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Drug Class Literature Scan: Asthma and COPD Maintenance Medications

Date of Review: November 2017

Date of Last Review: September 2016
Literature Search: 06/01/16 – 09/01/17

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

Conclusions:

- Since the last review, the following evidence has been identified: 3 new guidelines[1–3], 5 new systematic reviews and meta-analyses[4–8], 6 new randomized-controlled studies[9–14], 4 new formulations[15–18] and 2 new indications[19,20]. Important indicators of pharmacological efficacy for asthma and COPD are mortality benefits, hospitalizations, exacerbation, exercise tolerance, symptoms and quality of life. There is no new evidence that has demonstrated a mortality benefit of pharmacotherapy in asthma or COPD patients. The surrogate endpoint of change in FEV_1 is often used in clinical trials to demonstrate efficacy; however, measurements do not always correlate with clinical relevant outcomes. A change in FEV_1 of 100-140 ml is suggested as a minimal clinically relevant change.
- New asthma management guidelines and recommendations by the National Institute for Health and Care Excellence (NICE), 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) and European Respiratory Society/American Thoracic Society (ERS/ATS), in addition to the five high-quality systematic reviews, support our current preferred drug list (PDL) and prior authorization (PA) criteria.[1–3]

ASTHMA

- A high-quality systematic review and meta-analysis found moderate evidence that adding tiotropium to long-acting beta-agonist/inhaled corticosteroid (LABA/ICS) resulted in fewer exacerbations requiring oral corticosteroids compared to LABA/ICS in adult patients with severe asthma; however, the confidence intervals do not rule out that there may be no difference between the groups (OR 0.76; 95% CI, 0.57 to 1.02).[4] There was no significant difference in the number of patients with an exacerbation requiring hospital admission based on an incidence of 2.5% in patients taking tiotropium + LABA/ICS and an incidence of 4.3% in the LABA/ICS group (risk difference -0.01; 95%CI, -0.04 to 0.01).
- A high quality systematic review and meta-analysis compared increased ICS doses and stable ICS doses in children and adult patients with chronic asthma experiencing an exacerbation and found moderate evidence of similar rates of treatment failure (need for oral corticosteroids), odds ratio (OR) 0.89 (95% confidence interval [CI], 0.68 to 1.18).[5] The risk of unscheduled physician visits were similar between treatment strategies, OR 0.96 (95% CI, 0.66 to 1.41), suggesting no clear benefit of either treatment based on low quality of evidence. The incidence of unscheduled acute care, emergency department (ED) visit or hospital admission was 18 per 1000 patients for both groups (OR 0.98; 95% CI, 0.24 to 3.98).[5]

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

- Studies in patients with COPD taking LABA/ICS + tiotropium compared to tiotropium + placebo for at least 6 months were included in a high-quality review. The systematic review and meta-analysis found moderate evidence, based off of two studies with low risk of bias, that mortality occurred in 7 patients taking

combination therapy compared to 4 patients taking tiotropium + placebo (OR 1.80; 95% CI, 0.55 to 5.91). Wide confidence intervals prevent meaningful conclusions. Exacerbations were not analyzed due to a high degree of heterogeneity.[6]

- Long-acting muscarinic antagonists+long-acting beta-agonists (LAMA+LABA) were compared to LABA+ICS in patients with moderate to severe, stable COPD in a high quality systematic review and meta-analysis. Low quality evidence found LABA+LAMA to have less risk of exacerbations compared to LABA+ICS in trials lasting up to 52 weeks (ARR=3%/NNT=33; OR 0.82; 95% CI, 0.70 to 0.96; P=0.01). Pneumonia events occurred 61 times in patients treated with LABA+LAMA compared to 109 events in patients treated with LABA+ICS (ARR=1.2%/number needed to harm [NNH]=83) (low quality of evidence). [7]
- A fair quality, randomized, placebo-controlled study in patients with moderate COPD and an increased risk of cardiovascular disease found no effect of the combination of fluticasone furoate 100mcg/vilanterol 25 mcg on all-cause mortality rates compared to placebo (hazard ratio [HR] 0.88 (95%CI, 0.74 to 1.04; P=0.137).[13]

NEW FORMULATIONS/APPROVALS

- Four new products were approved since the last review. These include fluticasone propionate (Armonair™ RespiClick®) and fluticasone propionate/salmeterol (AirDuo™ RespiClick®) which are copy products of current formulations and beclomethasone dipropionate HFA (Qvar® Redihaler™), which will replace the current Qvar® formulation.[15,16,18] A fourth new product is a 3-drug combination of fluticasone furoate, umeclidinium, and vilanterol (Trelegy Ellipta) which is approved for patients with COPD.[17]
- Tiotropium (Spiriva® Respimat®) received approval for treatment of long-term, once-daily, maintenance treatment of asthma in patients 6 years and older and budesonide and formoterol (Symbicort®) received an indication for maintenance treatment of airflow obstruction and exacerbations in patients with COPD.[19,20]
- The evidence in this scan has high applicability to the Medicaid population. The highest prevalence of COPD is in patients 60 years and older which is older than the average Medicaid patient. No sub-group analyses were available for data specific to Medicaid patients.

Recommendations:

- Recommend no changes to the PDL for asthma and COPD maintenance drugs based on efficacy data.
- Recommend keeping new formulations as non-preferred drugs and subject to PA criteria with corresponding changes to the LAMA/LABA PA criteria to accommodate Trelegy Ellipta based on evidence.
- Recommend removing the coverage of uncomplicated chronic bronchitis from the ICS, LABA, LABA/ICS and LAMA/LABA PA criteria as this is no longer a funded diagnosis.
- No further review or research is needed at this time. No PDL changes were recommended after evaluation of comparative drug costs in executive session.

Previous Conclusions:

- There is low to moderate quality evidence of no *within-class* differences in efficacy or harms for long-acting inhaled (i.e., beta-agonists (LABAs), muscarinic antagonists (LAMAs), or corticosteroids (ICS) and long-acting oral medications (i.e., leukotriene modifiers [LM]) for patients with asthma or COPD.[1] There was insufficient evidence in subgroup populations with asthma or COPD to establish meaningful conclusions on efficacy or harms.[1]

Previous Recommendations:

- The Committee agreed that no further research is needed at this time and recommended no changes to the PMPDP based on the clinical evidence. The Committee recommended continuation of the current clinical PA criteria after amending to add “without COPD” to #3 in the LAMA/LABA criteria. After

comparative cost consideration in executive session the Committee recommended making Ipratropium/Albuterol (Combivent Respimat®) non-preferred while grandfathering current users for 6 months and to make Ventolin® HFA Preferred on the PMPDP.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. 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:

ASTHMA

Cochrane – LAMA Added to Combination LABA and ICS versus LABA/ICS for Adults with Asthma
In adults with asthma, the efficacy of adding a LAMA (tiotropium) to LABA/ICS was studied in a systematic review and meta-analysis.[4] Four double-blind studies lasting at least 12 weeks in duration were included. Patients enrolled in the trials were taking a LABA/ICS and had a mean FEV_1 of 55% of their predicted values, suggesting severe asthma.

Adding tiotropium to LABA/ICS resulted in an exacerbation requiring oral corticosteroids in 27% of patients compared to 33% in patients taking LABA/ICS (OR 0.76; 95% CI, 0.57 to 1.02) over 48 weeks, based on moderate evidence.[4] Imprecision in the effect and wide confidence intervals suggest that no difference between therapies could still exist. There was high quality evidence that there was no clinically significant difference between the quality of life scores, measured by at least a 0.5 difference on the Asthma Quality of Life Questionnaire (AQLA) 1 to 7 point scale, between LABA/ICS and the addition of tiotropium to LABA/ICS, mean score of 5.116 and 5.03, respectively.[4] There was imprecision in the results of risk of serious adverse events when LAMA was added to LABA/ICS and therefore no conclusions could be determined (low-quality evidence). Lung function, measured by trough FEV_1, was 0.07 L higher compared to LABA/ICS, 0.08 L and 0.15 L, respectively. There was insufficient data to determine the effect of LAMA added to LABA/ICS compared LABA/ICS on frequency of hospital admissions.

Cochrane – Increased versus Stable Doses of Inhaled Corticosteroids for Exacerbations of Chronic Asthma in Adults and Children
The effect of two ICS dosing strategies were compared in the management of exacerbations in children and adults.[5] Eight randomized trials comparing increased versus stable doses of ICS studied in patients managing exacerbations at home were included. Children and adults with persistent asthma who were receiving

maintenance ICS were included. Patients (n=1669) had mild to moderate asthma. Studies were found to be at low risk of bias. Seven of the eight studies followed patients for 6-12 months.

Outcomes studied were odds of treatment failure (need for oral corticosteroids), risk of unscheduled physician visits, unscheduled acute care (ED visits or hospital admission), duration of exacerbation and serious adverse events. The odds of treatment failure were similar between patients with increased ICS doses and stable ICS doses with an OR of 0.89 (95% CI, 0.68 to 1.18) (moderate quality evidence).[5] Treatment failure occurred 752 times in patients taking an increased dose of ICS compared to 768 events in patients taking stable ICS doses. Low quality evidence found increased doses of ICS did not reduce the risk of unscheduled physician visits (OR 0.96; 95% CI, 0.66 to 1.41) or acute visits (peto OR 0.98; 95% CI 0.24 to 3.98) compared to stable doses of ICS.[5] The peto OR is an alternative way of pooling data instead of using the traditional Mantel-Haenszel method. The peto OR is appropriate in many scenarios except when the control and treatment groups are significantly different in size, which may introduce bias. The evidence for durations of exacerbations was rated as moderate quality but due to the limitations of only one study providing data, there was insufficient evidence to draw conclusions between groups. Serious and non-serious adverse events were similar between groups based on moderate quality of evidence. Subgroup analyses on the impact of age, time to treatment initiation, doses used, smoking history and the fold increase of ICS on magnitude of effect were not done due to lack of studies.

Cochrane – Vilanterol and Fluticasone Furoate for Asthma

A systematic review and meta-analysis was done to compare the effect of vilanterol (VI) and fluticasone furoate (FF) compared to placebo or other ICS and/or LABA on the outcomes of acute exacerbations (hospital admissions or treatment with oral corticosteroids), health-related quality of life (HRQL) and severe adverse events in children and adults with chronic asthma.[8] Fourteen good-quality studies lasting between two and 78 weeks and enrolling 6641 patients were included. Doses studied were VI and FF 100/25 mcg (7 studies) and three studies of VI and FF 200/25 mcg. Comparators were placebo, FF 25 mcg, VI 100 mcg, fluticasone propionate (FP) 500 mcg twice-daily, fluticasone propionate/salmeterol (FP/SAL) 250/50 mcg twice-daily, FP 250/25 mcg twice-daily and FP/SAL 500/50.

One study found the HRQL to be improved with the use of VI/FF 100/25 mcg compared to placebo based on moderate evidence (mean difference [MD] 0.30; 95% CI, 0.14 to 0.46).[8] FEV_1 was improved with VI/FF compared to placebo with a MD of 0.17 (95% CI, 0.09 to 0.26) based on 2 studies (n= 393) with moderate quality of evidence. Peak expiratory flow was higher in VI/FF compared to placebo based on moderate quality evidence from one study (MD 33.30 L/min; 95% CI, 26.59 to 40.01). Asthma symptoms were lower for VI/FF compared to placebo based on moderate evidence (MD 17.90; 95% CI, 11.95 to 23.85).[8] Only very low quality of evidence was available for the outcomes of exacerbations and serious adverse events (results not estimable). There was insufficient data to determine the difference in efficacy outcomes between VI/FF and FP/SAL.

In conclusion, VI/FF was more effective than placebo for outcomes of lung function and HRQL based on moderate evidence. Evidence on active treatment comparisons was insufficient to draw conclusions.[8]

COPD

Cochrane – Combination of ICS and LABA in Addition to Tiotropium versus Tiotropium or LABA/ICS for COPD

A systematic review and meta-analysis was done to compare the effects of two maintenance treatment regimens in the management of COPD.[6] Two different regimens were compared. One comparison was between tiotropium + LABA/ICS (combined therapy) and tiotropium and the other comparison studied tiotropium

+ LABA/ICS (combined therapy) and LABA/ICS. Studied outcomes were exacerbations, symptoms, quality of life and lung function. Six randomized trials lasting at least three months were identified. Only one of the six studies compared combined therapy to LABA/ICS.

The analysis of two studies at low risk of bias found that there were no differences in mortality between combined therapy compared to tiotropium (OR 1.80; 95% CI, 0.55 to 5.91) based on moderate quality evidence.[6] There were 41 hospitalizations in patients taking combined therapy compared to tiotropium which was associated with 50 events, suggesting no difference between groups with an OR of 0.84 (95% CI, 0.53 to 1.33) (low quality evidence). Analysis of exacerbations could not be analyzed due to a high degree of heterogeneity. The SGRQ was used to measure quality of life and was found to be improved in patients taking combined therapy compared to tiotropium with a MD of -3.46 (95% CI, -5.05 to -1.87) based on four studies lasting up to six months based on low quality of evidence.[6] Lung function was found to be improved with combination therapy but changes were not clinically significant. There was insufficient evidence for exercise tolerance. Analysis of adverse events found no difference between groups for serious adverse events, adverse events and pneumonia.

The one study that evaluated combination therapy compared to LABA/ICS was underpowered and therefore no conclusions were made.[6]

Cochrane – LAMA + LABA versus LABA + ICS for stable COPD

In patients with COPD, a systematic review and meta-analysis compared the effect of LAMA+LABA to LABA+ICS.[7] Patients with moderate to severe COPD and no recent exacerbations in studies lasting at least one month were identified in 11 studies. The exception was one large trial (representing 37% of the participants) which enrolled COPD patients with recent exacerbations. Patients were diagnosed with the following grades of GOLD: Category B (5 studies), Category D (1 study), Category A/B (2 studies) and any category (3 studies). Ten studies were industry funded. Study follow-up was from 6-52 weeks.

The outcome results of the meta-analysis comparison of LAMA+LABA to LABA+ICS are presented in Table 1. Patients taking LAMA + LABA were found to have 1562 exacerbations compared to 1683 events in patients taking LABA/ICS (ARR=3%/NNT=33 studies lasting up to 52 weeks). Improvements in trough FEV_1 were higher with LAMA/LABA compared to LABA/ICS.[7] Quality of life scores were clinically improved for LAMA + LABA, as demonstrated by a 4 point or greater improvement in SGRQ, with LAMA + LABA compared to LABA + ICS. Risk of pneumonia was also found to be lower with LABA + LAMA compared to LABA + ICS (ARR=1.2%/NNH=83).

Table 1. Pooled Results of Meta-analysis Comparison Between LAMA + LABA and LABA + ICS[7]

Treatment	Comparator	Outcome	Results	Evidence Quality
LAMA+LABA	LABA+ICS	Exacerbations	OR 0.82 (95% CI, 0.70 to 0.96; P=0.01)	Low
		Serious Adverse Events	OR 0.91 (95% CI, 0.79 to 1.05, P = 0.18	Moderate
		SGRQ	MD -1.22 (95% CI, -2.52 to 0.07, P = 0.06)	Low
		Trough FEV_1 change from baseline	MD 0.08 L (95% CI, 0.06 to 0.09, P < 0.0001)	Moderate
		Pneumonia	OR 0.57 (95% CI, 0.42 to 0.79, P = 0.0006)	Low
		All-cause death	OR 1.01 (95% CI, 0.61 to 1.67, P = 0.88)	Low
		SGRQ change from baseline of 4 points or greater	OR 1.25 (95% CI, 1.09 to 1.44, P = 0.002)	Moderate

Abbreviations: CI – confidence interval; ICS – inhaled corticosteroid; LABA – long-acting beta-agonist; LAMA – long-acting muscarinic antagonist; MD – mean difference: OR – odds ratio; SGRQ – St. George's Respiratory Questionnaire

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New Guidelines:

NICE – Asthma Management

A draft guidance on the treatment of asthma was published by NICE in 2016.[1] A pharmacological treatment pathway outlines the treatment recommendations based on a review of the evidence. Treatment pathways were divided up by age: adults (over 16 years), children and young people (5-16 years of age) and children (under 5 years of age).

Recommendations

Initial Therapy[1]

1. In *adults* SABA should be offered as reliever therapy with newly diagnosed asthma. SABA treatment should be used with maintenance therapy regimens except maintenance and reliever therapy (MART) regimens.
2. Newly diagnosed *children and young people* should receive SABA as reliever therapy. SABA treatment should be used with maintenance therapy regimens except MART regimens.
3. In *children under 5 years of age* with suspected asthma, SABA should be offered as reliever therapy. SABA should be used with all maintenance therapy regimens.

The above recommendations were consensus based recommendations due to insufficient clinical evidence.

First-*line Prevention Therapy in Patients with Poor Asthma Control*[1]

1. Low-dose ICS should be offered as a first-line maintenance therapy for *adults* with uncontrolled asthma on SABA.
2. *Children and young people* should be offered low-dose ICS as the first-line maintenance therapy that is uncontrolled on SABA alone.
3. An 8-week trial of pediatric moderate dose ICS should be considered in *children under 5* with suspected asthma that is uncontrolled with SABA. Treatment should be reevaluated after 8-weeks.
    a. If symptoms did not improve consider an alternative diagnosis.
    b. If symptoms initially resolved but returned within 4 weeks, consider starting a pediatric low dose ICS for first-line maintenance therapy.
    c. If symptoms returned after 4 weeks of stopping ICS then restart 8-week trial of pediatric moderate dose ICS.
    d. Asthma dose should be confirmed once the child is old enough for testing.

The above recommendations are based on low to very quality of evidence due to bias and imprecision. The exception was evidence for adults which had moderate quality of evidence for reliever use, lung function and quality of life outcomes. There was moderate quality evidence for children and young people for FEV_1, reliever medication and AQLQ. High quality evidence was used for the outcomes of reliever use in children under the age of 5. Lack of evidence in children under 5 for most outcomes caused reliance on consensus and experience driven recommendations.

<u>Escalating Pharmacological Treatment in Patients Poorly Controlled on Low-dose ICS</u>[1]

1. *Adults* with uncontrolled asthma on low-dose ICS as maintenance therapy should be offered a leukotriene receptor antagonist (LTRA) in addition to ICS.
2. In *adults* that remained uncontrolled on combination therapy of low-dose ICS and LTRA, a LABA should be added to ICS and consider the following for LTRA treatment:

a. Consider patient preference on continuing LTRA
b. Evaluate patient response to LTRA

3. Consider a LTRA in combination with low-dose ICS in *children and young people* with uncontrolled asthma on pediatric low-dose ICS maintenance therapy.
4. In *children and young people* who have uncontrolled asthma on pediatric low-dose ICS and an LTRA as maintenance treatment, stop the LTRA and consider adding a LABA to ICS.
5. If *patients younger than 5* are suspected of having uncontrolled asthma on a pediatric low-dose ICS, consider a LTRA in combination with ICS.
6. If *patients younger than 5* continue to have uncontrolled asthma on the above, stop the LTRA refer the child to an asthma specialist.

The evidence for the above recommendations ranged from high quality to very low quality. There was insufficient evidence in children under 5 and limited data in children and young people.

Comparison of ICS + LABA as Preventer and Reliever Therapy Compared to ICS + LABA as Preventer and SABA as Reliever Therapy[1]

1. In *adult patients* who are uncontrolled on low-dose ICS and a LABA, with or without an LTRA, as maintenance therapy, suggest changing the therapy to a MART regimen with low-dose maintenance ICS.
2. If the *adult patient* remains uncontrolled on the above regimen, with or without an LTRA, consider increasing the ICS to a moderate maintenance dose. The patient can continue on the MART regimen or change to a fixed-dose ICS and LABA with a SABA reliever.
3. If asthma is uncontrolled in *children and young people* on pediatric low-dose ICS and a LABA, consider changing them to a MART regimen with pediatric low-dose maintenance ICS.
4. If *children or young people* continue to have uncontrolled asthma on the above, consider increasing the ICS to a pediatric moderate maintenance dose. The patient can continue on MART or change to a fixed dose ICS and LABA with SABA reliever therapy.

The majority of evidence used for the previous recommendation was of moderate or high quality.

Therapy for Patients Who Remain Uncontrolled on Optimal Preventer Therapy Beyond Low-dose ICS[1]

1. In *adults* who are uncontrolled on moderate maintenance ICS with LABA, either as MART or fixed dose regimen, and with or without LTRA, recommend increasing the ICS dose to high maintenance. This should be given as part of a fixed-dose regimen with a SABA reliever.
    a. NICE found low quality of evidence that the addition of LAMA to moderate-strength ICS compared to moderate-strength ICS to have a clinically important benefit on exacerbations based on 1 study and moderate quality evidence of benefit in severe exacerbations. There were no clinically important differences found for quality of life, asthma control, or lung function (moderate to high quality evidence).
2. In *children and young people* with uncontrolled asthma despite pediatric moderate maintenance ICS dose with LABA, either as MART or a fixed dose regimen, consider increasing the ICS to a pediatric high maintenance dose. Recommend in conjunction with a fixed-dose regimen with a SABA.
    a. The quality of evidence for this recommendation ranged from very low to high. The majority of the evidence was of low or moderate quality.

Therapy for children, young people and adults with asthma on ICS preventer therapy or requiring ICS

1. Recommend daily versus intermittent inhaled ICS, if required, to patients with asthma who require ICS maintenance treatment.
    a. Evidence for this recommendation was derived from mostly low or very low quality evidence. High quality evidence was available for treatment of adults but with only one study contributing to each outcome.

GOLD – COPD Guidelines

The GOLD annual update was released in January 2017.[2] Evidence was reviewed and assigned an evidence grade (Table 2). New recommendations pertaining to the assessment and treatment of COPD include refinement of the ABCD tool to rely on respiratory symptoms and exacerbations alone to determine the ABCD category. In patients with stable COPD, assessment of symptoms and risk of exacerbations is recommended to determine the pharmacological treatment approach. One of the changes to the recommendations is the inclusion of escalation and de-escalation strategies which are often required when caring for patients with COPD (Figure 1.).[2]

Table 2. Description of the Level of Evidence. [2]

Evidence Category	Sources of Evidence	Definition
A	• Randomized controlled trials (RCTs) • Rich body of high quality evidence without any significant limitation or bias	- Evidence is from endpoints of well-designed RCTs that provide consistent findings in the population for which the recommendation is made without any important limitations. - Requires high quality evidence from ≥2 clinical trials involving substantial number of subjects, or a single high quality RCT involving substantial numbers of patients without any bias.
B	• Randomized controlled trials (RCTs) with important limitations • Limited body of evidence	- Evidence is from RCTs that include only a limited number of patients, post hoc or subgroup analyses of RCTs or meta-analyses of RCTs. - Also pertains when few RCTs exist, or important limitations are evident (methodological flaws, small numbers, short duration, undertaken in a population that differs from the target population of the recommendation or the results are somewhat inconsistent.
C	• Non-randomized trials • Observational studies	- Evidence is from outcomes of uncontrolled or non-randomized trials or from observational studies.
D	• Panel consensus judgement	- Provision of guidance is deemed valuable but clinical literature addressing the subject is insufficient. - Panel consensus is based on clinical experience or knowledge that does not meet the above stated criteria.

Evidence for Treatment Selection

The management of stable COPD is accomplished through short- and long-acting maintenance therapies. No pharmacological treatment has demonstrated a reduction in the risk of long-term decline in lung function in patients with COPD. Short-acting and long-acting bronchodilator therapy is recommended for patients with COPD. The following recommendations are based on level A evidence for the treatment of stable COPD.[2]

- Inhaled bronchodilators are used for symptom management and given on a regular basis in many patients to prevent or reduce symptoms.
- Improvement in FEV_1 and symptoms has been demonstrated with regular and as-needed use of SABA and SAMA.
- FEV_1 and symptom improvement is greater with combination therapy of SABA and SAMA compared to either medication alone.
- Lung function, dyspnea, health status, and reduced exacerbation rates have been shown to significantly improve with LAMAs and LABAs.
- Combination of LAMA and LABA is more effective than monotherapy at increasing FEV_1 and reducing symptoms.

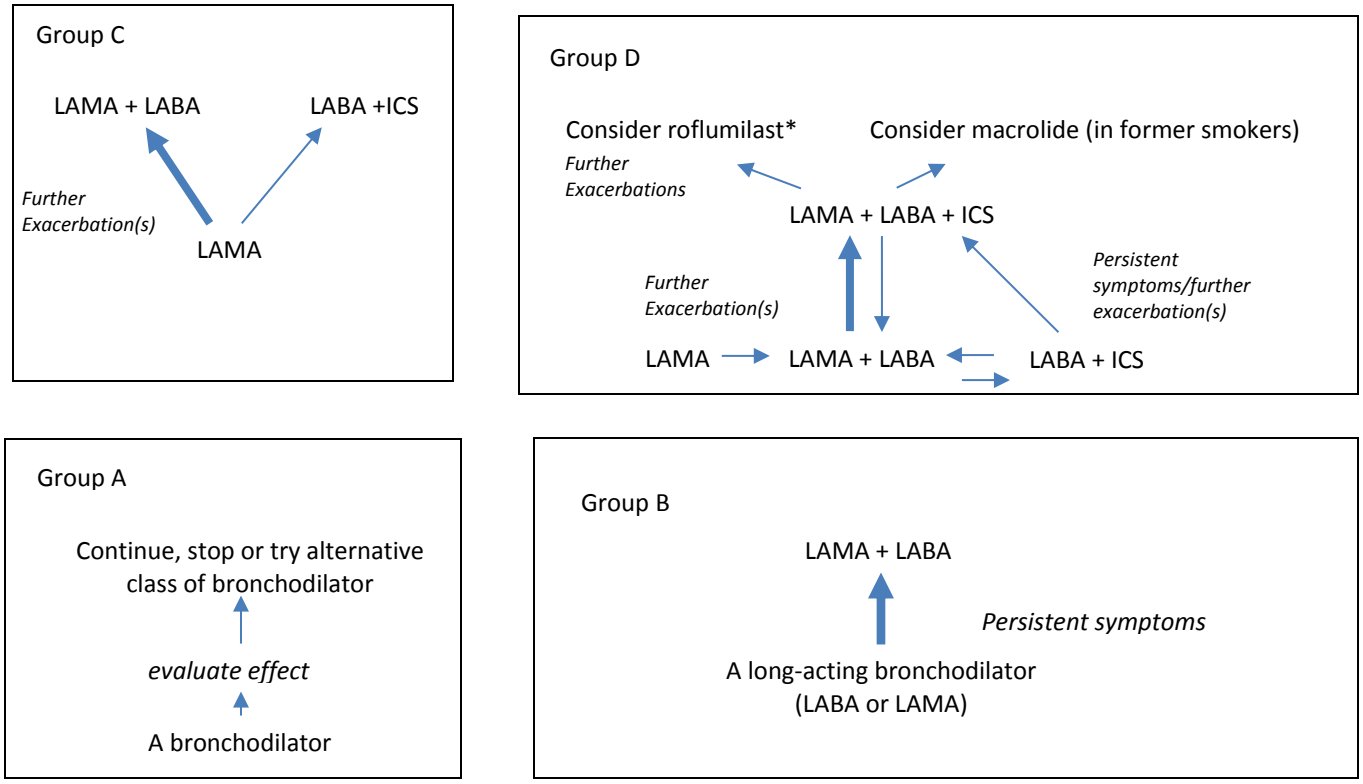
LAMAs have been shown to reduce exacerbation risk (Evidence A) and decrease hospitalizations (Evidence B) more than LABAs. Combinations of LABA and LAMAs have been shown to reduce exacerbations more than monotherapy of either component (Evidence B) and more than ICS/LABA (Evidence B).[2] Tiotropium has been shown to improve the effectiveness of pulmonary rehabilitation by increasing exercise performance (Evidence B). Modest symptomatic benefit has been demonstrated with theophylline in patients with stable COPD based on level B evidence and bronchodilation based on level A evidence.

Author: Kathy Sentena, PharmD Date: November 2017

The effect of ICS on COPD outcomes has lacked precision. GOLD guidelines recommend combination ICS/LABA compared to the individual components based on improved lung function and health status and exacerbation reduction in patients with exacerbations and moderate to severe COPD (Evidence A).[2] Regular use of ICS has been shown to increase the risk of pneumonia in patient with COPD especially in patients with severe COPD (Evidence A). Improvement in lung function, symptoms and health status have been demonstrated with triple therapy with ICS/LAMA/LABA (Evidence A) compared to ICS/LABA or LAMA monotherapy. Reduced risk of exacerbations was found with triple therapy ICS/LAMA/LABA compared to ICS/LABA or LAMA monotherapy (Evidence B).

The GOLD guidelines have some methodological issues that limit interpretation and application of the clinical evidence. The recommendations are given an evidence grade based on the source of the evidence but strength of the evidence is not provided. There is no objective determinant for the quantification of symptoms and exacerbations to determine escalation and de-escalation of therapy. While funding of the guideline comes from sales of the GOLD documents, a statement of any conflicts of interest with committee members was not available.

Figure 1. Treatment Algorithms by GOLD Grade[2]



* If FEV_1 < 50% predicated and patient has chronic bronchitis
Thick arrows = preferred treatment

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ERS/ATS – Prevention of COPD Exacerbations

The ERS/ATS published guidelines on preventing COPD exacerbations in 2017.[3] Literature was systematically reviewed and the evidence was graded using the GRADE approach. Recommendations pertaining to the role of maintenance medications in the prevention of COPD exacerbations were as follows:

1. In patients with moderate to severe airflow obstruction and a history of one or more COPD exacerbation during the previous year, the guidelines recommend LAMA over LABA monotherapy to prevent future exacerbations (strong recommendation, moderate quality of evidence).

The recommendation was based off of meta-analysis data that found a risk of a moderate to severe COPD exacerbation in 30.9% of LAMA treated patients compared 34.6% of LABA treated (RR 0.89; 95% CI, 0.85 to 0.94).[3] One trial found the risk of hospitalization to be lower with LAMA compared to LABA, 7.1% versus 9.2%, respectively (RR 0.77; 95%CI, 0.66 to 0.90). There were no significant differences in adverse events between LAMA and LABA treated patients.

New Formulations/Indications:

Beclomethasone: The inhaled corticosteroid beclomethasone dipropionate HFA (Qvar® Redihaler™) was approved for the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older at a dose of 40 or 80 mcg twice daily, which is to replace the current formulation of Qvar® inhaler.[18] Approval was based off of one 12-week, randomized, placebo-controlled, parallel-group study in patients 4-11 years of age (n=568) with persistent symptomatic asthma despite treatment with non-corticosteroid or low dose ICS (with or without LABA). Beclomethasone Redihaler 40 or 80 mcg, beclomethasone MDI 40 or 80 mcg or placebo was given as one inhalation twice daily. Patients 4-5 years old who were unable to perform spirometry were included in the safety population only. The primary endpoint, change from baseline in trough percent predicted FEV_1 area under the effect curve (AUEC) (0-12 weeks) was not statistically different between beclomethasone and placebo. Change in weekly average of daily morning peak expiratory flow (PEF, L/min) over the 12-week period was 11.3 (95% CI, 5.58 to 17.06) for beclomethasone 80 mcg/day and 8.5 (95% CI, 2.71 to 14.24) for beclomethasone 180 mcg/day which was nominally significant.[18]

Fluticasone propionate and fluticasone propionate and salmeterol: A copy of Flovent Diskus (fluticasone) and Advair (fluticasone/salmeterol) were approved by the FDA in January 2017 to be marketed by Teva Pharmaceuticals called Armonair™ RespiClick® and AirDuo™ RespiClick®, respectively.[15,16] Both products were studied together for the approval of treatment of asthma in patients aged 12 years and older. Recommended dosing for fluticasone is based on prior asthma therapy and available via one inhalation twice daily in concentrations of 55 mcg, 113 mcg and 232 mcg. The combination fluticasone/salmeterol combination is available as one inhalation twice daily in 3 concentrations: 55/14 mcg, 113/14 mcg, or 232/14 mcg.

Approval for both products was based on 2 phase 3, double-blind, parallel-group, 12-week studies in adolescents and adults with asthma not controlled on their current asthma regimen. Studies compared fluticasone/salmeterol 55/14 mcg and 113/14 mcg (1 inhalation twice daily) to fluticasone 55 mcg and 113 mcg and placebo in the first study. The second study compared fluticasone propionate 113 mcg and 232 mcg (1 inhalation twice daily) to fluticasone/salmeterol 113/14 mcg and 232/14 mcg (1 inhalation twice daily) and placebo. The primary endpoint was change in baseline trough FEV_1 at week 12 and standardized baseline-adjusted FEV_1 AUC 0-12h at week 12 for a subset of patients with post-dose serial spirometry.

In the first study the least squares (LS) mean change of 0.319 L was seen with fluticasone/salmeterol 55/14 mcg, LS mean change of 0.315 L with fluticasone/salmeterol 113/14 mcg and LS mean change of 0.175 L with fluticasone 55 mcg and a LS mean change of 0.204 L for fluticasone 113 mcg. The mean differences are presented in Table 3. The results of the second study were similar to study 1 and are presented in Table 4.

Table 3. Mean Difference Between Treatments in Study 1 based on the Primary Endpoint of Change in Trough FEV_1 at Week 12.[15,16]

Treatment	Comparator	Estimated Mean Difference
Fluticasone/salmeterol 55/14 mcg	Placebo	0.266 L (95% CI, 0.172 to 0.360)
Fluticasone 55 mcg	Placebo	0.119 L (95% CI, 0.025 to 0.212)*
Fluticasone/salmeterol 55/14 mcg	Fluticasone 55 mcg	0.147 (95% CI, 0.053 to 0.242)*
Fluticasone/salmeterol 113/14 mcg	Placebo	0.262 L (95% CI, 0.168 to 0.356)
Fluticasone 113 mcg	Placebo	0.151 L (95% CI, 0.057 to 0.244)*
Fluticasone/salmeterol 113/14 mcg	Fluticasone 113 mcg	0.111 L (95% CI, 0.017 to 0.206)*

* Results statistically significant (p-value not provided) for treatment

Table 4. Mean Difference Between Treatments in Study 2 based on the Primary Endpoint of Change in Trough FEV_1 at Week 12.[15,16]

Treatment	Comparator	Estimated Mean Difference
Fluticasone/salmeterol 113/14 mcg	Placebo	0.274 L (95% CI, 0.189 to 0.360)
Fluticasone 113 mcg	Placebo	0.123 L (95% CI, 0.038 to 0.208)*
Fluticasone/salmeterol 113/14 mcg	Fluticasone 113 mcg	0.152 (95% CI, 0.066 to 0.237)*
Fluticasone/salmeterol 232/14 mcg	Placebo	0.276 L (95% CI, 0.191 to 0.361)
Fluticasone 232 mcg	Placebo	0.183 L (95% CI, 0.098 to 0.268)*
Fluticasone/salmeterol 232/14 mcg	Fluticasone 232 mcg	0.093 (95% CI, 0.009 to 0.178)*

* Results statistically significant (p-value not provided) for treatment

Tiotropium: A new indication was approved for tiotropium bromide (Spiriva® Respimat®) in early 2017 for the long-term, once-daily, maintenance treatment of asthma in patients 6 years and older.[20] The recommended dose is 2 inhalations of the 1.25 mcg dose once-daily. Approval of the use of tiotropium in pediatric patients was based on two double-blind, randomized, placebo-controlled studies lasting 12 and 48 weeks. Patients treated for 12-weeks had severe asthma and were using an ICS plus one or more controller medication. The 48-week study was in patients with moderate asthma and on at least an ICS for maintenance therapy. The primary outcome was change in pre-treatment baseline in peak FEV_1, 0-3 h. The mean age was 9 years, 68% were male, and 87% were Caucasian. The results for the studies were imprecise. The 12-week study found no significant difference between tiotropium 2.5 mcg and placebo with a mean difference of 0.04 L (95% CI, -0.03 to 0.10) at 12 weeks. In the 48-week study the primary endpoint was measured at week 24 and found a mean difference of 0.17 L (95% CI, 0.11 to 0.23) between tiotropium 2.5 mcg and placebo.

Budesonide and formoterol fumarate dehydrate: The combination ICS/LABA product of budesonide and formoterol (Symbicort®) received approval for the long-term maintenance treatment of asthma in patients 6 years of age and older.[19] This approval was based on one 12-week efficacy and safety study in patients 6 to less than 12 years of age. The study was a randomized, double-blind, multicenter study in 184 pediatric patients. The result of the primary efficacy endpoint, change from baseline in 1-hour post-dose FEV_1, was improved by 0.28 L in patients receiving budesonide/formoterol 80/4.5 mcg compared to a change of 0.17 L in patients receiving budesonide 80 mcg (MD 0.12 L; 95% CI, 0.03 to 0.20; p=0.006).

This combination also received an indication to support the use of budesonide/formoterol (B/F) to reduce exacerbations in patients with COPD.[19] Two, randomized, double-blind, placebo-controlled studies were used for evidence. In the first study patients were a mean age of 64 years with a mean post-bronchodilator percent predicted normal FEV_1 of48.7%. The study evaluated B/F 160/4.5 compared to formoterol 4.5, 2 inhalations twice daily for 6 months. Patients randomized to B/F 160/4.5 had an annual rate estimate of 0.94 exacerbations compared to formoterol which had 1.27 (rate ratio of 0.74; 95% CI, 0.61 to 0.91). In a second study comparing B/F 160/4.5 to formoterol 4.5 mcg, 2 inhalations twice daily, for 12 months the patients were a mean age of 63 years with a mean post-bronchodilator percent predicted normal FEV_1 of 37.8%. Patients treated with combination therapy had an annual rate estimate of exacerbations of 0.68 compared to 1.05 in the formoterol 4.5 mcg group (rate ratio 0.65; 95% CI, 0.53 to 0.80).

Fluticasone furoate, umeclidinium and vilanterol: A new 3-drug combination product, of previously reviewed therapies, was recently approved by the FDA. The fluticasone furoate, umeclidinium and vilanterol (FF/U/V) (Trelegy Ellipta) is indicated for the long-term, once-daily maintenance treatment for patients with COPD, including chronic bronchitis and/or emphysema, who are on a fixed-dose combination of fluticasone furoate and vilanterol for airflow obstruction and reducing exacerbations in whom additional treatment of airflow obstruction is desired or for patients already receiving umeclidinium and a fixed-dose combination of fluticasone furoate and vilanterol. Clinical studies found a difference of 124 ml increase in trough FEV_1 from baseline in patients receiving umeclidinium + FF/VI compared to patients receiving placebo + FF/VI in one study and a difference of 122 ml in a second study both lasting 12-weeks.

New FDA Safety Alerts:
No new safety updates.

Author: Kathy Sentena, PharmD

Date: November 2017

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17. Trelegy Ellipta Prescribing Information. GlaxoSmithKline Research. Triangle Park, NC; 2017.

18. Qvar Redialed Prescribing Information. Teva Respiratory, LLC. Frazer, PA: 2017.

19. Symbicort Prescribing Information. AstraZeneca Pharmaceuticals LP, Wilmington, DE; 2017.

20. Spiriva Respimat Prescribing Information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT; 2017.

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Appendix 1: Current Preferred Drug List

Long-acting Anticholinergics (LAMA)

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INHALATION	CAP W/DEV	SPIRIVA	TIOTROPIUM BROMIDE	**Y**
INHALATION	AER POW BA	TUDORZA PRESSAIR	ACLIDINIUM BROMIDE	N
INHALATION	BLST W/DEV	INCRUSE ELLIPTA	UMECLIDINIUM BROMIDE	N
INHALATION	CAP W/DEV	SEEBRI NEOHALER	GLYCOPYRROLATE	N
INHALATION	MIST INHAL	SPIRIVA RESPIMAT	TIOTROPIUM BROMIDE	N

Inhaled Corticosteroids (ICS)

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	AMPUL-NEB	BUDESONIDE	BUDESONIDE	N
INHALATION	AMPUL-NEB	PULMICORT	BUDESONIDE	N
INHALATION	BLST W/DEV	ARNUITY ELLIPTA	FLUTICASONE FUROATE	N
INHALATION	HFA AER AD	ALVESCO	CICLESONIDE	N
INHALATION	HFA AER AD	ASMANEX HFA	MOMETASONE FUROATE	N

Long-acting Bronchodilators (LABA)

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

LAMA/LABA

ROUTE	FORMULATION	BRAND	GENERIC	PDL

INHALATION	BLST W/DEV	ANORO ELLIPTA	UMECLIDINIUM BRM/VILANTEROL TR	N
INHALATION	MIST INHAL	STIOLTO RESPIMAT	TIOTROPIUM BR/OLODATEROL HCL	N
INHALATION	PWD INHAL	UTIBRON NEOHALER	INDACATEROL/GLYCOPYRROLATE	N
INHALATION	MIST INHAL	BEVESPI AEROSPHERE	GLYCOPYRROLATE/FORMOTEROL	N

ICS/LABA

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 FUMARATE	**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
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: New Comparative Clinical Trials

A total of 489 citations were manually reviewed from the initial literature search. After further review, 483 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 6 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Stempel, et al[10] RCT, DB, PG	Fluticasone propionate + Salmeterol (100/50 mcg or 250/50 mcg) Vs. Fluticasone (100 or 200 mcg) 26 weeks	Children (4-11 years) with asthma requiring daily maintenance therapy and a history of asthma exacerbations N=6208	First serious asthma-related event (death, endotracheal intubation, or hospitalization)	Fluticasone/Salmeterol: 27 (0.9%) Fluticasone: 21 (0.7%) HR 1.28 (95% CI, 0.73 to 2.27) P=0.006 for non-inferiority
Hamelmann, et al[14] RCT, DB, PC, PG	Tiotropium 2.5 or 5.0 mcg * Vs. Placebo* * With ICS ± LRA 24 weeks	Adolescent patients (12-17 years) with moderate symptomatic asthma N=398	Peak $FEV_{1(0\text{-}3h)}$ Improvement at 24 weeks	Tiotropium 2.5 mcg: 484 mL Tiotropium 5.0 mcg: 524 mL Placebo: 350 mL Tiotropium 2.5 mcg vs. Placebo: 134 mL (95% CI, 34-234; P<0.01) Tiotropium 5.0 mcg vs. Placebo: 174 mL (95% CI, 76-272; P<0.001)
Vestbo, et al[13] (SUMMIT) RCT, DB, PC, PG	Fluticasone furoate 100 mcg Vs. Vilanterol 25 mcg Vs.	Adult patients (40-80 years) with moderate COPD and heightened CV risk N=16,485	All-cause mortality	Fluticasone furoate: 251 (6.1%) Vilanterol: 265 (6.4%) Combination Therapy: 246 (6.0%) Placebo: 275 (6.7%) Fluticasone vs. Placebo: HR 0.91 (95%CI, 0.77 to 1.08; P=0.284)

	Fluticasone furoate 100 mcg + Vilanterol 25 mcg Vs. Placebo * All given as one inhalation daily Median follow-up 1.8 years			Vilanterol vs. Placebo: HR 0.96 (95%CI, 0.81 to 1.14; P=0.655) Combination Therapy vs. Placebo: HR 0.88 (95%CI, 0.74 to 1.04; P=0.137)
Singh, et al[11] (TRILOGY) RCT, DB, PG	Beclomethasone dipropionate + formoterol fumarate + glycpyrronium bromide (BDP/FF/GB)* Vs. Beclomethasone dipropionate + formoterol fumarate (BDP/FF) * As a single inhaler 52 weeks	Adult patients 40 year and older with COPD, post-bronchodilator FEV_1 of less than 50%, one or more moderate-to-severe COPD exacerbation in the previous 12 months, COPD Assessment Test Score of 10 or more and Baseline Dyspnea Index focal score of 10 or less. N=1368	Three co-primary endpoints were pre-dose FEV_1, 2 h post-dose FEV_1 and Transition Dyspnea Index (TDI) focal score all measured at week 26	Pre-dose FEV_1: BDP/FF/GB: 0.082 L BDP/FF: 0.001 L MD 0.081 L (95% CI, 0.052 to 0.109; p<0.001) 2-h Post-dose FEV_1: BDP/FF/GB: 0.261 L BDP/FF: 0.145 L MD 0.117 : (0.086 to 0.147; p<0.001) Mean TDI Focal Scores*: BDP/FF/GB: 1.71 BDP/FF: 1.50 MD 0.21 (95% CI, -0.08 to 0.51; p=0.160)
Stempel, et al[12] (AUSTRI) RCT, DB, PG	Fluticasone + salmeterol Vs.	Adolescents and adults (12 and older) with persistent asthma and	First serious asthma-related event (death, endotracheal intubation, or hospitalization).	Fluticasone/Salmeterol: 36 events Fluticasone: 38 events HR 1.03 (95% CI, 0.64 to 1.66; P=0.003 for noninferiority)

	Fluticasone 26 weeks	history of severe asthma exacerbation within the last year but not previous month		
Wedzicha, et al[9] (FLAME) RCT, DB, DD, PG	Indacaterol 110 mcg + glycopyrronium 50 mcg once daily (I/G) Vs. Salmeterol 50 mcg + fluticasone 500 mcg twice daily (S/F) 52 weeks	Patients with a history of COPD and at least one exacerbation during the previous year N=3,362	Annual rate of COPD exacerbations	I/G: 3.59 S/F: 4.03 RR 0.89 (95% CI, 0.83 to 0.96; P=0.003 for noninferiority)

Abbreviations: CV – cardiovascular risk; DB – double-blind: DD – double-dummy; FEV_1- forced expiratory flow volume in one second; ICS – inhaled corticosteroid; LRA – leukotriene receptor antagonist; PC – placebo-controlled; PG – parallel group; RCT - randomized clinical trial.
*TDI – a score of 1 or more is considered the minimal clinically important difference.

Appendix 3: Abstracts of Comparative Clinical Trials

Safety of Adding Salmeterol to Fluticasone Propionate in Children with Asthma.
Stempel DA, Szefler SJ, Pedersen S, Zeiger RS, Yeakey AM, Lee LA, Liu AH, Mitchell H, Kral KM, Raphiou IH, Prillaman BA, Buaron KS, Yun Kirby S, Pascoe SJ; VESTRI Investigators.

BACKGROUND: Long-acting beta-agonists (LABAs) have been shown to increase the risk of asthma-related death among adults and the risk of asthma-related hospitalization among children. It is unknown whether the concomitant use of inhaled glucocorticoids with LABAs mitigates those risks. This trial prospectively evaluated the safety of the LABA salmeterol, added to fluticasone propionate, in a fixed-dose combination in children. METHODS: We randomly assigned, in a 1:1 ratio, children 4 to 11 years of age who required daily asthma medications and had a history of asthma exacerbations in the previous year to receive fluticasone propionate plus salmeterol or fluticasone alone for 26 weeks. The primary safety end point was the first serious asthma-related event (death, endotracheal intubation, or hospitalization), as assessed in a time-to-event analysis. The statistical design specified that noninferiority would be shown if the upper boundary of the 95% confidence interval of the hazard ratio for the primary safety end point was less than 2.675. The main efficacy end point was the first severe asthma exacerbation that led to treatment with systemic glucocorticoids, as assessed in a time-to-event analysis. RESULTS: Among the 6208 patients, 27 patients in the fluticasone-salmeterol group and 21 in the fluticasone-alone group had a serious asthma-related event (all were hospitalizations); the hazard ratio with fluticasone-salmeterol versus fluticasone alone was 1.28 (95% confidence interval [CI], 0.73 to 2.27), which showed the noninferiority of fluticasone-salmeterol (P=0.006). A total of 265 patients (8.5%) in the fluticasone-salmeterol group and 309 (10.0%) in the fluticasone-alone group had a severe asthma exacerbation (hazard ratio, 0.86; 95% CI, 0.73 to 1.01). CONCLUSIONS: In this trial involving children with asthma, salmeterol in a fixed-dose combination with fluticasone was associated with the risk of a serious asthma-related event that was similar to the risk with fluticasone alone.

Tiotropium add-on therapy in adolescents with moderate asthma: A 1-year randomized controlled trial.
Hamelmann E, Bateman ED, Vogelberg C, Szefler SJ, Vandewalker M, Moroni-Zentgraf P, Avis M, Unseld A, Engel M, Boner AL.

BACKGROUND: Results from phase III clinical trials in adults and phase II clinical trials in children and adolescents demonstrate that tiotropium is an effective treatment when added to inhaled corticosteroid (ICS) maintenance therapy. OBJECTIVE: We sought to assess the efficacy and safety of once-daily tiotropium Respimat added to ICSs with or without a leukotriene receptor antagonist in a phase III trial in adolescent patients with moderate symptomatic asthma. METHODS: In this 48-week, double-blind, placebo-controlled, parallel-group study, 398 patients aged 12 to 17 years were randomized to receive 5 μg (2 puffs of 2.5 μg) or 2.5 μg (2 puffs of 1.25 μg) of once-daily tiotropium or placebo (2 puffs) administered through the Respimat device every evening, each as add-on treatment to ICS background therapy, with or without a leukotriene receptor antagonist; long-acting β2-agonist therapy was not permitted during the study. RESULTS: Improvement in peak FEV1 within 3 hours after dosing at 24 weeks (primary end point) was statistically significant with both tiotropium doses compared with placebo: 5 μg of tiotropium, 174 mL (95% CI, 76-272 mL); 2.5 μg of tiotropium, 134 mL (95% CI, 34-234 mL). Significant improvements in trough FEV1 at week 24 (a secondary end point) were observed with the 5-μg dose only. Trends for improvement in asthma control and health-related quality of life over the 48-week treatment period were observed. CONCLUSIONS: Once-daily tiotropium significantly improved lung function and was safe and well tolerated when added to at least ICS maintenance therapy in adolescent patients with moderate symptomatic asthma. Larger responses were observed with the 5-μg tiotropium dose.

Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial.

Vestbo J, Anderson JA, Brook RD, Calverley PM, Celli BR, Crim C, Martinez F, Yates J, Newby DE; SUMMIT Investigators.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) often coexists with cardiovascular disease. Treatments for airflow limitation might improve survival and both respiratory and cardiovascular outcomes. The aim of this study was to assess whether inhaled treatment with a combined treatment of the corticosteroid, fluticasone furoate, and the long-acting β agonist, vilanterol could improve survival compared with placebo in patients with moderate COPD and heightened cardiovascular risk. METHODS: In this double-blind randomised controlled trial (SUMMIT) done in 1368 centres in 43 countries, eligible patients were aged 40-80 years and had a post-bronchodilator forced expiratory volume in 1 s (FEV1) between 50% and 70% of the predicted value, a ratio of post-bronchodilator FEV1 to forced vital capacity (FVC) of 0·70 or less, a smoking history of at least 10 pack-years, and a score of 2 or greater on the modified Medical Research Council dyspnoea scale. Patients had to have a history, or be at increased risk, of cardiovascular disease. Enrolled patients were randomly assigned (1:1:1:1) through a centralised randomisation service in permuted blocks to receive once daily inhaled placebo, fluticasone furoate (100 µg), vilanterol (25 µg), or the combination of fluticasone furoate (100 µg) and vilanterol (25 µg). The primary outcome was all-cause mortality, and secondary outcomes were on-treatment rate of decline in forced expiratory volume in 1 s (FEV1) and a composite of cardiovascular events. Safety analyses were performed on the safety population (all patients who took at least one dose of study drug) and efficacy analyses were performed on the intention-to-treat population (safety population minus sites excluded with Good Clinical Practice violations). This study is registered with ClinicalTrials.gov, number NCT01313676. FINDINGS: Between Jan 24, 2011, and March 12, 2014, 23 835 patients were screened, of whom 16 590 were randomised. 16 485 patients were included in the intention-to-treat efficacy population; 4111 in the placebo group, 4135 in the fluticasone furoate group, 4118 in the vilanterol group, and 4121 in the combination group. Compared with placebo, all-cause mortality was unaffected by combination therapy (hazard ratio [HR] 0·88 [95% CI 0·74-1·04]; 12% relative reduction; p=0·137) or the components (fluticasone furoate, HR 0·91 [0·77-1·08]; p=0·284; vilanterol, 0·96 [0·81-1·14]; p=0·655), and therefore secondary outcomes should be interpreted with caution. Rate of decline in FEV1 was reduced by combination therapy (38 mL per year [SE 2·4] vs 46 mL per year [2·5] for placebo, difference 8 mL per year [95% CI 1-15]) with similar findings for fluticasone furoate (difference 8 mL per year [95% CI 1-14]), but not vilanterol (difference -2 mL per year [95% CI -8 to 5]). Combination therapy had no effect on composite cardiovascular events (HR 0·93 [95% CI 0·75-1·14]) with similar findings for fluticasone furoate (0·90 [0·72-1·11]) and vilanterol (0·99 [0·80-1·22]). All treatments reduced the rate of moderate and severe exacerbation. No reported excess risks of pneumonia (5% in the placebo group, 6% in the combination group, 5% in the fluticasone furoate group, and 4% in the vilanterol group) or adverse cardiac events (17% in the placebo group, 18% in the combination group, and 17% in the fluticasone furoate group, and 17% in the vilanterol group) were noted in the treatment groups.INTERPRETATION: In patients with moderate COPD and heightened cardiovascular risk, treatment with fluticasone furoate and vilanterol did not affect mortality or cardiovascular outcomes, reduced exacerbations, and was well tolerated. Fluticasone furoate, alone or in combination with vilanterol, seemed to reduce FEV1 decline.

Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial.

Singh D, Papi A, Corradi M, Pavlišová I, Montagna I, Francisco C, Cohuet G, Vezzoli S, Scuri M, Vestbo J.

BACKGROUND: Few data are available for the efficacy of "triple therapy" with two long-acting bronchodilators and an inhaled corticosteroid in chronic obstructive pulmonary disease (COPD). We designed this study to assess efficacy of single-inhaler combination of an extra fine formulation of beclometasone dipropionate, formoterol fumarate, and glycopyrronium bromide (BDP/FF/GB) in COPD compared with beclometasone dipropionate and formoterol fumarate (BDP/FF) treatment. METHODS: TRILOGY was a randomised, parallel group, double-blind, active-controlled study done in 159 sites across 14 countries. The sites were a mixture of primary, secondary, and tertiary care providers, and specialist investigation units. Eligible patients with COPD had post-bronchodilator forced expiratory volume in 1 s (FEV1) of lower than 50%, one or more moderate-to-severe COPD exacerbation in the previous 12 months, COPD Assessment Test total score of 10 or more, and a Baseline Dyspnea Index focal score of 10 or less. Patients who met the inclusion and exclusion criteria at screening entered a 2-week open-label run-in period where they received beclometasone dipropionate (100 µg) and formoterol fumarate (6 µg) in two actuations twice daily. Patients were then randomly assigned (1:1) with an interactive response technology system to either continue BDP (100 µg) and FF (6 µg) or step-up to BDP (100 µg), FF (6 µg), and GB (12·5 µg) in two actuations twice daily for 52 weeks via pressurised metered-dose inhaler. The three co-primary endpoints were pre-dose FEV1, 2-h post-dose FEV1, and Transition Dyspnea Index (TDI) focal score, all measured at week 26 in the intention-to-treat population (all patients who were randomly assigned and received at least one dose of study drug and had at least one post-baseline efficacy assessment). Safety outcomes were measured in the safety population (all patients who were randomly assigned and received at least one dose of study drug). Secondary endpoints included moderate-to-severe COPD exacerbation rate over 52 weeks. This study is registered with ClinicalTrials.gov number NCT01917331. FINDINGS: Between March 21, 2014, and Jan 14, 2016, 1368 patients received either BDP/FF/GB (n=687) or BDP/FF (n=681). At week 26, BDP/FF/GB improved pre-dose FEV1 by 0·081 L (95% CI 0·052-0·109; p<0·001) and 2-h post-dose FEV1 by 0·117 L (0·086-0·147; p<0·001) compared with BDP/FF. Mean TDI focal scores at week 26 were 1·71 for BDP/FF/GB and 1·50 for BDP/FF, with a difference of 0·21 (95% CI -0·08 to 0·51; p=0·160). Adjusted annual moderate-to-severe exacerbation frequencies were 0·41 for BDP/FF/GB and 0·53 for BDP/FF (rate ratio 0·77 [95% CI 0·65-0·92]; p=0·005), corresponding to a 23% reduction in exacerbations with BDP/FF/GB compared with BDP/FF. Adverse events were reported by 368 (54%) patients with BDP/FF/GB and 379 (56%) with BDP/FF. One serious treatment-related adverse event occurred (atrial fibrillation) in a patient in the BDP/FF/GB group. INTERPRETATION: We provide evidence for the clinical benefits of stepping up patients with COPD from an inhaled corticosteroid/long-acting β2-agonist combination treatment to triple therapy using a single inhaler.

Serious Asthma Events with Fluticasone plus Salmeterol versus Fluticasone Alone.

Stempel DA, Raphiou IH, Kral KM, Yeakey AM, Emmett AH, Prazma CM, Buaron KS, Pascoe SJ; AUSTRI Investigators.

BACKGROUND: The safe and appropriate use of long-acting beta-agonists (LABAs) for the treatment of asthma has been widely debated. In two large clinical trials, investigators found a potential risk of serious asthma-related events associated with LABAs. This study was designed to evaluate the risk of administering the LABA salmeterol in combination with an inhaled glucocorticoid, fluticasone propionate. METHODS: In this multicenter, randomized, double-blind trial, adolescent and adult patients (age, ≥12 years) with persistent asthma were assigned to receive either fluticasone with salmeterol or fluticasone alone for 26 weeks. All the patients had a history of a severe asthma exacerbation in the year before randomization but not during the previous month. Patients were excluded from the trial if they had a history of life-threatening or unstable asthma. The primary safety end point was the first serious asthma-related event (death, endotracheal intubation, or hospitalization). Noninferiority of fluticasone-salmeterol to fluticasone alone was defined as an upper boundary of the 95%

confidence interval for the risk of the primary safety end point of less than 2.0. The efficacy end point was the first severe asthma exacerbation. RESULTS: Of 11,679 patients who were enrolled, 67 had 74 serious asthma-related events, with 36 events in 34 patients in the fluticasone-salmeterol group and 38 events in 33 patients in the fluticasone-only group. The hazard ratio for a serious asthma-related event in the fluticasone-salmeterol group was 1.03 (95% confidence interval [CI], 0.64 to 1.66), and noninferiority was achieved (P=0.003). There were no asthma-related deaths; 2 patients in the fluticasone-only group underwent asthma-related intubation. The risk of a severe asthma exacerbation was 21% lower in the fluticasone-salmeterol group than in the fluticasone-only group (hazard ratio, 0.79; 95% CI, 0.70 to 0.89), with at least one severe asthma exacerbation occurring in 480 of 5834 patients (8%) in the fluticasone-salmeterol group, as compared with 597 of 5845 patients (10%) in the fluticasone-only group (P<0.001). CONCLUSIONS: Patients who received salmeterol in a fixed-dose combination with fluticasone did not have a significantly higher risk of serious asthma-related events than did those who received fluticasone alone. Patients receiving fluticasone-salmeterol had fewer severe asthma exacerbations than did those in the fluticasone-only group.

Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD.
Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, Thach C, Fogel R, Patalano F, Vogelmeier CF; FLAME Investigators.

BACKGROUND: Most guidelines recommend either a long-acting beta-agonist (LABA) plus an inhaled glucocorticoid or a long-acting muscarinic antagonist (LAMA) as the first-choice treatment for patients with chronic obstructive pulmonary disease (COPD) who have a high risk of exacerbations. The role of treatment with a LABA-LAMA regimen in these patients is unclear. METHODS: We conducted a 52-week, randomized, double-blind, double-dummy, noninferiority trial. Patients who had COPD with a history of at least one exacerbation during the previous year were randomly assigned to receive, by inhalation, either the LABA indacaterol (110 µg) plus the LAMA glycopyrronium (50 µg) once daily or the LABA salmeterol (50 µg) plus the inhaled glucocorticoid fluticasone (500 µg) twice daily. The primary outcome was the annual rate of all COPD exacerbations. RESULTS: A total of 1680 patients were assigned to the indacaterol-glycopyrronium group, and 1682 to the salmeterol-fluticasone group. Indacaterol-glycopyrronium showed not only noninferiority but also superiority to salmeterol-fluticasone in reducing the annual rate of all COPD exacerbations; the rate was 11% lower in the indacaterol-glycopyrronium group than in the salmeterol-fluticasone group (3.59 vs. 4.03; rate ratio, 0.89; 95% confidence interval [CI], 0.83 to 0.96; P=0.003). The indacaterol-glycopyrronium group had a longer time to the first exacerbation than did the salmeterol-fluticasone group (71 days [95% CI, 60 to 82] vs. 51 days [95% CI, 46 to 57]; hazard ratio, 0.84 [95% CI, 0.78 to 0.91], representing a 16% lower risk; P<0.001). The annual rate of moderate or severe exacerbations was lower in the indacaterol-glycopyrronium group than in the salmeterol-fluticasone group (0.98 vs. 1.19; rate ratio, 0.83; 95% CI, 0.75 to 0.91; P<0.001), and the time to the first moderate or severe exacerbation was longer in the indacaterol-glycopyrronium group than in the salmeterol-fluticasone group (hazard ratio, 0.78; 95% CI, 0.70 to 0.86; P<0.001), as was the time to the first severe exacerbation (hazard ratio, 0.81; 95% CI, 0.66 to 1.00; P=0.046). The effect of indacaterol-glycopyrronium versus salmeterol-fluticasone on the rate of COPD exacerbations was independent of the baseline blood eosinophil count. The incidence of adverse events and deaths was similar in the two groups. The incidence of pneumonia was 3.2% in the indacaterol-glycopyrronium group and 4.8% in the salmeterol-fluticasone group (P=0.02). CONCLUSIONS: Indacaterol-glycopyrronium was more effective than salmeterol-fluticasone in preventing COPD exacerbations in patients with a history of exacerbation during the previous year. (Funded by Novartis; FLAME ClinicalTrials.gov number, NCT01782326.).

Appendix 4: Medline Search Strategy

Database(s): Ovid MEDLINE(R) without Revisions 1996 to August Week 5 2017
Search Strategy:

#	Searches	Results
1	Tiotropium Bromide/	920
2	aclidinium bromide.mp.	112
3	umeclidinium.mp.	102
4	glycopyrrolate.mp. or Glycopyrrolate/	633
5	Budesonide, Formoterol Fumarate Drug Combination/ or Budesonide/ or budesonide.mp.	4344
6	fluticasone propionate.mp. or Fluticasone/	3066
7	beclomethasone dipropionate.mp. or Beclomethasone/	1756
8	mometasone furoate.mp. or Mometasone Furoate/	730
9	fluticasone furoate.mp.	211
10	ciclesonide.mp.	306
11	salmeterol xinafoate.mp. or Salmeterol Xinafoate/	1797
12	formoterol fumarate.mp. or Formoterol Fumarate/	1432
13	arformoterol tartrate.mp.	11
14	indacaterol maleate.mp.	11
15	olodaterol.mp.	85
16	vilanterol.mp.	180
17	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	11729
18	limit 17 to (english language and humans and yr="2016 -Current")	489
19	limit 18 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comment or controlled clinical trial or meta-analysis or practice guideline or randomized controlled trial or systematic reviews)	

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Date: November 2017

Appendix 5: Prior Authorization Criteria

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:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3

Approval Criteria		
3. Does the patient have a diagnosis of asthma or reactive airway disease (ICD10 J45.20-J45.22, J45.901-45.998)?	**Yes:** Go to #7	**No:** Go to #4
4. Does the patient have a diagnosis of COPD (ICD10 J44.9), mucopurulent chronic bronchitis (ICD10 J41.1) and/or emphysema (ICD10 J43.9)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded (ICD10 J40, J41.0, J41.8, J42).
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: *11/17 (KS); 9/16; 9/15*
Implementation: *10/13/16; 10/9/15*

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:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #3
3. Does the patient have a diagnosis of asthma or reactive airway disease (ICD10 J4520-J4522; J45901-45998)?	**Yes:** Go to #6	**No:** Go to #4

Approval Criteria		
4. Does the patient have a diagnosis of COPD (ICD10 J449), mucopurulent chronic bronchitis (ICD10 J41.1) 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. Chronic bronchitis is unfunded (ICD10 J40, J41.0, J41.8, J42).
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: *11/17 (KS); 9/16; 9/15); 5/12; 9/09; 5/09*
Implementation: *10/9/15; 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
- Promote use that is consistent with Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines. See also: http://www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html
- Step-therapy required prior to coverage:
  - Asthma: short-acting beta-agonist and inhaled corticosteroid or moderate to severe persistent asthma.
  - COPD: short-acting bronchodilator and previous trial of a long-acting bronchodilator (inhaled anticholinergic or beta-agonist) or GOLD C/D COPD. Preferred LABA/ICS products do NOT require prior authorization.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred LABA/ICS products

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the provider consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of covered alternatives in class	**No:** Go to #3

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Date: November 2017

Approval Criteria		
3. Does the patient have a diagnosis of asthma or reactive airway disease (ICD10 J4520-J4522, J45901-45998)?	**Yes:** Go to #7	**No:** Go to #4
4. Does the patient have a diagnosis of COPD (ICD10 J449), mucopurulent chronic bronchitis (ICD10 J41.1) 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. Chronic bronchitis is unfunded (ICD10 J40, J41.0, J41.8, J42).
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 alternatively has the patient been assessed with GOLD C/D 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 moderate to severe persistent asthma (Step 3 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: *11/17 (KS); 9/16; 11/15; 9/15; 11/14; 11/13; 5/12; 9/09; 2/06*
Implementation: *10/13/16; 1/1/16; 1/15; 1/14; 9/12; 1/10*

Author: Kathy Sentena, PharmD Date: November 2017

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
- Promote COPD therapy that is consistent with Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines. See also: http://www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html
- Step-therapy required prior to coverage:
    - COPD: short-acting bronchodilator and previous trial of a long-acting bronchodilator (inhaled anticholinergic or beta-agonist) or GOLD C/D COPD. Preferred LAMA and LABA products do NOT require prior authorization.

Length of Authorization:

- Up to 12 months

Requires PA:

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

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of preferred LAMA and LABA products in each class	**No:** Go to #3

Author: Kathy Sentena, PharmD

Date: November 2017

Approval Criteria		
3. Does the patient have a diagnosis of asthma or reactive airway disease (ICD10 J4520-J4522, J45901-45998) without COPD?	**Yes:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review.	**No:** Go to #4
4. Does the patient have a diagnosis of COPD (ICD10 J449), mucopurulent chronic bronchitis (ICD10 J41.1) 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. Chronic bronchitis is unfunded (ICD10 J40, J41.0, J41.8, J42).
5. Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the request for the combination product fluticasone furoate, umeclidinium and vilanterol (Trelegy Ellipta)?	**Yes:** Go to #7	**No:** Go to #8
7. Has the patient been assessed with GOLD C/D COPD?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA, LABA and ICS inhalers.	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
8. Has the patient been assessed with GOLD C/D COPD?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA and LABA inhalers.	**No:** Go to #9
9. Is there a documented trial of a LAMA or LABA, or alternatively a trial of a fixed dose combination short-acting anticholinergic with beta-agonist (SAMA/SABA) (i.e., ipratropium/albuterol)?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA and LABA inhalers or scheduled SAMA/SABA inhalers (PRN SABA or SAMA permitted).	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *11/17 (KS); 9/16; 11/15; 9/15; 11/14; 11/13; 5/12; 9/09; 2/06*
Implementation: *10/13/16; 1/1/16; 1/15; 1/14; 9/12; 1/10*