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Class Update: Asthma / COPD Medications

Month/Year of Review: September 2015 **Date of Last Review:** July 2014

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

Purpose for Class Update:
The asthma/chronic obstructive pulmonary disease (COPD) drug classes will be reviewed for updated evidence to incorporate into the recommendations provided to the Oregon Health Plan (OHP). The last update was in July 2014 so evidence since that time will be reviewed.

Research Questions:

1. Is there new comparative evidence on the efficacy/effectiveness of asthma or COPD treatments?
2. Is there new comparative evidence of a meaningful difference in harms of medications used to treat asthma or COPD?

Conclusions:

- Guideline updates for COPD include: The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, The American College of Chest Physicians (ACCP) and Canadian Thoracic Society Guideline (CTS) on acute exacerbations of COPD and Veterans Administration (VA)/Department of Defense (DoD) Clinical Practice Guideline for the management of COPD. Recommendations in these guidelines support current placement of therapies on OHP Preferred Drug List (PDL).[1-3]
- The ACCP/CTS guidance concludes maintenance therapy in patients with COPD reduces exacerbations in patients with moderate and severe COPD, improves quality of life, improves lung function, reduces hospitalizations, and reduces dyspnea and need for rescue medication. There was no evidence of conclusive differences between effectiveness of pharmacologic agents within specific drug classes.[2]
- Updates to the GOLD guideline advocate for the use of salmeterol and formoterol in COPD due to evidence of reduced exacerbations with therapy. Low quality data of inhaled corticosteroids (ICS) withdrawal and increased risk of exacerbations was presented. No changes to the overall treatment pathway were made.[1]
- A recent European Respiratory Society (ERS) and American Thoracic Society (ATS) guideline on the treatment of severe asthma, a Cochrane review of omalizumab therapy and U.S. Food and Drug Administration (FDA) warnings on potential for increased risk of cardiac and cerebrovascular events with omalizumab support the recommendation of omalizumab use in patients with allergic asthma that have failed other treatments.[4-6]
- Seven Cochrane Systematic Reviews on asthma and COPD have been published since the last class update.[4, 7-12] The focus of these reviews was the impact of ICS on growth in children with asthma, omalizumab use in adult and children with asthma, safety of formoterol or salmeterol in adults, discontinuation of

long-acting beta-agonists (LABA) in adult patients with asthma, discontinuation of ICS in COPD patients and treatment of COPD patients with long-acting inhaled therapy. Results from these reviews support current placement of therapies for asthma and COPD on the PDL.

- The new combination of tiotropium/olodeterol (Stiolto™ Respimat®) demonstrated superiority over the monotherapy components for the outcomes of change from baseline in FEV_1 $AUC_{0\text{-}3hr}$ and trough FEV_1 at 24 weeks. There is insufficient evidence of comparative efficacy between tiotropium/olodeterol and other therapies.[13]
- The single component product, fluticasone furoate (Arnuity Ellipta), of the previously approved combination product, Breo Ellipta (fluticasone furoate/vivanterol trifenatate), was shown to be superior to placebo with a mean difference in baseline evening trough FEV_1 of 146 mL (95% CI, 36 to 257 mL; p=0.009) at 24 weeks.[14] There is insufficient evidence of comparative efficacy between fluticasone furoate and other therapies.[14]
- No new evidence was identified to suggest changes to leukotriene inhibitor prior authorization (PA) criteria or the PDL.
- COPD guidelines do not prefer one LABA over another and therefore current placement of indacaterol and olodaterol as non-preferred is supported.[1-3]

Recommendations:

- No changes are recommended to the current placement of preferred agents on the PDL. Evaluate comparative drug costs in the executive session.
- Place current clinical PA criteria requirement for omalizumab therapy under "Asthma Controller" PA criteria.
- Add a "Long-Acting Beta-Agonist" class to the PDL to accommodate LABAs indicated for asthma and COPD. Place current PA criteria for indacaterol to the LABA PA criteria.

Previous Conclusions:

- Overall findings from DERP systematic review did not suggest that a single medication within any of the classes evaluated is significantly more effective or harmful than other medications within the same class in the treatment of persistent asthma or COPD.[15]
- There is moderate quality evidence that ICS do not differ in their ability to control asthma symptoms, prevent asthma exacerbations, and reduce the need for additional rescue medication at equipotent doses administered through comparable delivery devices. There are no head trials comparing ICSs in he treatment of COPD.[15]
- For patients with COPD, results indicated that monotherapy with ICS and LABAs are similarly effective and have similar risk of experiencing any adverse event. However, there was low strength of evidence that treatment with ICS increases the risk of serious pneumonia.[15]
- Umeclidinium demonstrated a statistically and clinically significant increase in mean change from baseline in the change from baseline FEV1 relative to placebo (115 mL; 95% CI 76 to 155). There is insufficient comparative evidence demonstrating superior efficacy or safety of umeclidinium to other available agents.[16]
- There is low quality evidence that mometasone (Asmanex®) HFA improves change from baseline mean trough FEV1 at 12 weeks versus placebo (mometasone HFA 100mg difference from placebo 0.12 L; 95% CI 0.05 to 0.2). There is insufficient evidence to determine the efficacy and safety of mometasone HFA compared to mometasone Twisthaler.[17]
- There is moderate quality evidence that once daily umeclidinium/vilanterol is effective at improving lung function in patients with moderate to severe COPD, as measured by the change from baseline in trough FEV1 compared to placebo (0.17 L; 95% CI 0.13-0.21; p <0.001). Trials have been short-term, and the long-term safety and efficacy of umeclidinium/vilanterol is unknown. There is insufficient evidence to determine the comparative efficacy of umeclidinium/vilanterol. There is insufficient evidence to draw conclusions about the ability of umeclidinium/vilanterol to decrease exacerbations, reduce shortness of breath, or improve quality of life.[18-20]

- Serious adverse events were similar among treatment groups versus placebo. The most common adverse events are pharyngitis, sinusitis, lower respiratory tract infection, constipation, diarrhea, pain in extremity, muscle spasms, neck pain and chest pain (all ≥1% of patients and more common than with placebo).[18-20]
- There is insufficient evidence for differences in subpopulations in which umeclidinium/vilanterol is more effective or safer.

Previous Recommendations:
- Due to no evidence demonstrating clinical superiority of umeclidinium/vivanterol over current agents, the Committee recommended making it non-preferred on the PMPDP and apply prior authorization criteria to ensure it is being used appropriately and limit its use to patients with COPD.
- Due to no evidence demonstrating clinical superiority or safety of mometasone HFA over current agents, the Committee recommends making it non-preferred. Due to no evidence demonstrating clinical superiority, the Committee also recommended designating flunisolide HFA as non-preferred on the PMPDP.
- The Committee agreed with the staff to reorganize the PMPDP drug classes into: long-acting bronchodilators, short-acting beta-agonists, anticholinergic inhalers, combination inhalers, inhaled corticosteroids, and miscellaneous pulmonary drugs.
- After comparative cost consideration in executive session, the Committee recommended no changes to the PMPDP.

Background:

<u>ASTHMA</u>
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. A 2013 report on the Burden of Asthma in Oregon cited 3.5-4% of the OHP population as having an asthma diagnosis.[21] Total National asthma costs were projected to be over $20 billion in 2010.[21]

Asthma is characterized symptoms of wheezing, cough, dyspnea and chest tightness. Diagnosis is confirmed by spirometry (FEV_1 > 200 mL or ≥ 12% from baseline after 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).[22]

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.[22] Those patients with persistent asthma require long-term control medications to contain the underlying inflammation associated with asthma. Inhaled corticosteroids (ICS) 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.[22] Other maintenance therapy options include leukotriene inhibitors immunomodulators, methylxanthines, cromolyn sodium and nedocromil. SABAs, anticholinergics and systemic corticosteroids are recommended for acute symptom management.

Outcomes 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. Minimally important values from research in COPD patients suggest minimally important FEV_1 changes range from 100-140 ml.[23]

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.[24] Forty-one percent of these individuals were on at least one daily treatment for COPD.[24]

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; stage 1 (mild), stage 2 (moderate), stage 3 (severe), stage 4 (very severe) (Table 1). The 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. Important outcomes to access the effectiveness of therapies include: functional capacity, QoL, dyspnea, exacerbation rate and/or severity, mortality and harms. FEV_1 is the most common surrogate outcome used in studies to determine therapy effectiveness. Minimally important FEV_1 values for COPD changes have not been clearly defined but are suggested to range from 100-140 ml.[23]

Table 1. Classification of COPD Based on GOLD Guidelines*[1]

Classification	Severity	Post-Bronchodilator FEV_1
GOLD 1	Mild	FEV1 ≥ 80% predicted
GOLD 2	Moderate	50% ≤ FEV_1 < 80% predicted
GOLD 3	Severe	30% ≤ FEV_1 < 50% predicted
GOLD 4	Very severe	FEV_1 < 30% predicted

* For patients with a FEV1/FVC < 0.70

Pharmacotherapy prescribed in a step-wise manner is recommended for COPD management, usually starting with monotherapy and progressing to combination regimens. SABAs are recommended for acute management and bronchodilator therapy (LABAs and LAMAs) are used as monotherapy or in combination for maintenance treatment for chronic, stable COPD.[1] ICS are reserved for patients requiring additional treatment for chronic disease, despite LAMA and LABA therapy. SAMAs are appropriate for patients currently well controlled. No treatment has been shown to alter the long-term progression and decline in lung function associated with COPD.[1]

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls were 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), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, 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 drugs, indications, and safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. 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:

Cochrane – Inhaled Corticosteroids in Children with Persistent Asthma: Effects on Growth (Review)

A search of the literature ending in January 2014 evaluated the use of ICS in children (up to 18 years) with persistent asthma and the impact on linear growth.[7] Differing aspects of treatment utilization (e.g., dose, length of exposure, age of child, disease severity) was also explored. Twenty-five trials were identified that included 8471 children. Included trials were at least 3 months in duration and up to 6 years. Treatments given at low or medium doses were the following: beclomethasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone propionate and mometasone furoate.

In placebo-controlled comparisons of 13 trials, one year of ICS treatment reduced linear growth velocity, MD -0.48 cm/y, 95% CI -0.65 to -0.30, p value <0.0001 (moderate quality of evidence).[7] There was significant heterogeneity across trial results. In children treated for 3-5 months there was no significant difference between ICS and placebo. ICS treatment ranging from 6-8 months in duration demonstrated decreased linear growth velocity, based on 2 trials of 369 participants.

Analysis of 3275 children on ICS for over one year found change in height from baseline to be reduced based on moderate quality of evidence (MD -0.61 cm/y, 95% CI -0.83 to -0.38, $p < 0.00001$).[7] Children treated for 6-8 months were also found to have significant reductions in change in baseline height. Treatment durations less than 6 months were inconclusive on the impact of ICS on change in height from baseline.

Indirect comparisons did not demonstrate a significant difference in daily dose, inhalation device, or age of child on impact of ICS on linear growth velocity with one year of treatment.[7] Linear growth velocity was significantly reduced with all treatments compared to placebo. Growth suppression was most pronounced during the first year with less of an effect in subsequent years.

COCHRANE – Inhaled Corticosteroids in Children with Persistent Asthma: Dose-Response Effects on Growth (Review)

In children with persistent asthma and ICS use of a minimum of 3 months, the effect of increasing the dose of ICS on linear growth velocity, weight gain and skeletal maturation was the subject of a recent Cochrane review.[8] RCTs in children with mild to moderate asthma up to 17 years of age were used to evaluate the different doses of the same ICS using the same device and the effect on growth. Beclomethasone, budesonide, ciclesonide, fluticasone or mometasone monotherapy or in combination with a LABA were studied. Most comparisons were between low dose (50 to 100 µg) and medium dose (200 µg) of hydrofluoroalkane (HFA)-beclomethasone equivalent. Treatment durations ranged from 12 to 52 weeks.

High quality evidence demonstrated ICS treatment (ciclesonide, fluticasone, mometasone) lasting 12 months reduced growth velocity in children treated with higher doses, based on 4 trials (MD 0.20 cm/y, 95% CI 0.02 to 0.39, p=0.03).[8] A significant difference in height change was seen in treatment zero to three months, most pronounced with higher doses of ICS, but no other time points were significantly different between groups. No differences were seen in weight, bone and mass index and skeletal maturation based on low-quality evidence. Magnitude of effect appeared to be unrelated to type of ICS.

COCHRANE - Omalizumab for Asthma in Adults and Children (Review)

A 2014 Cochrane review evaluated the use of omalizumab versus placebo or conventional therapy in adults and children with moderate to severe asthma. All participants had a diagnosis of allergic asthma except for one that included severe non-allergic asthma patients.[4] Twenty-five studies met the inclusion criteria, eleven evaluated efficacy. Studies ranged from 8 to 60 weeks. In patients taking concomitant ICS therapy, asthma exacerbations were reduced with subcutaneous omalizumab compared to placebo (OR 0.55, 95% CI 0.42 to 0.60).[4] Omalizumab was shown to have a small effect in patients with severe asthma as demonstrated by wide confidence intervals associated with the findings. Pooled data from four studies showed a significant benefit in hospitalizations due to severe asthma with an absolute risk reduction of 3% with placebo to 0.5% with subcutaneous omalizumab. The ability to withdraw from ICS therapy was higher with omalizumab therapy compared to placebo (OR 2.50, 95% CI 2.00 to 3.13), however no change was seen in the number of patients able to withdraw from oral steroid treatment.[4] A small reduction in ICS dose was seen in patients taking omalizumab compared to placebo, with a more pronounced effect seen in patients with severe asthma. Improvement in asthma symptom scores and health-related quality of life and reduction in rescue medication use was seen with omalizumab use. No significant effect was seen on lung function measurements and mortality.[4]

COCHRANE – Safety of Regular Formoterol or Salmeterol in Adults with Asthma: An Overview of Cochrane Reviews (Review)

Serious adverse events associated with the use of formoterol or salmeterol was the focus of a 2014 Cochrane Review.[9] Maintenance formoterol or salmeterol therapy in adults with asthma was compared to placebo or when combined with an ICS in comparison to ICS monotherapy at equivalent doses.[9] Data on 61,366 adult patients was available from six previously reported Cochrane Reviews. Direct and indirect comparisons were evaluated separately to preserve the integrity of the data.

Direct comparisons did not demonstrate a significant increase in death from any cause based. Monotherapy comparisons of salmeterol and formoterol versus placebo and combination therapy compared to ICS findings could not exclude the possibility of a two-fold increase in mortality based on moderate evidence (Table 2). Absolute risk for mortality demonstrated small differences between monotherapy comparisons, an increase of 7 per 10,000, and for combination therapy comparisons, an increase of 3 per 10,000. Data was insufficient to make a mortality comparison between formoterol and salmeterol and for monotherapy trial risks compared to combination therapy trials. Comparisons of non-fatal adverse events from any cause were significantly higher for patients receiving salmeterol monotherapy (OR 1.14, 95% CI 1.01 to 1.28) but not for any other direct comparisons.[9]

Table 2. Risk of Death of Any Cause in Patients Taking Formoterol or Salmeterol[9]

Therapy	Odds Ratio	95% Confidence Interval	Trials	Participants
Formoterol monotherapy	4.49	0.24 to 84.80	13	4824
Salmeterol monotherapy	1.33	0.85 to 2.08	10	29,128
Formoterol combination*	3.56	0.79 to 16.03	25	11,271
Salmeterol combination*	0.90	0.31 to 2.6	35	13,447
* Combination therapy includes formoterol or salmeterol and ICS				

COCHRANE – Stopping Long-Acting Beta-Agonists (LABA) for Adults with Asthma Well Controlled by LABA and Inhaled Corticosteroids

A 2015 Cochrane review evaluated the effect of discontinuing LABA therapy in patients with well-controlled asthma. Trials lasting at least eight weeks that evaluated the change from combination ICS/LABA to ICS alone were included (n=2781).[10] Outcomes of interest are loss of asthma control, deterioration in quality of life, increase in asthma attacks or exacerbations, incidence of serious adverse events from any cause upon discontinuation of the LABA.

Exacerbations and the need for oral corticosteroids was increased with the discontinuation of LABA (OR 1.74, 95% CI 0.83 to 3.65), however, the large confidence interval makes these findings uncertain. Small differences in Asthma Control Questionnaire and quality of life scores were shown to benefit those continuing LABA therapy. Conclusions on the effect of discontinuing LABA on serious adverse event risk were not able to be determined due to a low number of events. Discontinuation of LABA therapy showed a non-significant decrease in incidence of adverse events.

COCHRANE- Inhaled Steroids and Risk of Pneumonia for Chronic Obstructive Pulmonary Disease (Review)

A Cochrane review of studies lasting at least 12 weeks was done to determine the risk of pneumonia in participants with COPD using fluticasone and budesonide.[11] Placebo comparisons or one of the ICS agents in combination with a LABA compared to LABA monotherapy were included. Twenty-six fluticasone and 17 budesonide studies qualified for inclusion. Forty percent of these had a high degree of bias due to high or uneven dropout rates, however, a sensitivity analysis, which removed studies with high bias risk, did not change the primary outcome findings.

An increase in non-fatal serious adverse pneumonia events requiring hospitalization were increased in both fluticasone and budesonide groups, OR 1.78 [95% CI 1.50 to 2.12, (high-quality evidence)] and OR 1.62 [95% CI 1.00 to 2.62, (moderate-quality evidence)], respectively.[11] The risk of pneumonia was not altered by combining fluticasone with salmeterol or vivanterol or by adjusting the dose, trial duration or baseline severity of COPD. The budesonide findings were less precise which was thought to be due to the use of two different doses. Moderate-quality evidence showed risk of any pneumonia event was higher with fluticasone compared to budesonide (OR 1.86, 95% CI 1.04 to 3.34) based on indirect comparisons and potentially different methods for determining pneumonia diagnosis. Monotherapy indirect comparisons between budesonide and fluticasone found no significant differences in the outcomes of mortality or serious adverse events, including pneumonia (moderate to high-quality evidence for fluticasone and moderate to very low quality evidence for budesonide). High-quality evidence found no difference in mortality between the ICS agents and the comparison treatments. There was insufficient evidence to determine pneumonia-related deaths.

COCHRANE – Long-Acting Inhaled Therapy (Beta-Agonists, Anticholinergics and Steroids) for COPD: A Network Meta-Analysis (Review)

A recent COCHRANE network meta-analysis evaluated the long-term efficacy of treatments for COPD in patients not controlled by short-acting treatments alone.[12] Trials lasting at least 6 months were included. Treatment comparisons are listed in table 2. St George's Respiratory Questionnaire (SGRQ) total score and trough forced expiratory volume in one second (FEV_1) were the efficacy outcomes studied. Seventy-one similar trials were included comprising patients with mostly severe COPD and long history of smoking (40+ pack-years).

Table.3 Treatment Comparisons of Included Studies[12]

Drug Class	Specific Therapies
Long-acting Beta-agonists (LABAs)	Formoterol and salmeterol
Long-acting Muscarinic antagonists (LAMA)	Aclidinium, glycopyroonium and tiotropium
Inhaled Corticosteroids (ICS)	Budesonide, fluticasone and mometasone
Combination LABA/ICS	Formoterol/budesonide, formoterol/mometasone, salmeterol/

For the outcome of SGRQ combination therapy of LABA/ICS demonstrated the greatest improvement at six months when compared to placebo [-3.89 units, 95% credible interval (CrI) -4.70 to -2.97].[12] LAMA, LABA and ICS improvement in SGRQ scores at six months were: -2.63 units, -2.29 units and -2.0 units. Placebo controlled comparisons favored LABA/ICS therapy with trough FEV1 changes of 133.3 mL (95% CrI 100.6 to 164.0) at six months.[12] LAMA and LABAs had similar

results with ICS showing less of a benefit. SGRQ and FEV1 differences in treatment seen at six months were less pronounced at twelve months. Individual treatment comparisons were not precise.

New Guidelines:

ACCP/CTS – Prevention of Acute Exacerbations of COPD

The American College of Chest Physicians (ACCP) and Canadian Thoracic Society Guideline (CTS) formed a unique collaboration between two agencies to develop this evidence-based guideline on acute exacerbations of COPD (AECOPD).[2] The quality of the evidence was rated as high to very low, using GRADEpro software. The CHEST grading system was used to grade recommendations as strong (high-quality evidence [1A]) to consensus based. Maintenance pharmacotherapy has shown to: reduce exacerbations of moderate and severe COPD, improve quality of life, improve lung function, reduce hospitalizations, reduce dyspnea and need for rescue medication. Table 4 provides therapy recommendations for maintenance therapy and exacerbation prevention.

Table 4. Treatment Recommendations for Acute Exacerbations of COPD.[2]

Recommendation	COPD Exacerbation Type	Grade	Comments
Maintenance Inhaled Therapy			
Use of long-acting β_2-agonists compared with placebo*	Moderate to severe	1B	- no significant differences in serious adverse events or mortality found between long-acting β_2-agonists and placebo in this population
Use of muscarinic antagonists compared with placebo*	Moderate to severe	1A	- shown to reduce COPD related hospitalization - no significant differences in severe adverse events or mortality found between long-acting β_2-agonists and placebo in this population
Use of long-acting muscarinic antagonists compared with long-acting β_2-agonists*	Moderate to severe	1C	- recommendation based on lower rate of nonfatal serious adverse events compared to long-acting β_2-agonists
Use of short-acting muscarinic antagonists compared with short acting β_2-agonists monotherapy*	Mild to moderate	2C	- recommendation based on improved quality of life and lung function with short-acting muscarinic antagonists
Use of short-acting muscarinic antagonists plus short acting β_2-agonists compared with short acting β_2-agonists alone*	Moderate	2B	- recommendation based on improved quality of life, exercise tolerance and lung function with short-acting over monotherapy
Use of long-acting β_2-agonists monotherapy compared with short-acting muscarinic antagonists monotherapy*	All	2C	- recommendation based on improved quality of life, dyspnea scores and lung function with long-acting β_2-agonists
Use of long-acting muscarinic antagonists compared with a short-acting muscarinic antagonists monotherapy*	Moderate to severe	1A	- recommendation based on improved quality of life and lung function with long-acting muscarinic antagonists
Use of short-acting muscarinic antagonists plus long-acting β_2-agonists compared with long-acting β_2-agonists alone**	Mild to moderate	2C	- recommendation based on improved quality of life, dyspnea scores and lung function combination therapy
Use of maintenance combination inhaled corticosteroid/long-acting β_2-agonists therapy (and not inhaled corticosteroid monotherapy) compared with placebo**	All	1B	- recommendation based on slowing the rate of decline in health-related quality of life, reduced dyspnea, less rescue medication, and improved lung function
Use of maintenance combination inhaled corticosteroid/long-acting β_2-agonists therapy compared with long-acting β_2-agonists monotherapy**	All	1C	- recommendation based on slowing the rate of decline in health-related quality of life, reduced dyspnea, less rescue medication, and improved lung function

Use of maintenance combination inhaled corticosteroid/long-acting β_2-agonists therapy compared with inhaled corticosteroid monotherapy**	All	1B	- recommendation based on mortality benefit of combination therapy
Use of maintenance combination inhaled long-acting anticholinergic/long-acting β_2-agonists therapy or inhaled long-acting anticholinergic monotherapy in stable COPD patients	All	1C	- recommendation based acute exacerbation benefits
Use of maintenance combination inhaled long-acting inhaled corticosteroid/long-acting β_2-agonists therapy or inhaled long-acting anticholinergic monotherapy in stable COPD patients	All	1C	- recommendation based acute exacerbation benefits
Use of maintenance combination inhaled long-acting anticholinergic/corticosteroid/long-acting β_2-agonists therapy or inhaled long-acting anticholinergic monotherapy in stable COPD patients	All	2C	- recommendation based acute exacerbation benefits
Exacerbation Prevention in Adults >40 years with Previous or Current Smoking History			
Use of roflumilast in patients with chronic bronchitis and history of at least one exacerbation in the previous year*	All	2A	- limited data on supplemental effectiveness in patients using inhaled therapies
Use of oral slow-release theophylline twice daily	All	2B	- theophylline has been shown to potentially reduce the number of exacerbations in patients being treated with maintenance bronchodilator therapy and inhaled corticosteroids and who continue to have periodic exacerbations
Use of oral N-acetylcysteine in patients with a history of two or more exacerbations in the previous 2 years	All	2B	- May reduce exacerbations in patients being treated with maintenance bronchodilator therapy and inhaled corticosteroids and who continue to have periodic exacerbations
Use of oral carbocysteine in patients who continue to experience exacerbations despite maximal therapy designed to reduce exacerbations in outpatients with stable COPD	All	Con-sensus based	- May reduce exacerbations and has minimal risk
* Recommendations are for patients with moderate to severe COPD ** Recommendations are for patients with stable moderate, severe and very severe COPD			

<u>VA/DoD Clinical Practice Guideline for the Management of Chronic Obstructive Pulmonary Disease</u>

In December of 2014 the Veterans Administration (VA)/Department of Defense (DoD) updated their 2007 guidance on COPD. Evidence level and quality was considered to formulate best practice clinical guidance recommendations.[3] The strength of the recommendations were based on the GRADE rating for the strength of the evidence as well as desirable versus undesirable outcomes, values and preferences and other considerations to formulate a strength of recommendation as “Strong For”, “Weak For”, “Strong Against”, or “Weak Against”. Pharmacotherapy from the following classes were considered: LABAs, SABAs, SAMAs, LAMAs, ICS, PDE4, theophylline, and NAC. Important clinical outcomes of interest were quality of life (QoL), morbidity, dyspnea, functional capacity, exacerbation rate and/or severity, mortality, harms, and healthcare utilization. Twenty-five systematic reviews were evaluated to develop pharmacological recommendations.

Recommendations for COPD Management in the Outpatient Setting:

- SABAs for patients with confirmed COPD for rescue therapy as needed (Strong For)
    - Based on improvements in FEV1, respiratory symptoms, and reduction in exacerbations in COPD exacerbations in stable COPD.
- Long-acting bronchodilators for patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea and cough) (Strong For)
    - LAMAs have been shown to improve FEV1 and QoL and reduce the rate of COPD exacerbations and exacerbations requiring hospitalization. LABAs have been shown to improve FEV1 and QoL.
- Inhaled LAMA tiotropium as first-line maintenance therapy for patients with confirmed, stable COPD, who continue to have respiratory symptoms (e.g., dyspnea, cough) (Weak For)
    - LAMAs have been shown to be superior to LABAs for preventing COPD exacerbations and COPD-related hospitalizations with fewer adverse events.
- Inhaled tiotropium as first-line therapy for patients with confirmed, stable COPD who have respiratory symptoms (e.g., dyspnea, cough) and severe airflow obstruction (i.e., post bronchodilator FEV1 <50%) or a history of COPD exacerbations (Strong For)
    - LAMAs have been shown to be superior to LABAs for preventing COPD exacerbations and COPD-related hospitalizations with fewer adverse events.
- For patients on SAMA that are clinically stable with a confirmed diagnosis of COPD and who have not had exacerbations, the recommendation is to continue treatment rather than switching to long-acting bronchodilators (Weak For)
    - Ipratropium has been shown to improve FEV1 and respiratory symptoms compared to placebo.
- For patients taking a SAMA who are started on a LAMA, the recommendation is to discontinue the SAMA (Weak For)
    - LAMA have been shown to be superior to SAMA and placebo for the outcomes of FEV1 improvement, exacerbations, respiratory symptoms and COPD –related QoL.
- ICS are not recommended for first-line monotherapy in symptomatic patients with confirmed, stable COPD (Strong Against)
    - ICS has not been shown to be as beneficial as LABAs on lung function.
- Recommend against using a LABA without an ICS in patients with COPD who may have concomitant asthma (Strong Against)
    - LABA monotherapy use in asthma patients has been associated with an increased risk of death.
- Combination therapy of a LABA and LAMA is recommended for patients with confirmed, stable COPD who are on inhaled LAMAs (tiotropium) or inhaled LABAs and have persistent dyspnea on monotherapy (Strong For)
    - Combination therapy with LAMAs and LABAs has been shown to improve FEV1, QoL, and dyspnea compared to tiotropium alone.
- For patients on a LAMA (tiotropium) and LABA with confirmed, stable COPD and have persistent dyspnea or COPD exacerbations, ICS as a third medication is recommended (Weak For)
    - Limited data suggest improvement in QoL, lung function, and symptoms in patients taking triple therapy.
- Roflumilast is not recommended for patients with confirmed, stable COPD in primary care without the consultation with a pulmonologist (Weak Against)
    - Only modest benefit in FEV1 improvements have been demonstrated when compared to placebo.
- Theophylline is not recommended for patients with confirmed, stable COPD in primary care without the consultation with a pulmonologist (Weak Against)
- There is insufficient evidence to recommend for or against the use of NAC in patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough) (Not graded)

Author: K. Sentena, Pharm.D. Date: September 2015

GOLD Guidelines

In January of 2015 the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines were updated.[1] The 2015 guideline builds on the framework established with the 2011 guidelines with the addition of evidenced based updates in 2013, 2014 and now 2015. Treatment recommendations were unchanged from previous updates (Table 5). Evidence to support the use of salmeterol and formoterol, based on decreased exacerbations, was added. Data on increased exacerbation rates with ICS withdrawal was cited, however, these findings were not reproduced in a second study in patients with severe and very severe COPD. The use of N-acetylcysteine in GOLD stage 2 patients showed decreased exacerbation rates.[1]

Table 5. Initial Pharmacological Management of COPD[1]

Patients	First Choice	Alternative Choice	Other Possible Treatments
Group A: Few symptoms and low risk of exacerbations (GOLD 1 or 2)	Short-acting anticholinergic prn *or* Short-acting beta2-agonist prn	Long-acting anticholinergic *or* Long-acting beta2-agonist *or* Short-acting beta2-agonist and short-acting anticholinergic	Theophylline
Group B: More symptoms and low risk of exacerbations (GOLD 1 or 2)	Long-acting anticholinergic *or* Long-acting beta2-agonist	Long-acting anticholinergic *and* Long-acting beta2-agonist	Short-acting beta2-agonist *and/or* Short-acting anticholinergic Theophylline
Group C: Few symptoms but high risk of exacerbations (GOLD 3 or 4)	Inhaled corticosteroid + long-acting beta2-agonist *or* Long-acting anticholinergic	Long-acting anticholinergic and long-acting beta2-agonist *or* Long-acting anticholinergic and phosphodiesterase-4 inhibitor *or* Long-acting beta2-agonist and phosphodiesterase-4 inhibitor	Short-acting beta2-agonist *and/or* Short-acting anticholinergic Theophylline
Group D: Many symptoms and high risk of exacerbations (GOLD 3 or 4)	Inhaled corticosteroid + long-acting beta2-agonist *and/or* Long-acting anticholinergic	Inhaled corticosteroid + long-acting beta2-agonist and long-acting anticholinergic *or* Inhaled corticosteroid + long-acting beta2-agonist and phosphodiesterase-4 inhibitor *or* Long-acting anticholinergic and long-acting beta2-agonist *or* Long-acting anticholinergic and phosphodiesterase-4 inhibitor	Carbocysteine N-acetylcysteine Short-acting beta2-agonist *and/or* Short-acting anticholinergic Theophylline

*Medications in each box are mentioned in alphabetical order, and therefore not necessarily in order of preference.
**Medications in this column can be used alone or in combination with other options in the Recommended First Choice and Alternative Choice columns.

Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014. Available at: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015_Apr2.pdf. Accessed on July 26, 2015.

International ERS/ATS Guidelines on Definition, Evaluation, and Treatment of Severe Asthma

The European Respiratory Society and American Thoracic Society released guidance on the treatment of severe asthma in children and adults.[5] Severe asthma is defined as asthma that requires treatment with high dose ICS and a second controller and/or systemic corticosteroids to prevent symptoms from being uncontrolled or asthma that remains uncontrolled even with this therapy. Pharmacotherapy includes a low (adults) and very low (children) recommendation for the use of anti-IgE antibody therapy (omalizumab) for patients with severe allergic asthma. Candidates for omalizumab therapy should have confirmed IgE-dependent allergic asthma uncontrolled despite optimal treatment with other agents. Exhaled nitric oxide, methotrexate and macrolide antibiotics are not recommended based on low and very low quality of evidence. In adults with asthma and recurrent exacerbations of allergic bronchopulmonary aspergillosis (ABPA) antifungal agents are recommended based on very low quality of evidence.[5]

New Safety Alerts:

Omalizumab (Xolair) – In September of 2014 the FDA released a Drug Safety Communication for omalizumab and the slightly increased risk of cerebrovascular and cardiovascular severe adverse events.[6] These risks have been added to omalizumab labeling. A warning about the uncertain increased risk of cancer with omalizumab therapy has also been added.

New Formulations or Indications:

Tiotropium/olodeterol (Stiolto™ Respimat®)

Combination therapy with an anticholinergic, tiotropium, and a LABA (olodeterol) was approved in May of 2015 for maintenance treatment for airflow obstruction in patients with COPD.[13] The dose of tiotropium/olodeterol is 2 inhalations once daily, at the same time every day. Efficacy data comes primarily from two, 52-week, double-blind, randomized-controlled, confirmatory trials involving 5162 patients. Tiotropium/olodeterol combination therapy was compared to tiotropium 5 mcg and olodeterol 5 mcg, administered via the RESPIMAT inhaler, in both studies. Trial participants were COPD patients, mean age of 64, with a smoking history of 10+ pack years and moderate to very severe pulmonary dysfunction (GOLD stage 2-4). Concomitant ICS therapy was used in 47% of patients. The primary outcome measures were change from baseline in FEV_1 AUC $_{0\text{-}3hr}$ and trough FEV_1 measured at 24-weeks of treatment. Tiotropium/olodeterol was statistically superior to tiotropium and olodeterol for the outcome of FEV_1 AUC $_{0\text{-}3hr}$ improvements in both trials (difference ranges from 0.103-.0117L for tiotropium and 0.123-0.132L for olodeterol). Changes in trough FEV1 ranged from a difference of 0.050-0.071L for tiotropium and 0.082-0.088 for olodeterol. Less rescue medication was used in patients randomized to tiotropium/olodeterol compared to the individual components.

Fluticasone furoate (Arnuity Ellipta)

The single entity product of Breo Ellipta (fluticasone furoate/vivanterol trifenatate) was approved in August of 2014.[14] Fluticasone furoate is an ICS indicated for the maintenance treatment of asthma in patients 12 and older.[14] Fluticasone furoate is an inhalation powder dosed as 100 mcg or 200 mcg once daily. There were 4 confirmatory trials in patients with uncontrolled asthma on ICS or LABA/ICS combination therapy. The primary outcome was change in baseline evening trough FEV_1 measured after the final dose of study medication in trials lasting 12 to 24 weeks. Fluticasone furoate 100 mcg was superior to placebo with a mean difference of 146 mL (95% CI, 36 to 257; p=0.009). Similar results were demonstrated in a second 12 week trial comparing the 100 mcg dose to placebo. In a study of fluticasone furoate 100 mcg and fluticasone 200 mcg, changes in FEV1 from baseline were 208 mL and 284 mL, respectively.

Randomized Controlled Trials:

None identified.

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Appendix 1: Current Status on Preferred Drug List

Anticholinergics, Inhaled

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INHALATION	AMPUL-NEB	DUONEB	IPRATROPIUM/ALBUTEROL SULFATE	Y
INHALATION	AMPUL-NEB	IPRATROPIUM-ALBUTEROL	IPRATROPIUM/ALBUTEROL SULFATE	Y
INHALATION	CAP W/DEV	SPIRIVA	TIOTROPIUM BROMIDE	Y
INHALATION	HFA AER AD	ATROVENT HFA	IPRATROPIUM BROMIDE	Y
INHALATION	MIST INHAL	COMBIVENT RESPIMAT	IPRATROPIUM/ALBUTEROL SULFATE	Y
INHALATION	SOLUTION	IPRATROPIUM BROMIDE	IPRATROPIUM BROMIDE	Y
INHALATION	AER POW BA	TUDORZA PRESSAIR	ACLIDINIUM BROMIDE	N
INHALATION	BLST W/DEV	ANORO ELLIPTA	UMECLIDINIUM BRM/VILANTEROL TR	N
INHALATION	BLST W/DEV	INCRUSE ELLIPTA	UMECLIDINIUM BROMIDE	N
INHALATION	MIST INHAL	SPIRIVA RESPIMAT	TIOTROPIUM BROMIDE	N
INHALATION	MIST INHAL	STIOLTO RESPIMAT	TIOTROPIUM BR/OLODATEROL HCL	

Beta-agonists, Inhaled Long-acting

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INHALATION	BLST W/DEV	SEREVENT DISKUS	SALMETEROL XINAFOATE	Y
INHALATION	CAP W/DEV	FORADIL	FORMOTEROL FUMARATE	Y
INHALATION	CAP W/DEV	ARCAPTA NEOHALER	INDACATEROL MALEATE	N
INHALATION	MIST INHAL	STRIVERDI RESPIMAT	OLODATEROL HCL	N
INHALATION	VIAL-NEB	BROVANA	ARFORMOTEROL TARTRATE	N
INHALATION	VIAL-NEB	PERFOROMIST	FORMOTEROL FUMARATE	N

Beta-agonists, Inhaled Short-acting

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INHALATION	HFA AER AD	PROAIR HFA	ALBUTEROL SULFATE	Y
INHALATION	HFA AER AD	PROVENTIL HFA	ALBUTEROL SULFATE	Y
INHALATION	SOLUTION	ALBUTEROL SULFATE	ALBUTEROL SULFATE	Y
INHALATION	SOLUTION	PROVENTIL	ALBUTEROL SULFATE	Y
INHALATION	SOLUTION	VENTOLIN	ALBUTEROL SULFATE	Y
INHALATION	VIAL-NEB	AIRET	ALBUTEROL SULFATE	Y
INHALATION	VIAL-NEB	ALBUTEROL SULFATE	ALBUTEROL SULFATE	Y
INHALATION	AER POW BA	PROAIR RESPICLICK	ALBUTEROL SULFATE	N
INHALATION	AER REFILL	ALBUTEROL	ALBUTEROL	N
INHALATION	AER W/ADAP	ALUPENT	METAPROTERENOL SULFATE	N
INHALATION	AEROSOL	PROVENTIL	ALBUTEROL	N
INHALATION	AEROSOL	VENTOLIN	ALBUTEROL	N
INHALATION	HFA AER AD	ALBUTEROL SULFATE HFA	ALBUTEROL SULFATE	N
INHALATION	HFA AER AD	PROAIR HFA	ALBUTEROL SULFATE	N
INHALATION	HFA AER AD	VENTOLIN HFA	ALBUTEROL SULFATE	N
INHALATION	HFA AER AD	XOPENEX HFA	LEVALBUTEROL TARTRATE	N
INHALATION	SOLUTION	ALUPENT	METAPROTERENOL SULFATE	N
INHALATION	VIAL-NEB	LEVALBUTEROL CONC	LEVALBUTEROL HCL	N
INHALATION	VIAL-NEB	LEVALBUTEROL HCL	LEVALBUTEROL HCL	N
INHALATION	VIAL-NEB	XOPENEX	LEVALBUTEROL HCL	N
INHALATION	VIAL-NEB	XOPENEX CONCENTRATE	LEVALBUTEROL HCL	N
INHALATION	VIAL-NEB	LEVALBUTEROL CONC	LEVALBUTEROL HCL	
INHALATION	VIAL-NEB	LEVALBUTEROL HCL	LEVALBUTEROL HCL	

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Corticosteroids, Inhaled

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INHALATION	AER POW BA	PULMICORT FLEXHALER	BUDESONIDE	Y
INHALATION	AER W/ADAP	FLOVENT HFA	FLUTICASONE PROPIONATE	Y
INHALATION	AER W/ADAP	QVAR	BECLOMETHASONE DIPROPIONATE	Y
INHALATION	BLST W/DEV	FLOVENT DISKUS	FLUTICASONE PROPIONATE	Y
INHALATION	AER POW BA	ASMANEX	MOMETASONE FUROATE	N
INHALATION	AER W/ADAP	AEROBID	FLUNISOLIDE	N
INHALATION	AER W/ADAP	AEROBID-M	FLUNISOLIDE/MENTHOL	N
INHALATION	AER W/ADAP	AZMACORT	TRIAMCINOLONE ACETONIDE	N
INHALATION	AMPUL-NEB	BUDESONIDE	BUDESONIDE	N
INHALATION	AMPUL-NEB	PULMICORT	BUDESONIDE	N
INHALATION	BLST W/DEV	ARNUITY ELLIPTA	FLUTICASONE FUROATE	N
INHALATION	HFA AER AD	AEROSPAN	FLUNISOLIDE	N
INHALATION	HFA AER AD	ALVESCO	CICLESONIDE	N
INHALATION	HFA AER AD	ASMANEX HFA	MOMETASONE FUROATE	N

Corticosteroids/LABA Combination, Inhaled

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INHALATION	BLST W/DEV	ADVAIR DISKUS	FLUTICASONE/SALMETEROL	Y
INHALATION	HFA AER AD	ADVAIR HFA	FLUTICASONE/SALMETEROL	Y
INHALATION	HFA AER AD	SYMBICORT	BUDESONIDE/FORMOTEROL	Y
INHALATION	BLST W/DEV	BREO ELLIPTA	FLUTICASONE/VILANTEROL	N
INHALATION	HFA AER AD	DULERA	MOMETASONE/FORMOTEROL	N

Miscellaneous Pulmonary Agents

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TAB CHEW	MONTELUKAST SODIUM	MONTELUKAST SODIUM	Y
ORAL	TAB CHEW	SINGULAIR	MONTELUKAST SODIUM	Y
ORAL	TABLET	MONTELUKAST SODIUM	MONTELUKAST SODIUM	Y
ORAL	TABLET	SINGULAIR	MONTELUKAST SODIUM	Y
SUB-Q	VIAL	XOLAIR	OMALIZUMAB	N
ORAL	TABLET	DALIRESP	ROFLUMILAST	N
ORAL	GRAN PACK	MONTELUKAST SODIUM	MONTELUKAST SODIUM	N
ORAL	GRAN PACK	SINGULAIR	MONTELUKAST SODIUM	N
ORAL	TABLET	ACCOLATE	ZAFIRLUKAST	N
ORAL	TABLET	ZAFIRLUKAST	ZAFIRLUKAST	N
ORAL	TABLET	ZYFLO	ZILEUTON	N
ORAL	TBMP 12HR	ZYFLO CR	ZILEUTON	N

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to July Week 3 2015

Search Strategy:

#	Searches	Results
1	Ipratropium/	749
2	tiotropium.mp.	1007
3	aclidinium.mp.	83
4	umeclidinium.mp.	29
5	salmeterol.mp.	2113
6	formoterol.mp.	1561
7	indacaterol.mp.	214
8	olodaterol.mp.	28
9	arformoterol.mp.	29
10	albuterol.mp. or Albuterol/	5613
11	metaproteranol.mp.	1
12	levalbuterol.mp. or Levalbuterol/	120
13	budesonide.mp. or Budesonide/	3890
14	fluticasone.mp.	3156
15	beclomethasone diproprionate.mp.	26
16	mometasone.mp.	672
17	flunisolide.mp.	191
18	triamsinolone.mp.	2
19	budesonide.mp. or Budesonide/	3890
20	fluticasone furoate.mp.	141
21	ciclesonide.mp.	274
22	montelukast.mp.	1707
23	omalizumab.mp.	1066
24	roflumilast.mp.	336
25	zafirulukast.mp.	1
26	zileuton.mp.	402
27	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 or 22 or 23 or 24 or 25 or 26	16473
28	limit 27 to (english language and yr="2014 -Current")	905
29	limit 28 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	313

Long-acting Beta-agonists (LABA)

Goal:

- The purpose of this prior authorization policy is to ensure that non-preferred long-acting beta-agonists are used appropriately.

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

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

Approval Criteria		
1. Does the patient have an asthma or COPD diagnosis?	Yes: Go to #2.	**No:** Pass to RPH; Deny for medical appropriateness.
2. Is the request for indacaterol or olodaterol?	Yes: Go to #3.	No: Go to #6.
3. Does patient have COPD (ICD-9 496)?	Yes: Go to #4.	No: Deny (medical inappropriateness)
4. Will the prescriber consider a change to a preferred product? - Preferred products do not require PA	Yes: Inform provider of covered alternatives in class.	No: Go to #5.
5. Does patient have a documented previous trial of salmeterol AND formoterol?	Yes: Approve for one year.	No: Pass to RPh, Deny for OHP Coverage.
6. Is this a continuation of current therapy (i.e. filled prescription within prior 90 days)? Verify via pharmacy claims.	Yes: Document prior therapy in PA record. Approve for 1 year.	No: Go to #7.

Approval Criteria		
7. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Drug Use Review (DUR / Pharmacy & Therapeutics (P&T) Committee.	Yes: Inform provider of covered alternatives in class.	No: Approve for 1 year or length of prescription, whichever is less.

P&T/DUR Review: *9/15; 5/12; 9/09; 5/09*
Implementation: *8/12; 1/10*

Long-acting Beta-agonists with Inhaled Corticosteroids (LABA/ICS Inhalers)

Goals:

- Approve LABA/ICS only for covered diagnosis (e.g. COPD or Asthma and on concurrent controller medication).
- LABA are only indicated for use in clients with Asthma already receiving treatment with an asthma controller medication (e.g. Inhaled corticosteroids or leukotriene receptor antagonists,).

Initiative:

- LABA/ICS Step Therapy

Length of Authorization:

6-12 months

Requires PA:

- All combination inhaled corticosteroid/long-acting beta-agonist inhalers

Covered Alternatives:

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

Step Therapy Required Prior to Coverage:

Asthma: oral corticosteroid inhalers (see preferred drug list options at

(http://www.orpdl.org/drugs/)

COPD: short and long-acting beta-agonist inhalers, anticholinergics and inhaled corticosteroids (see preferred drug list options at http://www.orpdl.org/drugs/), DO NOT require prior authorization.

Approval Criteria		
1. Does patient have asthma or reactive airway disease (ICD-9: 493, 493.0-493.93)?	**Yes:** Go to #2.	**No:** Go to #4.
2. Is the medication for Breo Ellipta™ (fluticasone furoate / vilanterol)?	**Yes:** Pass to RPH; Deny for medical appropriateness.	**No:** Go to #3.
3. Has patient: • failed an inhaled corticosteroid or other controller medication OR • Had ≥2 exacerbations requiring oral systemic corticosteroids in the past year, OR • Is there documentation of step 3 asthma or higher OR • Is there a hospital admission or ER visit related to asthma or reactive airway disease within last 365 days?	**Yes:** Document the following: Date of trial, drug, reason(s) for failure or contraindications OR chart notes of asthma severity in the PA record Approve for 1 year if this is patient's first prescription for a combination inhaler or if this is a continuation of therapy and patient is well controlled on current dose.	**No:** Pass to RPH; Deny, (Medical Appropriateness).
4. Does patient have COPD (ICD-9 496) or Chronic bronchitis (491.1-2.) and/or emphysema (492.xx)?	**Yes:** Approve for 12 months.	**NO:** Pass to RPH. Deny (Medical Appropriateness). Need a supporting diagnosis. If prescriber believes diagnosis appropriate inform them of the provider reconsideration process for Medical Director Review.

P&T/DUR Review: *9/15; 11/14; 11/13; 5/12; 9/09; 2/06*
Implementation: *1/15; 1/14; 9/12; 1/10*

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Leukotriene Inhibitors

Goals:

- Approve montelukast only for covered diagnosis.
- Allergic rhinitis treatment is covered by the OHP only when complicated by other diagnoses (e.g. Asthma, sleep apnea).
- Promote use that is consistent with medical evidence.

Length of Authorization:

6 months or 2 years (diagnosis specific)

Requires PA:

- Non-preferred drugs
- Montelukast (Singulair®)

Covered Alternatives:

- Preferred alternatives listed at http://www.orpdl.org/drugs/
- Allergic Rhinitis: Certirizine, chlorpheniramine, diphenhydramine, loratidine & hydroxyzine DO NOT require prior authorization.
- Asthma: Oral corticosteroid inhalers. Long-acting beta-agonist inhalers and zarfirlukast (Accolate®) DO NOT require prior authorization.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Does client have asthma or reactive airway disease (ICD-9: 493.xx)?	Yes: Approve for 2 years	No: Go to #3.
3. Does client have diagnosis allergic rhinitis, allergic conjunctivitis, or chronic rhinitis/pharyngitis/nasopharyngitis? (ICD-9: 472.xx, 372.01-05, 372.14, 372.54, 372.56, 477.xx, 995.3, V07.1	Yes: Go to #4.	No: Go to #6.

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Approval Criteria		
4. Does client have other co-morbid conditions or complications that are above the line? • Acute or chronic inflammation of the orbit (376.0 – 376.12) • Chronic Sinusitis (473.xx) • Acute Sinusitis (461.xx) • Sleep apnea (327.20,327.21,327.23-327.29,780.51, 780.53, 780.57) • Wegener's Granulomatosis (ICD-446.4)	Yes: Go to #5.	No: Pass to RPH; Deny, (Not Covered by the OHP).
5. Does client have contraindications (e.g. Pregnant) or had insufficient response to at least 2 available alternatives? Document.	Yes: Approve 6 months	No: Pass to RPH; Deny, (Cost-Effectiveness)
6. Is the diagnosis COPD (496) or Obstructive Chronic Bronchitis? (491.1-491.2)	Yes: Pass to RPH; Deny, (Medical Appropriateness). Leukotriene not indicated	No: Pass to RPH; Go to #7.
7. Is the diagnosis Chronic Bronchitis? (491.0, 491.8, 491.9)	Yes: Pass to RPH; Deny, (Not Covered by the OHP)	No: Pass to RPH Go to #8.

Approval Criteria		
8. RPH only: Is the diagnosis above the line or below the line?	Above: Deny with yesterday's date (Medically Appropriateness) Use clinical judgment to approve for 1 month starting today to allow time for appeal. Message: "Although the request has been denied for long term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal."	Below: Deny, (Not covered by the OHP) "The treatment for your condition is not a covered service on the Oregon Health Plan." (e.g. URI - 465.9 or Uticaria – 708.0, 708.1, 708.5, 708.8, 995.7 should be denied)

Refer questions regarding coverage to DMAP.

P&T/DUR Review: *9/15; 5/12; 9/08; 2/06; 9/04; 5/04*
Implementation: *8/12; 7/09; 9/06; 7/06; 5/05; 4/05; 11/04*

Roflumilast

Goals:

- Decrease the number of COPD exacerbations in patients with severe COPD and chronic bronchitis and a history of prior 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 ICD9 code.	
2. Is the diagnosis an OHP covered diagnosis?	Yes: Go to #3.	No: Pass to RPh, Deny for OHP Coverage.
3. Does the patient have documented severe or very severe (Stage III or Stage IV) COPD?	Yes: Go to #4	No: Deny (medical inappropriateness)
4. Does the patient have a history of chronic bronchitis AND Prior COPD exacerbations?	Yes: Go to #5	No: Deny (medical inappropriateness)
5. Is the patient currently on a long-acting bronchodilator?	Yes: Go to #6	No: Deny. Recommend trial of preferred long-acting bronchodilators
6. Has the patient tried an inhaled corticosteroid (ICS), and ICS combination, or tiotropium (LAMA)?	Yes: Approve up to 1 year	No: Deny. Recommend trial of preferred long-acting ICS or LAMA

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Date: September 2015

P&T/DUR Review: *9/15; 5/13; 2/12*
Implementation: *1/14; 5/12*

Asthma Controller Drugs

Goal:

- The purpose of this prior authorization policy is to ensure that non-preferred asthma controller drugs are used for an above the line condition.

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

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

Approval Criteria		
1. Is the requested drug montelukast?	Yes: Refer to Leukotriene Inhibitor Criteria	No: Go to #2.
2. Is the request for a LABA or LABA/ICS combination product?	Yes: Refer to LABA or LABA/ICS PA Criteria	No: Go to #3
3. What diagnosis is being treated?	Record ICD9 code.	
4. Is this an OHP covered diagnosis?	Yes: Go to #5.	No: Pass to RPH; Deny, (Not Covered by the OHP).
5. Is this a continuation of current therapy (i.e. filled prescription within prior 90 days)? Verify via pharmacy claims.	Yes: Document prior therapy in PA record. Approve for 1 year.	No: Go to #6.

Approval Criteria		
6. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Drug Use Review (DUR / Pharmacy & Therapeutics (P&T) Committee.	Yes: Inform provider of covered alternatives in class.	No: Approve for 1 year or length of prescription, whichever is less.

P&T/DUR Review: *9/15; 5/12; 9/09; 5/09*
Implementation: *8/12; 1/10*