 3) 1.42 4) 1.24 1 vs. 3 RR 0.76 (95% CI, 0.69 to 0.83) P<0.001 1 vs. 4 RR 0.87 (95% CI, 0.79 to 0.95) P = 0.003 2 vs. 3 RR 0.75 (95% CI, 0.69 to 0.83) P<0.001 2 vs. 4 RR 0.86 (95% CI, 0.79 to 0.95) P=0.002	*Triple therapy with budesonide/glycopyrrolate/ formoterol (low [160 µg budesonide dose] and high [320 µg budesonide dose]) was more effective than glycopyrrolate/formoterol and budesonide/formoterol for reducing the rate of COPD exacerbations. The absolute reduction in exacerbations was less than 1 exacerbation per patient per year.*
Ferguson, et al[27] (KRONOS)	1) Budesonide 320 µg/ Glycopyrrolate 18 µg/ Formoterol fumarate 9.6 µg inhaled twice daily Vs. 2) Glycopyrrolate 18 µg/ Formoterol fumarate 9.6 µg inhaled twice daily	Patients with moderate to severe COPD without a requirement for a history of exacerbations	FEV_1 area under the curve from 0-4 hours (AUC_{0-4}) for 1) versus 3) and 1) versus 4) and analysis of change from baseline in morning pre-dose	FEV_1 AUC_{0-4}mL 1) 305 mL 2) 288 mL 3) 201 mL 4) 214 mL 1 vs. 2	*There was no difference between triple therapy (budesonide/glycopyrrolate/fo rmoterol fumarate) and glycopyrrolate/formoterol fumarate in changes in FEV_1 AUC_{0-4}mL . Triple therapy was*

24-week, phase 3, DB, MC, PG, RCT	Vs. 3) Budesonide 320 µg/ Formoterol fumarate 9.6 µg inhaled twice daily 4) Budesonide 400 µg/ Formoterol fumarate 12 µg inhaled twice daily (open-label)	(n = 3047)	trough FEV_1 for 1) versus 2) and non-inferiority analysis of 3) versus 4) (non-inferiority analysis of -50 mL from lower bound of 95% CI)	LSM 16 mL (95% CI, -6 to 38) P=0.1448 1 vs. 3 LSM 104 mL (95% CI, 77 to 131) P<0.0001 1 vs. 4 91 (95% CI, 64 to 117) P<0.0001 Change from baseline in morning pre-dose trough FEV_1 1) 147 mL 2) 125 mL 3) 73 mL 4) 88 mL 1 vs. 2 22 mL (95% CI, 4 to 39) P=0.0139 1 vs. 3 (prespecified secondary endpoint) 74 mL (95% CI, 52 to 95) P<0.0001 1 vs. 4	*more eff*ective in increasing FEV_1 AUC_{0-4}mL *compared to budesonide/formoterol fumarate.* *Increases in baseline morning pre-dose trough FEV_1 were larger for budesonide/glycopyrrolate/formoterol fumarate compared to glycopyrrolate/formoterol fumarate and budesonide/formoterol fumarate.* *Differences between groups in lung function for both groups is small and unlikely to be clinically significant.*

				59 mL (95% CI, 38 to 80) P<0.0001	
Criner, et al[14] (GALATHEA) Phase 3, DB, PC, RCT 56 weeks	Benralizumab 30 mg given every 8 weeks* Benralizumab 100 mg given every 8 weeks* Vs. Placebo given every 8 weeks*	Patients with moderate to very severe COPD with frequent exacerbations despite receiving guideline-based inhaled treatment (n=1120)	Annualized COPD exacerbation rate ratio at week 56 in patients with blood eosinophil counts of 220 per cubic millimeter or greater (same as microliter)	Benralizumab 30 mg: 1.19 Benralizumab 100mg: 1.03 Placebo: 1.24 Benralizumab 30 mg vs. placebo: RR 0.96 (95% CI 0.80 to 1.15) P=0.65 Benralizumab 100 mg vs. placebo: RR 0.83 (95% CI, 0.69 to 1.00) P=0.05	*Benralizumab was not found to reduce annualized rate of COPD exacerbations more than placebo*
Criner, et al[14] (TERRANOVA) Phase 3, DB, PC, RCT 56 weeks	Benralizumab 10 mg given every 8 weeks* Benralizumab 30 mg given every 8 weeks* Benralizumab 100 mg given every 8 weeks* Vs. Placebo given every 8 weeks*	Patients with moderate to very severe COPD with frequent exacerbations despite receiving guideline-based inhaled treatment (n=1545)	Annualized COPD exacerbation rate ratio at week 56 in patients with blood eosinophil counts of 220 per cubic millimeter or greater (same as microliter)	Benralizumab 10 mg: 0.99 Benralizumab 30 mg: 1.21 Benralizumab 100mg: 1.09 Placebo: 1.17 Benralizumab 10 mg vs. placebo: RR 0.85 (95% CI, 0.71 to 1.01) P=0.6 Benralizumab 30 mg vs. placebo: RR 1.04 (95% CI, 0.88 to 1.23)	*Benralizumab was not found to reduce annualized rate of COPD exacerbations more than placebo*

				P=0.066 Benralizumab 100 mg vs. placebo: RR 0.93 (95% CI, 0.78 to 1.10) P=0.40	
Virchow, et al[30] (TRIMARAN) PG, DB, Phase 3, RCT	1) Beclometasone dipropionate 100 µg /formoterol 6 µg /glycopyrronium 10 µg, 2 inhalations twice daily Vs. 2) Beclometasone 100 µg dipropionate/formoterol 6µg, 2 inhalations twice daily	Adults with uncontrolled asthma, a history of one or more exacerbations in the previous year and previously treated with ICS and LABA (n=1155)	Pre-dose expiratory volume in 1 second (FEV_1) at week 26 and rate of moderate and severe exacerbations over 52 weeks	Pre-dose FEV_1 change from baseline 1) 185 mL 2) 127 mL MD 57 mL (95% CI, 15 to 99) P=0.0080 Annualized rate of moderate to severe exacerbations 1) 1.83 2) 2.16 RR 0.85 (95% CI, 0.73 to 0.99) P=0.033	*The addition of a long-acting muscarinic antagonist to existing ICS and LABA therapy improves lung function and exacerbations (difference in FEV_1 less than MCID of 100 mL)*
Virchow, et al[30] (TRIGGER) PG, DB, Phase	1) Beclometasone dipropionate 200 µg /formoterol 6 µg /glycopyrronium 10 µg, 2 inhalations twice daily Vs. 2) Beclometasone dipropionate 200 µg /formoterol 6 µg, 2 inhalations twice daily Vs.	Adults with uncontrolled asthma, a history of one or more exacerbation in the previous year and previously treated with ICS and LABA	Pre-dose expiratory volume in 1 second (FEV_1) at week 26 and rate of moderate and severe exacerbations over 52 weeks	Pre-dose FEV_1 change from baseline 1) 229 mL 2) 157 mL 3) 274 mL 1 vs. 2 MD 73 mL (95% CI, 26 to 120 mL) P= 0.0025	*The addition of a long-acting muscarinic antagonist to existing ICS and LABA therapy improves lung function. There was no difference in lung function or exacerbations upon comparison of glycopyrronium and tiotropium.*

	3) Beclometasone dipropionate 200 µg /formoterol 6 µg, 2 inhalations twice daily + tiotropium 2.5 µg, 2 inhalations once daily (open-label)	(n=1437)		1 vs. 3 MD -45 mL (95% CI, -103 to 13 mL) P= 0.13 Annualized rate of moderate to severe exacerbations 1) 1.73 2) 1.96 3) 1.61 1 vs. 2 RR 0.88 (95% CI, 0.75 to 1.03) P= 0.11 1 vs. 3 RR 1.07 (95% CI, 0.88 to 1.30) P= 0.50	

Key: * Given every 4 weeks for the first 3 doses

Abbreviations: COPD – chronic obstructive pulmonary disease; DB – double-blind; FEV_1 – forced expiratory volume in 1 second; ICS – inhaled corticosteroids; LABA – long-acting Beta 2 agonist; LSM – least squares mean; MCID – minimal clinically important difference; MD – mean difference; PC – placebo-controlled; PG – parallel group; RCT – randomized controlled trial; RR – rate ratio

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Appendix 1: Current Preferred Drug List

LABA/LAMA Combination, Inhalers

Generic	Brand	Form	PDL
aclidinium brom/formoterol fum	DUAKLIR PRESSAIR	AER POW BA	N
fluticasone/umeclidin/vilanter	TRELEGY ELLIPTA	BLST W/DEV	N
glycopyrrolate/formoterol fum	BEVESPI AEROSPHERE	HFA AER AD	N
indacaterol/glycopyrrolate	UTIBRON NEOHALER	CAP W/DEV	N
tiotropium Br/olodaterol HCl	STIOLTO RESPIMAT	MIST INHAL	N
umeclidinium brm/vilanterol tr	ANORO ELLIPTA	BLST W/DEV	N
budesonide/glycopyrrol/form fum	BREZTRI AEROSPHERE	MIST INHAL	N

Beta-agonists, Inhaled Long-acting

Generic	Brand	Form	PDL
salmeterol xinafoate	SEREVENT DISKUS	BLST W/DEV	Y
arformoterol tartrate	BROVANA	VIAL-NEB	N
formoterol fumarate	PERFOROMIST	VIAL-NEB	N
indacaterol maleate	ARCAPTA NEOHALER	CAP W/DEV	N
olodaterol HCl	STRIVERDI RESPIMAT	MIST INHAL	N

Anticholinergics, Inhaled

Generic	Brand	Form	PDL
aclidinium bromide	TUDORZA PRESSAIR	AER POW BA	Y
ipratropium bromide	ATROVENT HFA	HFA AER AD	Y
ipratropium bromide	IPRATROPIUM BROMIDE	SOLUTION	Y
ipratropium/albuterol sulfate	IPRATROPIUM-ALBUTEROL	AMPUL-NEB	Y
tiotropium bromide	SPIRIVA	CAP W/DEV	Y
glycopyrrol/nebulizer/accessor	LONHALA MAGNAIR STARTER	VIAL-NEB	N
glycopyrrolate	SEEBRI NEOHALER	CAP W/DEV	N
glycopyrrolate/neb.accessories	LONHALA MAGNAIR REFILL	VIAL-NEB	N
ipratropium/albuterol sulfate	COMBIVENT RESPIMAT	MIST INHAL	N
revefenacin	YUPELRI	VIAL-NEB	N
tiotropium bromide	SPIRIVA RESPIMAT	MIST INHAL	N
umeclidinium bromide	INCRUSE ELLIPTA	BLST W/DEV	N

Corticosteroids, Inhaled

Generic	Brand	Form	PDL

budesonide	PULMICORT FLEXHALER	AER POW BA	Y
fluticasone propionate	FLOVENT DISKUS	BLST W/DEV	Y
fluticasone propionate	FLOVENT HFA	AER W/ADAP	Y
mometasone furoate	ASMANEX	AER POW BA	Y
beclomethasone dipropionate	QVAR REDIHALER	HFA AEROBA	N
budesonide	BUDESONIDE	AMPUL-NEB	N
budesonide	PULMICORT	AMPUL-NEB	N
ciclesonide	ALVESCO	HFA AER AD	N
fluticasone furoate	ARNUITY ELLIPTA	BLST W/DEV	N
mometasone furoate	ASMANEX HFA	HFA AER AD	N
fluticasone propionate	ARMONAIR DIGIHALER	INHAL PWD	N

Corticosteroid/LABA Combination, Inhalers

Generic	Brand	Form	PDL
budesonide/formoterol fumarate	BUDESONIDE-FORMOTEROL FUMARATE	HFA AER AD	Y
budesonide/formoterol fumarate	SYMBICORT	HFA AER AD	Y
fluticasone propion/salmeterol	ADVAIR DISKUS	BLST W/DEV	Y
fluticasone propion/salmeterol	ADVAIR HFA	HFA AER AD	Y
fluticasone propion/salmeterol	FLUTICASONE-SALMETEROL	BLST W/DEV	Y
fluticasone propion/salmeterol	WIXELA INHUB	BLST W/DEV	Y
mometasone/formoterol	DULERA	HFA AER AD	Y
fluticasone propion/salmeterol	AIRDUO RESPICLICK	AER POW BA	N
fluticasone propion/salmeterol	FLUTICASONE-SALMETEROL	AER POW BA	N
fluticasone/vilanterol	BREO ELLIPTA	BLST W/DEV	N
Fluticasone propion/salmeterol	AIRDUO DIGIHALER	AER PW BAS	N

Miscellaneous Pulmonary Agents

Generic	Brand	Route	Form	PDL
montelukast sodium	MONTELUKAST SODIUM	PO	TAB CHEW	Y
montelukast sodium	MONTELUKAST SODIUM	PO	TABLET	Y
montelukast sodium	SINGULAIR	PO	TAB CHEW	Y
montelukast sodium	SINGULAIR	PO	TABLET	Y
benralizumab	FASENRA	SQ	SYRINGE	N
benralizumab	FASENRA PEN	SQ	AUTO INJCT	N

mepolizumab	NUCALA	SQ	AUTO INJCT	N
mepolizumab	NUCALA	SQ	SYRINGE	N
mepolizumab	NUCALA	SQ	VIAL	N
montelukast sodium	MONTELUKAST SODIUM	PO	GRAN PACK	N
montelukast sodium	SINGULAIR	PO	GRAN PACK	N
omalizumab	XOLAIR	SQ	SYRINGE	N
omalizumab	XOLAIR	SQ	VIAL	N
reslizumab	CINQAIR	IV	VIAL	N
roflumilast	DALIRESP	PO	TABLET	N
zafirlukast	ACCOLATE	PO	TABLET	N
zafirlukast	ZAFIRLUKAST	PO	TABLET	N
zileuton	ZILEUTON ER	PO	TBMP 12HR	N
zileuton	ZYFLO	PO	TABLET	N

Appendix 2: Abstracts of Comparative Clinical Trials

Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD

Klaus F. Rabe , Fernando J Martinez , Gary T Ferguson , Chen Wang , Dave Singh , Jadwiga A Wedzicha , Roopa Trivedi , Earl St Rose , Shaila Ballal , Julie McLaren , Patrick Darken , Magnus Aurivillius , Colin Reisner , Paul Dorinsky , ETHOS Investigators

Background: Triple fixed-dose regimens of an inhaled glucocorticoid, a long-acting muscarinic antagonist (LAMA), and a long-acting β_2-agonist (LABA) for chronic obstructive pulmonary disease (COPD) have been studied at single dose levels of inhaled glucocorticoid, but studies at two dose levels are lacking.

Methods: In a 52-week, phase 3, randomized trial to evaluate the efficacy and safety of triple therapy at two dose levels of inhaled glucocorticoid in patients with moderate-to-very-severe COPD and at least one exacerbation in the past year, we assigned patients in a 1:1:1:1 ratio to receive twice-daily inhaled doses of triple therapy (inhaled glucocorticoid [320 µg or 160 µg of budesonide], a LAMA [18 µg of glycopyrrolate], and a LABA [9.6 µg of formoterol]) or one of two dual therapies (18 µg of glycopyrrolate plus 9.6 µg of formoterol or 320 µg of budesonide plus 9.6 µg of formoterol). The primary end point was the annual rate (the estimated mean number per patient per year) of moderate or severe COPD exacerbations, as analyzed in the modified intention-to-treat population with the use of on-treatment data only.

Results: The modified intention-to-treat population comprised 8509 patients. The annual rates of moderate or severe exacerbations were 1.08 in the 320-µg-budesonide triple-therapy group (2137 patients), 1.07 in the 160-µg-budesonide triple-therapy group (2121 patients), 1.42 in the glycopyrrolate-formoterol group (2120 patients), and 1.24 in the budesonide-formoterol group (2131 patients). The rate was significantly lower with 320-µg-budesonide triple therapy than with glycopyrrolate-formoterol (24% lower: rate ratio, 0.76; 95% confidence interval [CI], 0.69 to 0.83; P<0.001) or budesonide-formoterol (13% lower: rate ratio, 0.87; 95% CI, 0.79 to 0.95; P = 0.003). Similarly, the rate was significantly lower with 160-µg-budesonide triple therapy than with glycopyrrolate-formoterol (25% lower: rate ratio, 0.75; 95% CI, 0.69 to 0.83; P<0.001) or budesonide-formoterol (14% lower: rate ratio, 0.86; 95% CI, 0.79 to 0.95; P = 0.002). The incidence of any adverse event was similar across the treatment groups (range, 61.7 to 64.5%); the incidence of confirmed pneumonia ranged from 3.5 to 4.5% in the groups that included inhaled glucocorticoid use and was 2.3% in the glycopyrrolate-formoterol group.

Conclusions: Triple therapy with twice-daily budesonide (at either the 160-µg or 320-µg dose), glycopyrrolate, and formoterol resulted in a lower rate of moderate or severe COPD exacerbations than glycopyrrolate-formoterol or budesonide-formoterol. (Funded by AstraZeneca, ETHOS ClinicalTrials.gov number, NCT02465567.).

Benralizumab for the Prevention of COPD Exacerbations

Gerard J Criner , Bartolome R Celli , Christopher E Brightling , Alvar Agusti , Alberto Papi , Dave Singh , Don D Sin , Claus F Vogelmeier , Frank C Sciurba , Mona Bafadhel , Vibeke Backer , Motokazu Kato , Alejandra Ramírez-Venegas , Yu-Feng Wei , Leif Bjermer , Vivian H Shih , Maria

Jison , Sean O'Quinn , Natalya Makulova , Paul Newbold , Mitchell Goldman , Ubaldo J Martin , GALATHEA Study Investigators; TERRANOVA Study Investigators

Background: The efficacy and safety of benralizumab, an interleukin-5 receptor alpha-directed cytolytic monoclonal antibody, for the prevention of exacerbations in patients with moderate to very severe chronic obstructive pulmonary disease (COPD) are not known.

Methods: In the GALATHEA and TERRANOVA trials, we enrolled patients with COPD (at a ratio of approximately 2:1 on the basis of eosinophil count [≥220 per cubic millimeter vs. <220 per cubic millimeter]) who had frequent exacerbations despite receiving guideline-based inhaled treatment. Patients were randomly assigned to receive benralizumab (30 or 100 mg in GALATHEA; 10, 30, or 100 mg in TERRANOVA) every 8 weeks (every 4 weeks for the first three doses) or placebo. The primary end point was the treatment effect of benralizumab, measured as the annualized COPD exacerbation rate ratio (benralizumab vs. placebo) at week 56 in patients with baseline blood eosinophil counts of 220 per cubic millimeter or greater. Safety was also assessed.

Results: In GALATHEA, the estimates of the annualized exacerbation rate were 1.19 per year (95% confidence interval [CI], 1.04 to 1.36) in the 30-mg benralizumab group, 1.03 per year (95% CI, 0.90 to 1.19) in the 100-mg benralizumab group, and 1.24 per year (95% CI, 1.08 to 1.42) in the placebo group; the rate ratio as compared with placebo was 0.96 for 30 mg of benralizumab (P = 0.65) and 0.83 for 100 mg of benralizumab (P = 0.05). In TERRANOVA, the estimates of the annualized exacerbation rate for 10 mg, 30 mg, and 100 mg of benralizumab and for placebo were 0.99 per year (95% CI, 0.87 to 1.13), 1.21 per year (95% CI, 1.08 to 1.37), 1.09 per year (95% CI, 0.96 to 1.23), and 1.17 per year (95% CI, 1.04 to 1.32), respectively; the corresponding rate ratios were 0.85 (P = 0.06), 1.04 (P = 0.66), and 0.93 (P = 0.40). At 56 weeks, none of the annualized COPD exacerbation rate ratios for any dose of benralizumab as compared with placebo reached significance in either trial. Types and frequencies of adverse events were similar with benralizumab and placebo.

Conclusions: Add-on benralizumab was not associated with a lower annualized rate of COPD exacerbations than placebo among patients with moderate to very severe COPD, a history of frequent moderate or severe exacerbations, and blood eosinophil counts of 220 per cubic millimeter or greater (Funded by AstraZeneca [GALATHEA and TERRANOVA] and Kyowa Hakko Kirin [GALATHEA]; GALATHEA and TERRANOVA ClinicalTrials.gov numbers, NCT02138916 and NCT02155660.).

Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomised, controlled phase 3 trials

Johann Christian Virchow , Piotr Kuna , Pierluigi Paggiaro , Alberto Papi , Dave Singh , Sandrine Corre , Florence Zuccaro , Andrea Vele , Maxim Kots , George Georges , Stefano Petruzzelli , Giorgio Walter Canonica

Background: To date, no studies have assessed the efficacy of single-inhaler triple therapy in asthma. Here we report on two studies that compared the single-inhaler extrafine combination of beclometasone dipropionate (BDP; inhaled corticosteroid), formoterol fumarate (FF; long-acting β_2 agonist), and glycopyrronium (G; long-acting muscarinic antagonist) with the combination of BDP with FF.

Methods: Two parallel-group, double-blind, randomised, active-controlled, phase 3 trials (Triple in Asthma With Uncontrolled Patients on Medium Strength of ICS + LABA [TRIMARAN] and Triple in Asthma High Strength Versus ICS/LABA HS and Tiotropium [TRIGGER]) recruited patients from 171 sites across 16 countries (TRIMARAN), and from 221 sites across 17 countries (TRIGGER). The sites were a mixture of secondary and tertiary care centres and specialised investigation units. Eligible patients were adults (aged 18-75 years) with uncontrolled asthma, a history of one or more exacerbations in the previous year, and previously treated with inhaled corticosteroid (TRIMARAN: medium dose; TRIGGER: high dose) plus a long-acting β_2 agonist. Enrolled patients were initially treated with BDP/FF (TRIMARAN: 100 µg BDP and 6 µg FF; TRIGGER: 200 µg BDP and 6 µg FF) for 2 weeks, then randomly assigned to treatment using an interactive response technology system with a balanced block randomisation scheme stratified by country. Patients, investigators, site staff, and sponsor staff were masked to BDP/FF/G and BDP/FF assignment. In TRIMARAN, patients were randomly assigned (1:1) to 52 weeks of BDP/FF/G (100 µg BDP, 6 µg FF, and 10 µg G) or BDP/FF (100 µg BDP and 6 µg FF), two inhalations twice daily. In TRIGGER, patients were randomly assigned (2:2:1) to 52 weeks of BDP/FF/G (200 µg BDP, 6 µg FF, and 10 µg G) or BDP/FF (200 BDP and 6 µg FF), both two inhalations twice daily, or open-label BDP/FF (200 µg BDP and 6 µg FF) two inhalations twice daily plus tiotropium 2·5 µg two inhalations once daily. Coprimary endpoints for both trials (BDP/FF/G vs BDP/FF) were pre-dose forced expiratory volume in 1 s (FEV_1) at week 26 and rate of moderate and severe exacerbations over 52 weeks. Safety was assessed in all patients who received at least one dose of study treatment. These trials were registered with ClinicalTrials.gov, NCT02676076 (TRIMARAN), NCT02676089 (TRIGGER).

Findings: Between Feb 17, 2016, and May 17, 2018, 1155 patients in TRIMARAN were given BDP/FF/G (n=579) or BDP/FF (n=576). Between April 6, 2016, and May 28, 2018, 1437 patients in TRIGGER were given BDP/FF/G (n=573), BDP/FF (n=576), or BDP/FF plus tiotropium (n=288). Compared with the BDP/FF group, week 26 predose FEV_1 improved in the BDP/FF/G group by 57 mL (95% CI 15-99; p=0·0080) in TRIMARAN and by 73 mL (26-120; p=0·0025) in TRIGGER, with reductions in the rate of moderate and severe exacerbations of 15% (rate ratio 0·85, 95% CI 0·73-0·99; p=0·033) in TRIMARAN and 12% (0·88, 0·75-1·03; p=0·11) in TRIGGER. Four patients had treatment-related serious adverse events, one in TRIMARAN in the BDP/FF/G group and three in TRIGGER-one in the BDP/FF/G and two in the BDP/FF group. Three patients in the BDP/FF/G group in TRIMARAN and two patients in TRIGGER-one in the BDP/FF/G group and one in the BDP/FF group-had adverse events leading to death. None of the deaths were considered as related to treatment.

Interpretation: In uncontrolled asthma, addition of a long-acting muscarinic antagonist to inhaled corticosteroid plus long-acting β_2-agonist therapy improves lung function and reduces exacerbations.

Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial

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Abstract

Background: Inhaled corticosteroids have been used in patients with chronic obstructive pulmonary disease (COPD), but the potential benefits of their use in triple therapy are not well known. We aimed to compare the efficacy of a triple therapy with corresponding dual therapies in symptomatic patients with moderate to very severe COPD, without a requirement for a history of exacerbations.

Methods: In this double-blind, parallel-group, multicentre phase 3 randomised controlled trial, we recruited patients from hospitals and care centres in Canada, China, Japan, and the USA. Eligible patients were 40-80 years of age, were current or former smokers (with a smoking history of ≥10 pack-years), had an established clinical history of COPD, and were symptomatic for COPD, despite receiving two or more inhaled maintenance therapies for at least 6 weeks before screening. We randomly assigned patients (2:2:1:1) using an interactive web response system to receive budesonide/glycopyrrolate/formoterol fumarate metered-dose inhaler 320/18/9·6 μg (BGF MDI), glycopyrrolate/ formoterol fumarate metered-dose inhaler 18/9·6 μg (GFF MDI), budesonide/formoterol fumarate metered-dose inhaler 320/9·6 μg (BFF MDI), or open-label budesonide/formoterol fumarate dry-powder inhaler 400/12 μg (BUD/ FORM DPI). Primary endpoints for the Europe/Canada statistical analysis approach were FEV1 area under the curve from 0-4 h (AUC0-4) for BGF MDI versus BFF MDI and BGF MDI versus BUD/FORM DPI over 24 weeks; and change from baseline in morning pre-dose trough FEV1 for BGF MDI versus GFF MDI and non-inferiority of BFF MDI versus BUD/FORM DPI (margin of -50 mL from lower bound of 95% CI) over 24 weeks. Comparisons with BUD/FORM DPI were made for the Europe/Canada statistical analysis approach only. This study is registered with ClinicalTrials.gov, number NCT02497001.

Findings: Between Aug 20, 2015, and Jan 5, 2018, 3047 patients were screened from 215 sites, and 1902 were randomly assigned to receive BGF MDI (n=640), GFF MDI (n=627), BFF MDI (n=316), or BUD/FORM DPI (n=319). Over 24 weeks, BGF MDI significantly improved FEV1 AUC0-4 versus BFF MDI (least squares mean difference 104 mL, 95% CI 77 to 131; p<0·0001) and BUD/FORM DPI (91 mL, 64 to 117; p<0·0001). BGF MDI also significantly improved pre-dose trough FEV1 versus GFF MDI (22 mL, 4 to 39; p=0·0139) and was non-inferior to BUD/FORM DPI (-10 mL, -36 to 16; p=0·4390). At week 24, patients in the BGF MDI group had a significantly improved FEV1 AUC0-4 compared with patients receiving BFF MDI (116 mL, 95% CI 80 to 152; p<0·0001); there was a non-significant improvement in the change from baseline in morning pre-dose trough FEV1 at week 24 versus GFF MDI (13 mL, -9 to 36 mL; p=0·2375). The most common treatment-emergent adverse events were nasopharyngitis (n=49 [8%] in the BGF MDI group; n=41 [7%] in the GFF MDI group; n=26 [8%] in the BFF MDI group; and n=30 [9%] in the BUD/FORM DPI group) and upper respiratory tract infection (n=65 [10%]; n=38 [6%]; n=18 [6%]; and n=22 [7%]). Pneumonia incidence was low (<2%) and similar across treatments. There were two treatment-related deaths, both in the GFF MDI group.

Interpretation: BGF MDI was efficacious, well tolerated, and could be a more appropriate treatment than the corresponding dual therapies for symptomatic patients with moderate to very severe COPD, irrespective of exacerbation history.

Appedix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to July 08, 2020

Search Strategy:

#	Searches	Results
1	vilanterol.mp.	371
2	salmeterol.mp. or Salmeterol Xinafoate/	2991
3	arformoterol.mp. or Formoterol Fumarate/	1684
4	formoterol.mp. or Formoterol Fumarate/	2537
5	indacterol.mp.	2
6	olodaterol.mp.	195
7	aclidinium.mp.	224
8	Ipratropium/ or ipratropium.mp.	2574
9	tiotropium.mp. or Tiotropium Bromide/	1804
10	glycopyrrolate.mp. or Glycopyrrolate/	1451
11	revefenacin.mp.	31
12	umeclidinium.mp.	219
13	Budesonide/ or budesonide.mp.	6265
14	fluticasone.mp. or Fluticasone/	4602
15	mometasone.mp. or Mometasone Furoate/	1115
16	beclomethasone.mp. or Beclomethasone/	3822
17	ciclesonide.mp.	375
18	montelukast.mp.	2487
19	roflumilast.mp.	617
20	zafirlukast.mp.	574
21	zileuton.mp.	695
22	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	24574
23	limit 22 to (english language and humans and yr="2019 -Current")	545
24	limit 23 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	64

Database(s): **Ovid MEDLINE(R) ALL** 1946 to August 07, 2020

Search Strategy:

#	Searches	Results
1	benralizumab.mp.	288
2	mepolizumab.mp.	713
3	omalizumab.mp. or Omalizumab/	2620
4	reslizumab.mp.	251
5	1 or 2 or 3 or 4	3327
6	limit 5 to (english language and humans and yr="2018 -Current")	587
7	limit 6 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	66

Appendix 4: Key Inclusion Criteria

Population	Adults and children with asthma and adults with chronic obstructive pulmonary disease (COPD)
Intervention	Oral, inhaled and biological maintenance treatments for asthma and/or COPD
Comparator	Placebo or active therapies
Outcomes	Mortality, exacerbations, hospitalizations
Timing	As needed
Setting	Outpatient

Inhaled Corticosteroids (ICS)

Goals:

- To optimize the safe and effective use of ICS therapy in patients with asthma and COPD.
- Step-therapy required prior to coverage for non-preferred ICS products:
  - Asthma: inhaled short-acting beta-agonist.
  - COPD: short-acting and long-acting bronchodilators (inhaled anticholinergics and beta-agonists). Preferred short-acting and long-acting bronchodilators do NOT require prior authorization. See preferred drug list options at http://www.orpdl.org/drugs/.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred ICS products

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/

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 Code

Approval Criteria		
2. Will the prescriber consider a change to a preferred product? Message: Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Is the request for treatment of asthma or reactive airway disease?	**Yes:** Go to #7	**No:** Go to #4
4. Is the request for treatment of COPD, mucopurulent chronic bronchitis and/or emphysema?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded.
5. Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
6. Does the patient have an active prescription for an inhaled long-acting bronchodilator (anticholinergic or beta-agonist)?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
7. Does the patient have an active prescription for an on-demand short-acting beta-agonist (SABA) or an alternative rescue medication for acute asthma exacerbations?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: *10/20 (KS), 5/19 (KS), 1/18; 9/16; 9/15*
Implementation: *11/1/20; 3/1/18; 10/13/16; 10/9/15*

Long-acting Beta-agonists (LABA)

Goals:

- To optimize the safe and effective use of LABA therapy in patients with asthma and COPD.
- Step-therapy required prior to coverage of non-preferred LABA products:
  - Asthma: inhaled corticosteroid and short-acting beta-agonist.
  - COPD: inhaled short-acting bronchodilator.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred LABA products

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/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #3
3. Does the patient have a diagnosis of asthma or reactive airway disease?	**Yes:** Go to #6	**No:** Go to #4
4. Does the patient have a diagnosis of COPD, mucopurulent chronic bronchitis and/or emphysema?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded
5. Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
6. Does the patient have an active prescription for an on-demand short-acting beta-agonist (SABA) or an alternative rescue medication for acute asthma exacerbations?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Does the patient have an active prescription for an inhaled corticosteroid (ICS) or an alternative asthma controller medication?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: *10/20 (KS), 5/19 (KS); 1/18; 9/16; 9/15); 5/12; 9/09; 5/09*
Implementation: *11/1/20; 3/1/18; 10/9/15; 8/12; 1/10*

Long-acting Beta-agonist/Corticosteroid Combination (LABA/ICS)

Goals:
- To optimize the safe and effective use of LABA/ICS therapy in patients with asthma and COPD.
- Step-therapy required prior to coverage:
  - Asthma: short-acting beta-agonist and inhaled corticosteroid or moderate to severe persistent asthma.
  - COPD: short-acting bronchodilator and previous trial of a long-acting bronchodilator (inhaled anticholinergic or beta-agonist). Preferred LABA/ICS products do NOT require prior authorization.

Length of Authorization:
- Up to 12 months

Requires PA:
- Non-preferred LABA/ICS products

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/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the provider consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of covered alternatives in class	**No:** Go to #3
3. Does the patient have a diagnosis of asthma or reactive airway disease?	**Yes:** Go to #7	**No:** Go to #4
4. Does the patient have a diagnosis of COPD, mucopurulent chronic bronchitis and/or emphysema?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded.
5. Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
6. Is there a documented trial of an inhaled long-acting bronchodilator (anticholinergic or beta-agonist)?	**Yes:** Approve for up to 12 months. Stop coverage of all other LABA and ICS inhalers.	**No:** Pass to RPh. Deny; medical appropriateness.
7. Does the patient have an active prescription for an on-demand short-acting beta-agonist (SABA) or an alternative rescue medication for acute asthma exacerbations?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is there a documented trial of an inhaled corticosteroid (ICS) or does the patient have moderate or severe persistent asthma?	**Yes:** Approve for up to 12 months. Stop coverage of all other ICS and LABA inhalers.	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: *10/20 (KS), 5/19 (KS); 1/18; 9/16; 11/15; 9/15; 11/14; 11/13; 5/12; 9/09; 2/06*
Implementation: *11/1/20; 3/1/18; 10/13/16; 1/1/16; 1/15; 1/14; 9/12; 1/10*

Long-acting Muscarinic Antagonist/Long-acting Beta-agonist (LAMA/LABA) and LAMA/LABA/Inhaled Corticosteroid (LAMA/LABA/ICS) Combinations

Goals:

- To optimize the safe and effective use of LAMA/LABA/ICS therapy in patients with COPD.
- Step-therapy required prior to coverage:
    - COPD: short-acting bronchodilator and previous trial of a long-acting bronchodilator (inhaled anticholinergic or beta-agonist). Preferred LAMA and LABA products do NOT require prior authorization.

Length of Authorization:

- Up to 12 months

Requires PA:

- All LAMA/LABA and LAMA/LABA/ICS products

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/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of preferred LAMA and LABA products in each class	**No:** Go to #3
3. Does the patient have a diagnosis of asthma or reactive airway disease without COPD?	**Yes:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review.	**No:** Go to #4

Approval Criteria		
4. Does the patient have a diagnosis of COPD, mucopurulent chronic bronchitis and/or emphysema?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded.
5. Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the request for a LAMA/LABA combination product?	**Yes:** Go to #7	**No:** Go to #8
7. Is there a documented trial of a LAMA or LABA, or alternatively a trial of a fixed dose combination short-acting anticholinergic with beta-agonist (SAMA/SABA) (i.e., ipratropium/albuterol), or ≥ 2 moderate exacerbations or ≥ 1 leading to a hospitalization?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA and LABA inhalers or scheduled SAMA/SABA inhalers (PRN SABA or SAMA permitted).	**No:** Pass to RPh. Deny; medical appropriateness.
8. Is the request for a 3 drug ICS/LABA/LAMA combination product and is there a documented trial of a LAMA and LABA, or ICS and LABA or ICS and LAMA?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA, LABA and ICS inhalers.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *10/20 (KS), 5/19 (KS); 1/18; 9/16; 11/15; 9/15; 11/14; 11/13; 5/12; 9/09; 2/06*
Implementation: *11/1/20; 3/1/18; 10/13/16; 1/1/16; 1/15; 1/14; 9/12; 1/10*

Roflumilast

Goals:

- Decrease the number of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and with a history of exacerbations.

Length of Authorization:

- Up to 12 months

Covered Alternatives:

- Preferred alternatives listed at http://www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis an OHP-funded diagnosis?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; not covered by the OHP
3. Does the patient have documented severe or very severe COPD (e.g., FEV_1 of $\leq$ 50% predicted)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny for medical appropriateness
4. Does the patient have a diagnosis of chronic bronchitis (ICD10 J410-J42; J440-J449)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny for medical appropriateness

Approval Criteria		
5. Does the patient have documented prior COPD exacerbations?	**Yes:** Go to #6	**No:** Pass to RPh. Deny for medical appropriateness
6. Does the patient have an active prescription for a long-acting bronchodilator (long-acting anticholinergic agent or long-acting beta-agonist) and inhaled corticosteroid (ICS)?	**Yes:** ~~Approve for up to 12 months~~ Go to #7	**No:** Pass to RPh. Deny; recommend trial of preferred long-acting bronchodilator and ICS
7. Is the prescriber a specialist in respiratory medicine or is the request in consultation with a specialist?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny for medical appropriateness

P&T/DUR Review: *10/20 (KS), 9/15 (KS); 5/13; 2/12*
Implementation: *11/1/20; 10/15; 1/14; 5/12*

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
This PA does not apply to dupilumab, which is subject to separate clinical PA criteria.

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
Wixela Inhub (fluticasone/salmeterol)	500/50 mcg BID
Airduo RespiClick (fluticasone/salmeterol)	464/28 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

Approval Criteria		
4. Is the request for a newly approved monoclonal antibody for severe asthma and does the indication match the FDA-approved indication?	**Yes:** Go to #9	**No:** Go to #5
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
6. Is the claim for mepolizumab in a patient under 6 years of age or benralizumab in a patient under 12 years of age?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #7
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
9. Does the patient have a concurrent prescription for EpiPen® or equivalent so they are prepared to manage delayed anaphylaxis if it occurs after monoclonal antibody therapy?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
10. Is the diagnosis an OHP-funded diagnosis? Note: chronic urticaria is not an OHP-funded condition	**Yes:** Go to #11	**No:** Pass to RPh. Deny; not funded by the OHP.
11. Is the prescriber a pulmonologist or an allergist who specializes in management of severe asthma?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
12. Has the patient required at least 1 hospitalization or ≥ 2 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, theophylline)?	**Yes:** Go to #13 Document number of hospitalizations or ED visits in past 12 months: _____. This is the baseline value to compare to in renewal criteria.	**No:** Pass to RPh. Deny; medical appropriateness.
13. Has the patient been adherent to current asthma therapy in the past 12 months?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness.
14. Is the patient currently receiving another monoclonal antibody for asthma (e.g., omalizumab, mepolizumab, benralizumab or reslizumab)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #15

Approval Criteria		
15. 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 #16
16. If the claim is for mepolizumab, benralizumab or reslizumab, can the prescriber provide documentation of severe eosinophilic asthma, confirmed by blood eosinophil count ≥300 cells/µL 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.

Renewal Criteria		
3. Is the patient currently taking an inhaled corticosteroid and 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, theophylline)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Has the number of ED visits or hospitalizations in the last 12 months been reduced from baseline, or has the patient reduced their systemic corticosteroid dose by ≥50% compared to baseline?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *10/20 (KS),7/19 (DM); 7/18; 7/16*
Implementation: *11/1/20; 8/19/19, 8/15/18, 8/16*