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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. Evidence since that time will be reviewed.

Research Questions:

1. Is there new comparative evidence on the efficacy/effectiveness of treatments for asthma or treatments for COPD?
2. Is there new comparative evidence of harms associated with medications used to treat asthma or COPD?
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:

- There is insufficient new comparative evidence for efficacy/effectiveness for the treatment of COPD. Evidence-based recommendations in new clinical practice guidelines from The Global Initiative for Chronic Obstructive Lung Disease (GOLD), The American College of Chest Physicians (ACCP) and Canadian Thoracic Society (CTS), and the Veterans Administration (VA)/Department of Defense (DoD) do not differentiate between drugs within a pharmacological class.[1-3] Therefore, these guidelines cannot be used to support placement of specific therapies on Practitioner-Managed Prescription Drug Plan (PMPDP).[1-3]
- There is insufficient new comparative evidence for efficacy/effectiveness for the treatment of asthma. New evidence primarily focuses on the use of omalizumab for severe asthma and continues to support the recommendation to reserve omalizumab to patients with allergic asthma who have failed other treatments.[4-6]
- There is insufficient new comparative safety data for the treatment of COPD or asthma. New evidence primarily focuses on individual treatments and do not support a change to current placement of therapies for asthma or COPD on the Preferred Drug List (PDL).[4,7-12]
- Two new formulations of drug products for COPD previously reviewed by the Pharmacy & Therapeutics Committee were identified. Both products were approved by the FDA based on short-term, 24-week studies that evaluated surrogate outcomes of lung function.
    - Tiotropium/olodaterol (Stiolto™ Respimat®) is indicated for long-term management of COPD. Tiotropium is a preferred inhaled anticholinergic for COPD and olodaterol is a non-preferred long-acting beta-agonist for COPD. Over 5,000 patients from two replicate studies with moderate to very

severe COPD were studied for 52 weeks. Patients were randomized to one of 5 treatment arms: tiotropium 2.5 mcg, tiotropium 5 mcg, olodaterol 5 mcg, tiotropium 2.5 mcg/olodaterol 5 mcg and tiotropium 5 mcg/olodaterol 5 mcg. There is moderate level of evidence that tiotropium/olodaterol fixed-dose combination products are superior compared to its monotherapy components for the outcomes of change from baseline in FEV_1 AUC_{0-3hr} ($p<0.0001$ for all comparisons) and trough FEV_1 ($p<0.05$ for all comparisons) at 24 weeks. There is insufficient evidence of comparative efficacy or safety between tiotropium/olodaterol and other drugs for the management of COPD.[13]

- Fluticasone furoate (Arnuity™ Ellipta®) is an ICS indicated for the maintenance treatment of asthma in patients 12 years and older. Fluticasone furoate demonstrated superiority over 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]

- A new indication for asthma in patients 18 years of age or older was identified for fluticasone furoate/vilanterol (Breo® Ellipta®). Approval for asthma by the FDA for the 100/25 mcg and 200/25 mcg dose of fluticasone furoate/vilanterol was based on short-term, 12 to 24-week studies.[27]
  - There is moderate quality evidence that the once-daily fixed dose combination products are more effective than their fluticasone furoate monotherapy counterparts in the ability to improve weighted mean FEV_1 (0-24 hours) from baseline. In addition, fluticasone furoate 100 mcg/vilanterol 25 mcg decreased time to first asthma exacerbation compared to fluticasone furoate 100 mcg alone (HR 0.80; 95% CI, 0.64 to 0.99; p=0.036).[27]

Recommendations:

- Make tiotropium/olodaterol, fluticasone furoate and fluticasone furoate/vilanterol products non-preferred at this time due to limited evidence.
- Create new PDL class for long-acting muscarinic antagonist/long-acting beta-agonist (LAMA/LABA) fixed-dose combination inhaler products.
- Re-organize and modify clinical PA criteria to promote step-therapy that is consistent with Oregon Asthma Guidelines and with medical evidence for COPD (see **Appendix 3**):
  - All non-preferred LABA inhalers must go through the LABA PA criteria for appropriate step therapy.
  - All non-preferred inhaled corticosteroids (ICS) must go through the ICS PA criteria for appropriate step therapy.
  - Remove clinical PA for "asthma controllers" and indacaterol. Drugs under these PAs will be incorporated into the ICS or LABA PA criteria.
  - Remove clinical PA for leukotriene inhibitors. Non-preferred leukotriene inhibitors will go through the generic non-preferred PDL PA.
  - Clerical changes to the roflumilast PA criteria.
  - Update LABA/ICS clinical PA and LABA/LAMA clinical PA to reflect best practices for initial COPD management. Bring back PAs to next P&T meeting.

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 FEV_1 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 FEV_1 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 FEV_1 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.
- There is low quality evidence of no difference in mean change in lung function from baseline to 24 weeks, as measured by trough FEV_1, between olodaterol 5 mcg daily via Respimat inhaler and formoterol 12 mcg twice daily.[21,22]
- There is low quality evidence that once daily olodaterol improves lung function from baseline to 24 weeks in patients with moderate to severe COPD compared to placebo, as measured by FEV_1 and FEV_1 area under the curve from 0 to 3 hours (AUC0-3). This improvement in lung function is not considered clinically meaningful but may be explained in the context that use of other COPD medications were permitted during the study periods.[21,22]
- There is insufficient evidence that olodaterol decreases COPD exacerbations, hospitalizations, mortality or health-related quality of life. There is low quality evidence that olodaterol does not improve dyspnea compared to placebo.[21,22]

Previous Recommendations:

- Due to no evidence demonstrating clinical superiority of umeclidinium/vilanterol over current agents, the Committee recommended making it non-preferred on the PMPDP and applies 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.
- Designate olodaterol as non-preferred due to lack of quality evidence demonstrating clinical effectiveness.

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. A 2013 report on the Burden of Asthma in Oregon cited 3.5-4% of the OHP population as having an asthma diagnosis.[23] Total National asthma costs were projected to be over $20 billion in 2010.[23]

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 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).[24]

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.[24] 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.[24] 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.[25]

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.[26] Forty-one percent of these individuals were on at least one daily treatment for COPD.[26]

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), grade 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.[25]

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:

<u>Cochrane – Inhaled Corticosteroids in Children with Persistent Asthma: Effects on Growth</u>

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) were 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 or non-steroidal comparisons of 14 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 or non-steroidal drugs. 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

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

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

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, four of which focused on the safety and efficacy of formoterol, salmeterol or combination therapy. 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. 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

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 vilanterol 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

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 3. 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, salmeterol or indacaterol
Long-acting Muscarinic antagonists (LAMA)	Aclidinium, glycopyrronium or tiotropium
Inhaled Corticosteroids (ICS)	Budesonide, fluticasone or mometasone
Combination LABA/ICS	Formoterol/budesonide, formoterol/mometasone, or salmeterol/fluticasone

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 Pharmacological Management of COPD.[2]

Recommendation	Grade
In patients with moderate to severe COPD the use of LABAs is recommended over placebo	1B
In patients with moderate to severe COPD the use of LAMAs is recommended over placebo	1A
In patients with moderate to severe COPD the use of LAMAs is recommended over LABAs	1C
In patients with moderate to severe COPD the use of SAMAs are recommended over SABAs	2C
In patients with moderate to severe COPD the use of SAMA + SABA are recommended over SABA alone	2B
In patients with moderate to severe COPD the use of LABA monotherapy is recommended over SAMA monotherapy	2C
In patients with moderate to severe COPD the use of LAMA is recommended over SAMA	1A
In patients with moderate to severe COPD the use of combination SAMA + LABA is recommended over LABA monotherapy	2C
In patients with stable moderate, severe, and very severe COPD the use of maintenance combination ICS/LABA therapy is recommended over the use of placebo	1B
In patients with stable moderate, severe, and very severe COPD the use of maintenance combination ICS/LABA therapy is recommended over the use of LABA monotherapy	1C
In patients with stable moderate to very severe COPD the use of ICS/LABA is recommended over ICS monotherapy	1B
In patients with stable COPD the use of LAMA/LABA or LAMA monotherapy are recommended	1C
In patients with stable COPD the use of maintenance combination ICS/LABA or LAMA are recommended	1C
In patients with stable COPD the use of maintenance combination LAMA/ICS/LABA or LAMA are recommended	2C
In patients with moderate to severe COPD with chronic bronchitis and history of at least one exacerbation in the previous year, roflumilast is recommended	2A
In patients with COPD oral slow-release theophylline twice daily is recommended (if already on maintenance long-acting bronchodilator therapy and ICS)	2B
In patients with moderate to severe COPD and a history of two or more exacerbations in the previous 2 years, N-acetylcysteine is recommended (if already on maintenance long-acting bronchodilator therapy and ICS)	2B
In stable outpatients with COPD the use of oral carbocysteine is recommended in patients who continue to experience exacerbations despite maximal therapy designed to reduce exacerbations	Con-sensus based
Abbreviations: COPD – chronic obstructive pulmonary disease; ICS – inhaled corticosteroid; LABA – long-acting beta2-agonist; LAMA – long-acting muscarinic antagonists; SABA – short-acting beta2-agonist	

<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 compared to placebo.

- 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)

<u>GOLD Guidelines</u>

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 *or* Short-acting beta2-agonist *and* 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 *or* Short-acting beta2-agonist *and* 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	Short-acting beta2-agonist *and/or* Short-acting anticholinergic *or* Short-acting beta2-agonist *and* Theophylline or carbocysteine *or* N-acetylcysteine

*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/olodaterol (Stiolto™ Respimat®)

Combination therapy with an anticholinergic, tiotropium, and a LABA (olodaterol) was approved in May of 2015 for maintenance treatment for airflow obstruction in patients with COPD.[13] The dose of tiotropium/olodaterol 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. In both studies tiotropium/olodaterol combination therapy was studied using five treatment arms; tiotropium 2.5 mcg, tiotropium 5 mcg, olodaterol 5 mcg, tiotropium 2.5 mcg/olodaterol 5 mcg and tiotropium 5 mcg + olodaterol 5 mcg. 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.

For the outcome of FEV_1 AUC $_{0\text{-}3hr}$ tiotropium/olodaterol was superior to tiotropium 5 mcg (difference 0.117 L [95%CI 0.094 to 0.140 L; p≤0.001] in trial 1 and difference 0.103 [95%CI 0.078 to 0.127; p≤0.001] in trial 2). Tiotropium/olodaterol was also superior to olodaterol 5 mcg for the outcome of FEV_1 AUC $_{0\text{-}3hr}$ (difference 0.123 L [95% CI 0.100 to 0.146 L; p≤0.001) for trial 1 and difference 0.132 L [95% CI 0.108 to 0.157 L; p≤0.001) for trial 2].

Fluticasone furoate (Arnuity™ Ellipta®)

The single entity product of Breo Ellipta (fluticasone furoate/vilanterol) 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.

Fluticasone furoate/vilanterol (Breo® Ellipta®)

An indication for the once-daily treatment of asthma in patients 18 years and older was added to the labeling of fluticasone furoate/vilanterol inhalation powder in April of 2015.[27] This ICS/LABA combination was previously approved for COPD maintenance treatment in 2013. The dose for asthma patients is 1 inhalation of fluticasone furoate 100 mcg/vilanterol 25 mcg or fluticasone furoate 200 mcg/vilanterol 25 mcg once-daily.

Four, randomized, double-blind confirmatory trials lasting 12 to 24 weeks and one active-comparator trial lasting 24 weeks provided evidence for the efficacy of fluticasone furoate/vivanterol.[27] Patients received once daily fluticasone furoate 100 mcg/vilanterol 25 mcg, fluticasone furoate 100 mcg, or placebo in the first trial. In the second trial, patients were randomized to once daily fluticasone furoate 100 mcg/vilanterol 25 mcg, fluticasone furoate 200 mcg/vilanterol 25 mcg, or fluticasone furoate 100 mcg. The third study randomized patients to fluticasone furoate 200 mcg/vilanterol 25 mcg, fluticasone 200 mcg or fluticasone proprionate 500 mcg (twice daily). In an active-comparator trial, fluticasone furoate 100 mcg/vilanterol 25 mcg was compared to fluticasone furoate 100 mcg daily on the rate of exacerbations. The primary endpoint in trials 1 and 3 was change from baseline in weighted mean FEV_1 (0-24 hours) and change from baseline trough FEV_1 at approximately 24 hours after the last dose at study endpoint (12 and 24 weeks). In trial 2, the primary endpoint was change from baseline in weighted FEV_1 (0-24 hours) at week 12.[27]

Fluticasone furoate 100 mcg/vilanterol 25 mcg was superior to placebo for the change from baseline in weighted mean FEV_1 (0-24 hours) and for change from baseline in trough FEV_1 in trial 1. Fluticasone furoate 100 mcg/vilanterol 25 mcg was not superior to fluticasone furoate 100 mcg in this same trial. In trials 2 and 3 fluticasone furoate 100 mcg/vilanterol 25 mcg was superior to fluticasone furoate 100 mcg and fluticasone furoate 200 mcg /vilanterol 25 mcg was superior to fluticasone furoate 200 mcg, respectively, in change from baseline in weighted mean FEV_1 (0-24 hours). In the active comparison trial (n=2019), fluticasone furoate 100 mcg/vilanterol 25 mcg decreased time to first asthma exacerbation compared to fluticasone furoate 100 mcg (HR 0.80, 95% CI, 0.64 to 0.99; p=0.036).[27]

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	

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

Inhaled Corticosteroids (ICS)

Goals:

- Promote use that is consistent with Oregon Asthma Guidelines and the NIH EPR 3 Guidelines on Asthma. See also: http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Asthma/Pages/index.aspx and http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report
- 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:

- Preferred alternatives listed at http://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 do not require PA or a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the 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 (ICD10 J440-J4522, J45901-45998)?	Yes: Go to #7	No: Go to #4

Approval Criteria		
4. Does the patient have a diagnosis of COPD (ICD10 J449), chronic bronchitis (ICD10 J410-418, J42, J440-449) and/or emphysema (ICD10 J439)?	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.
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. 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: *9/15 (KS)*
Implementation: *TBA*

Long-acting Beta-agonists (LABA)

Goals:

- Promote use that is consistent with Oregon Asthma Guidelines and the NIH EPR 3 Guidelines on Asthma. See also: http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Asthma/Pages/index.aspx and http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report
- 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:

- Preferred alternatives listed at http://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 do not require PA or a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the 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 (ICD10 J440-J4522, J45901-45998)?	Yes: Go to #6	No: Go to #4

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Approval Criteria		
4. Does the patient have a diagnosis of COPD (ICD10 J449), chronic bronchitis (ICD10 J410-418, J42, J440-449) and/or emphysema (ICD10 J439)?	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.
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.
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: *9/15 (KS); 5/12; 9/09; 5/09*
Implementation: *8/12; 1/10*

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

Goals:

- Promote use that is consistent with Oregon Asthma Guidelines and the NIH EPR 3 Guidelines on Asthma. See also: http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Asthma/Pages/index.aspx and http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report
- Step-therapy required prior to coverage:
  - Asthma: short-acting beta-agonist and inhaled corticosteroid or moderate to severe persistent asthma.
  - 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 LABA/ICS products

Covered Alternatives:

- Preferred alternatives listed at http://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 do not require PA or a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the 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 (ICD10 J440-J4522, J45901-45998)?	Yes: Go to #7	No: Go to #4

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Approval Criteria		
4. Does the patient have a diagnosis of COPD (ICD10 J449), chronic bronchitis (ICD10 J410-418, J42, J440-449) and/or emphysema (ICD10 J439)?	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.
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 there a documented trial of an inhaled long-acting bronchodilator (anticholinergic or beta-agonist) or does the patient have documented severe (GOLD 3) or very severe (GOLD 4) COPD?	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 documented severe persistent asthma (Step 4 or higher per NIH EPR 3)?	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: *9/15 (KS); 11/14; 11/13; 5/12; 9/09; 2/06*
Implementation: *1/15; 1/14; 9/12; 1/10*

Long-acting Muscarinic Antagonist/Long-acting Beta-agonist Combination (LAMA/LABA)

Goals:

- Promote use that is consistent with Oregon Asthma Guidelines and the NIH EPR 3 Guidelines on Asthma. See also: http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Asthma/Pages/index.aspx and http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report
- Step-therapy required prior to coverage:
  - COPD: short-acting, long-acting bronchodilators (inhaled anticholinergics and beta-agonists) and inhaled corticosteroid. Preferred short-acting, long-acting bronchodilators and inhaled corticosteroids 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:

- All LAMA/LABA products

Covered Alternatives:

- Preferred alternatives listed at http://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 do not require PA or a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	Yes: Inform prescriber of preferred LAMA and LABA products in each class	No: Go to #3

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Approval Criteria		
3. Does the patient have a diagnosis of asthma or reactive airway disease (ICD10 J440-J4522, J45901-45998)?	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
4. Does the patient have a diagnosis of COPD (ICD10 J449), chronic bronchitis (ICD10 J410-418, J42, J440-449) and/or emphysema (ICD10 J439)?	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.
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. Does the patient have an active prescription for an inhaled corticosteroid?	Yes: Go to #7	No: Pass to RPh. Deny; medical appropriateness.
7. Is there a documented trial of an inhaled long-acting bronchodilator (anticholinergic or beta-agonist) or does the patient have documented severe (GOLD 3) or very severe (GOLD 4) COPD?	Yes: Approve for up to 12 months. Stop coverage of all other LAMA and LABA inhalers.	No: Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: *9/15 (KS); 11/14; 11/13; 5/12; 9/09; 2/06*
Implementation: *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 (GOLD 3) or very severe (GOLD 4) COPD?	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
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	No: Pass to RPh. Deny; recommend trial of preferred long-acting bronchodilator and ICS

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

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