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Drug Class Update with New Drug Evaluation: Asthma and COPD Maintenance Medications

Date of Review: May 2019

Date of Last Review: January 2018
Dates of Literature Search: 01/01/2014- 02/25/2019
Brand Name (Manufacturer): Yupelri (Mylan)
Dossier Received: yes

Generic Name: Revefenacin

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

Purpose for Class Update:
The purpose of this class update is to provide new comparative effectiveness and safety evidence for asthma and chronic obstructive pulmonary disease (COPD) maintenance medications published since the last review. A new drug evaluation for revefenacin, a long-acting anticholinergic nebulization solution, which was approved in November 2018, will be included.

Research Questions:
1. Is there new comparative evidence on the efficacy/effectiveness of maintenance treatments for asthma and COPD?
2. Is there new comparative evidence of harms associated with maintenance medications used to treat asthma and 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 maintenance treatments for asthma or COPD differ in efficacy/effectiveness or frequency of adverse events?
4. What is the comparative evidence for efficacy and harms for revefenacin compared to other maintenance treatments for COPD?

Conclusions:
New evidence for this review comes from three new guidelines from the National Institute for Health and Care Excellence (NICE) and Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD), five systematic reviews and meta-analyses from Cochrane Systematic Reviews and Agency for Healthcare Research and Quality (AHRQ), and seven randomized controlled trials.

ASTHMA

Efficacy

- Guidance from NICE supports current policy for Oregon Health Plan (OHP) fee-for-service patients. Treatment recommendations are consistent with prior recommendations with the exception of the use of a leukotriene receptor antagonist (LTRA) in children, 5 and older, and in adults as a second-line treatment option, instead of a long-acting beta-agonists (LABA).[1]

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Exacerbations

- In patients 0-4 years of age there is moderate evidence that intermittent inhaled corticosteroid (ICS) in combination with a short-acting beta-agonist (SABA) is more effective than SABA alone at the onset of an upper respiratory infection reduces the risk of needing oral corticosteroids, 38% and 56%, respectively.[2]
- In patients 12 years and older with persistent asthma:
    - There is moderate strength of evidence that risk of exacerbations (composite outcome of requiring systemic corticosteroids, hospitalization or emergency department [ED] visit) was lower with inhaled corticosteroid (ICS) + long-acting beta-agonist (LABA) as controller and quick relief compared to ICS alone, relative risk (RR) 0.64 (95% CI [confidence interval], 0.53 to 0.78; P<0.05) (absolute risk reduction [ARR] not provided).[2] This was also true for ICS + LABA as *controller and quick relief* compared to ICS + LABA as a *controller*, RR 0.68 (95% CI, 0.58 to 0.80; P<0.05;ARR not provided).[2]
    - There is high strength of evidence that the risk of exacerbations requiring corticosteroids is lower with the combination of ICS and a LABA as a *controller and quick relief* compared to the combination of ICS and LABA only as a *controller*. Evidence was of moderate strength for exacerbations requiring ED visits for the same comparison (RR 0.74; 95% CI, 0.59 to 0.93; P<0.05/ARR not reported).[2]
- In patients 12 years and older with uncontrolled asthma and persistent exacerbations the risk of exacerbations requiring systemic corticosteroids was reduced with the combination of LAMA and ICS versus ICS and placebo, 4% vs. 7% (RR 0.67; 95% CI, 48 to 0.92; P<0.05; high strength of evidence).[2]
- The efficacy of using ICS/LABA as controller and quick relief therapy (referred to as single maintenance and reliever therapy [SMART]) compared to ICS with or without LABA controller therapy and SABA for relief therapy in individuals with persistent asthma was studied in a systematic review and meta-analysis. Overall the use of SMART was associated with a lower incidence of exacerbations compared to ICS, with or without LABA, and use of SABA as reliever therapy.[3]

Hospitalizations

- In patients 12 years and older with persistent asthma:
    - The combination of ICS and LABA as a *controller and quick relief* reduced the risk of hospitalizations and ED visits more than ICS and LABA as a *controller* based on high strength of evidence (RR 0.69; 95% CI, 0.63 to 0.76; P<0.05/ARR not reported).[2]

Rescue Medication Use

- The use of rescue medication was reduced with the combination of ICS and LABA as a *controller and quick relief* compared to ICS with or without LABA in patients 12 and older with persistent asthma based on moderate evidence (pooled results not available).[2]

Spirometry

- There is high strength of evidence that long-acting muscarinic antagonists (LAMA) in combination with ICS improves trough forced expiratory volume in one second (FEV1) more than ICS and placebo by a mean difference (MD) of 0.13 L (95% CI, 0.10 to 0.17; P<0.05) in patients 12 years and older with uncontrolled, persistent asthma.[2]
- There was a statistically significant, but most likely not clinically significant, increase in trough FEV1 with the use of ICS and LABA + LAMA compared to ICS and LABA alone (MD 0.07 L ;95% CI, 0.00 to 0.14; P>0.05) based on moderate strength of evidence.[2]

Safety

- A Cochrane systematic review of 14,233 patients found moderate quality evidence of no difference in mortality between salmeterol/ICS compared to ICS (same ICS dose in each group), 11 deaths versus 13 deaths, respectively (odds ratio [OR] 0.80; 95% CI, 0.36 to 1.78).[4] This translates to 1 death per 1000 patients in each group treated for 25 weeks.[4] Recent findings have prompted the Food and Drug Administration (FDA) to remove boxed warning from LABA/ICS products regarding the risks of mortality associated with LABA therapy.[5]

Chronic Obstructive Pulmonary Disease

- Recent guideline updates on the management of COPD support current recommendations.[6,7]

Revefenacin

- Low quality evidence from two short-term, non-published trials demonstrated more trough FEV1 lowering in COPD patients using revefenacin nebulized solution compared to placebo.[8] Limited safety data suggests a similar adverse event profile as other LAMAs. There is insufficient evidence to recommend revefenacin over preferred maintenance treatments for COPD.

Recommendations:

- No changes to the PDL are recommended based on the review of clinical efficacy.
- Recommend clerical revisions to prior authorization (PA) criteria to remove references to guideline classifications of COPD.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

- Previous reviews have found 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. There was insufficient evidence in subgroup populations with asthma or COPD to establish meaningful conclusions on efficacy or harms.
- Preferred therapies for asthma and COPD maintenance medications are:
    a. Anticholinergics: ipratropium (aerosol and solution), tiotropium and ipratropium/albuterol (nebulized solution)
    b. LABA: salmeterol
    c. ICS: budesonide, fluticasone propionate, beclomethasone, fluticasone (Flovent® diskus)
    d. ICS/LABA: fluticasone/salmeterol (diskus and hydrofluoroalkane [HFA]), budesonide/formoterol
    e. LAMA/LABA and LAMA/LABA/ICS combination inhalers: no preferred drugs
- Non-preferred therapies require a prior authorization to verify diagnosis and medical appropriateness.
- There is high utilization (greater than 70%) of preferred therapies in all classes with dedicated preferred options. Maintenance therapies for asthma and COPD represent a substantial cost to OHP, with the LAMA, ICS and LABA/ICS representing the costliest classes.

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.[9] Total national asthma costs were projected to be over $20 billion in 2010.[9] Asthma is characterized by symptoms of wheezing, cough, dyspnea and chest tightness. Diagnosis of asthma includes assessment of physical presentation, laboratory evaluation, and confirmation with spirometry (FEV_1 > 200 mL or ≥ 12% from baseline after SABA use). The severity of asthma is differentiated as intermittent or persistent (and further divided into mild, moderate or severe disease).[10]

Asthma treatment can be divided into two categories, quick-relief (rescue) medication and long-term maintenance medications. The Expert Panel Report 3 (EPR3) recommends asthma treatment be approached in a stepwise manner based on the severity of asthma symptoms.[10] 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 most commonly recommended in combination with ICS.[10] Other maintenance therapy options include LTRA, methylxanthines, and cromolyn sodium.

Outcomes used in asthma trials are spirometry (e.g., 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.[11]

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. Forty-one percent of these individuals were on at least one daily treatment for COPD.[12] The national incidence of COPD is estimated at 5%, contributing to substantial morbidity and mortality.[13]

Chronic cough or sputum production and dyspnea are common symptoms of COPD. The diagnosis and management of COPD is based on spirometry (post-bronchodilator ratio of FEV1/FVC <0.70), symptom severity, risk of exacerbations and comorbidities.[7] COPD is classified into four stages based on spirometric measurements of FEV1/FVC; grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (very severe).[7] Therapeutic approaches are often based on disease burden as well as FEV_1, which classifies patients into groups A-D (low to high risk of symptoms and exacerbations).[7] This type of classification system shifts the focus from including just FEV1 measurements, as these are not always indicative of COPD status. Important outcomes to access the effectiveness of therapies include: functional capacity, Quality of Life (QoL) (i.e., St. George's Respiratory Questionnaire [SGRQ]), dyspnea, exacerbation rate and/or severity, mortality and harms. FEV1 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.[11]

Pharmacotherapy prescribed in a step-wise manner is recommended for COPD management, usually starting with monotherapy and progressing to combination regimens. Short-acting beta-agonists 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.[7] Inhaled corticosteroids are reserved for patients requiring additional treatment for chronic disease, despite LAMA and LABA therapy. Maintenance reliever therapy (MART) combines ICS and a fast-acting LABA (e.g., formoterol) in a single inhaler for use as maintenance therapy and symptom relief.[6] No treatment has been shown to alter the long-term progression and decline in lung function associated with COPD.[7]

Methods:

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

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

Systematic Reviews:

AHRQ – Intermittent Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists for Asthma

AHRQ assessed the efficacy of using intermittent ICS in patients with asthma and to determine if adding a LAMA helps to improve outcomes in patients with uncontrolled, persistent asthma.[2] The review focused on 3 groups: patients 0 to 4 years old with recurrent wheezing, patients 5 years and older with persistent asthma (with or without LABA) and patients 12 years and older with uncontrolled, persistent asthma for the assessment of efficacy of adding a LAMA. Three classes of asthma controllers were included in the review: ICS, LABA and LAMA (**Table 1**). Fifty-six trials were included and were assessed for risk of bias and graded for strength of evidence. Outcomes of interest where exacerbations, mortality, asthma control composite scores, spirometry, asthma-specific quality of life and rescue medication use.[2]

Table 1. Drugs Eligible for Inclusion in AHRQ review[2]

Inhaled Corticosteroids	
beclomethasone budesonide ciclesonide	flunisolide fluticasone mometasone triamcinolone
Long-acting beta-agonists	
arformoterol formoterol	olodaterol salmeterol vilanterol
Long-acting muscarinic antagonists	
aclidinium glycopyrrolate	tiotropium umeclidinium

Results, including ARRs when available, for the three groups of patients and outcomes with moderate to high levels of evidence are presented in **Table 2**. Evidence for patients 0-4 years of age with recurrent wheezing is limited with most outcomes designated as having low strength of evidence or insufficient evidence to prevent conclusions. Outcomes available for analysis in patients 5 to 11 years with persistent asthma had low or insufficient evidence. For patients 12 and older with uncontrolled, persistent asthma, adding a LAMA to an ICS compared to doubling the ICS dose found no difference between treatments based on low strength of evidence for all outcomes of asthma management. This statement was also true for adding a LAMA to ICS compared to adding a LABA to ICS. Mortality rates were too low to draw conclusions regarding safety.

Table 2. Results for Patients with Asthma for Outcomes with Moderate or High Quality Findings[2]

Intervention	Outcome	Results	Strength of Evidence‡
Patients 0-4 Years with Recurrent Wheezing			
Intermittent ICS with SABA as needed vs. SABA as needed*	Reduction in the risk of exacerbation requiring oral corticosteroids	*Favors ICS + SABA* Intermittent ICS + SABA: 70 (38%) SABA: 79 (56%) RR 0.67 (95% CI, 0.46 to 0.98) P<0.05	Moderate
Patients 12 Years or Older with Persistent Asthma			
Intermittent ICS vs. ICS controller	No difference in QOL∞, spirometry or rescue albuterol use	Pooled results not reported	Moderate to high
ICS + LABA as controller and quick relief vs. ICS†	Reduction in the risk of exacerbations (composite outcome of requiring systemic corticosteroid, hospitalization or ED visit)	*Favors ICS/LABA as controller and quick relief* RR 0.64 (95% CI, 0.53 to 0.78) P<0.05	Moderate
	Improvement in spirometry	*Favors ICS/LABA as controller and quick relief* MD 0.10 (95% CI, 0.07 to 0.13) P<0.05	Moderate
ICS + LABA as controller and quick relief vs. ICS + LABA as controller†	Reduction in the risk of exacerbations (composite outcome of requiring systemic corticosteroid, hospitalization or ED visit)	*Favors ICS/LABA as controller and quick relief* RR 0.68 (95% CI, 0.58 to 0.80) P<0.05	High
	Reduction in exacerbations requiring systemic corticosteroids	*Favors ICS/LABA as controller and quick relief* (pooled results not available)	High

	Reduction in exacerbations requiring ED visit	*Favors ICS/LABA as controller and quick relief* RR 0.74 (95% CI, 0.59 to 0.93) P<0.05	Moderate
	Reduction in hospitalization or ED visit	*Favors ICS/LABA as controller and quick relief* RR 0.69 (95% CI, 0.63 to 0.76) P<0.05	High
	Reduction in systemic corticosteroid, hospitalization, ED visit or unscheduled visit	*Favors ICS/LABA as controller and quick relief* RR 0.79 (95% CI, 0.65 to 0.95) P<0.05	Moderate
	Improvement in asthma control scores^	*Favors ICS/LABA as controller and quick relief* RR 1.14 (95% CI, 1.05 to 1.24) P<0.05	Moderate
	No difference in death, mild exacerbations, or spirometry	Not applicable	Moderate
ICS + LABA as controller and quick relief (ICS/LABA Quick) **vs.** **ICS + LABA as controller at a higher ICS dose (ICS/LABA)**	Reduction in the risk of exacerbations (composite outcome of systemic corticosteroid, hospitalization, or ED visit)	*Favors ICS/LABA as controller and quick relief* ICS/LABA Quick: 296 (8.8%) ICS/LABA: 394 (12%) RR 0.75 (95% CI, 0.59 to 0.96) P<0.05	High
	No difference in exacerbations requiring systemic corticosteroid, hospitalizations or ED visits, mild exacerbations, all-cause death, quality of life scores (ACQ-5 and AQLQ[S]), spirometry and rescue medication used	Not applicable	Moderate to high
ICS + LABA as controller and quick relief (ICS/LABA Quick) **vs.** **ICS +/- with or without LABA as a controller (ICS)**	Reduction in the risk of exacerbations (composite outcome of systemic corticosteroid, hospitalization, or ER visit)	*Favors ICS + LABA as controller and quick relief* ICS/LABA Quick: 223 (6.5%) ICS: 238 (8%) RR 0.78 (95% CI, 64 to 0.95) P<0.05	Moderate
	Reduction in rescue medication use	*Favors ICS + LABA as controller and quick relief*	Moderate

		Pooled results not reported	
	Improvement in asthma quality scores	*Favors ICS + LABA as controller and quick relief* Pooled results not reported	Moderate
Patients 12 Years or Older with Uncontrolled, Persistent Asthma			
LAMA + ICS **vs.** **ICS + placebo**	Reduction in risk of exacerbations requiring systemic corticosteroids	*Favors LAMA/ICS* ICS/LABA + LAMA: 86 (4%) ICS/LABA: 74 (7%) RR 0.67 (95% CI, 0.48 to 0.92) P<0.05	High
	Asthma worsening	*Favors LAMA/ICS* ICS/LABA + LAMA: 356 (22%) ICS/LABA: 223 (27%) RR 0.81 (95% CI, 0.68 to 0.97) P<0.05	High
	Improvement in spirometry	*Favors LAMA/ICS* FEV1 trough: MD 0.13 L (95% CI, 0.10 to 0.17) P<0.05	High
	No difference in QOL∞, asthma control scores^, or reduction in medication use	Not applicable	Moderate to high
LAMA + ICS **vs.** **LABA + ICS**	No difference in exacerbations (asthma worsening), asthma control scores^, spirometry or quality of life scores	Not applicable	Moderate to high
	Asthma worsening	*Favors addition of LAMA* ICS/LABA + LAMA: 159 (22%) ICS/LABA: 312 (53%) RR 0.78 (95% CI, 0.72 to 0.86) P<0.05	High
	Improvement in asthma control scores^	Pooled results not available	Moderate-high
	Improvement in spirometry	FEV1 trough MD 0.07 L (95% CI, 0.00 to 0.14) P>0.05	Moderate
	No difference in rescue medication use, exacerbations requiring systemic corticosteroids, exacerbations requiring hospitalizations	Not applicable	Moderate

Key: * At onset of an upper respiratory infection, † Same comparative ICS dose, ‡ Strength of evidence assigned by AHRQ, ^ Asthma Control Scores – composite measure of Asthma Control Test (ACT), Asthma Control Questionnaire (ACQ), various versions, ∞ Asthma-specific QOL scores – Asthma Quality of Life Questionnaire (AQLQ), Pediatric Asthma Quality of Life Questionnaire (PAQLQ), Pediatric Asthma Caregiver's Asthma Quality of Life Questionnaire (PACQLQ)
Abbreviations: ED – emergency department; FEV1 - forced expiratory volume in one second; ICS – inhaled corticosteroids; LABA – long-acting beta-agonists; LAMA – long-acting muscarinic antagonists; MD – mean difference; OR – odds ration; QOL – quality of life; RR – relative risk

Cochrane – Inhaled Steroids with and without regular Salmeterol for Asthma: Serious Adverse Events

A 2018 Cochrane review evaluated the risk of mortality and non-fatal serious adverse events in patients with asthma taking salmeterol and ICS compared to ICS alone (in separate or combined inhalers) for at least 12 weeks.[4] The ICS dose was the same in both comparison groups. A total of 41 studies were included in the review with a majority of subjects taking salmeterol/ICS in one combination inhaler. Main outcomes of interest were death or serious adverse events. Serious adverse events were defined as: death or life-threatening events requiring hospitalization or prolongation of existing hospitalization, resulting in significant disability or incapacity, or resulting in a congenital anomaly/birth defect.

- Out of a total of 14,233 patients included in the analysis, 11 adults taking salmeterol/ICS died compared to 13 taking ICS at the same dose (OR 0.80; 95% CI, 0.36 to 1.78)(moderate evidence).[4] This translates to 1 death per 1000 patients treated in each group treated for 25 weeks. No deaths occurred in children and no deaths in any group were caused by asthma.
- Moderate evidence found adults taking salmeterol/ICS was associated with 332 non-fatal severe adverse events compared to 282 adults receiving regular ICS (OR 1.14; 95% CI 0.97 to 1.33).[4]
- Severe adverse events occurred in 65 children taking salmeterol/ICS compared to 62 children receiving ICS (OR 1.04; 95% CI, 0.73 to 1.48).[4]
- Asthma-related non-fatal severe adverse events were similar between both groups of children, 29 and 23, respectively (moderate quality evidence).

One limitation to this analysis is the absence of death due to asthma in both groups, limiting conclusions on comparative harms. Treatment durations did not exceed 25 weeks which may underestimate adverse events associated with long-term therapy, which is used chronically in patients with asthma.

Cochrane – Umeclidinium Bromide versus Placebo for People with COPD

The focus of a 2017 Cochrane review looked the safety and efficacy of umeclidinium compared to placebo in COPD patients.[14] Patients were a mean age of 60-64 years old with moderate to severe COPD, a 39-52 mean smoking pack-years and baseline FEV1 less than or equal to 70% of predicted normal. There were four studies that met inclusion criteria which lasted 12-52 weeks.[14] For the primary outcome of exacerbations requiring a short course of oral steroid or antibiotic or both, the risk of moderate exacerbations with umeclidinium occurred 55 per 1000 patients less than placebo (OR 0.61; 95% CI, 0.46 to 0.80) (high quality evidence).[14] Therefore, for every 18 people treated with umeclidinium, one additional person was free from a moderate exacerbation (number needed to benefit [NNTB] 18).[14] Moderate quality evidence found umeclidinium to improve the quality of life (based on an improvement of 4 or more on the total score of the SGRQ) in 429 patients per 1000 compared to 342 patients per 1000 taking placebo (OR 1.45; 95% CI, 1.16 to 1.82). Non-fatal serious adverse events were not clinically or statistically different between groups (moderate evidence). Changes in trough FEV1 of 140 ml in umeclidinium treated patients more than placebo,

which was clinically significant (high quality of evidence).[14] Limitations to the review are that all evidence came from manufactured studies lending a high degree of publication bias and the review did not include any active treatment comparisons to provide evidence on comparative effectiveness to other COPD therapies.

Sobieraj, et al – ICS/LABA as Controller and Quick Relief Therapy for Exacerbations and Symptom Control in Persistent Asthma

A 2018 systematic review and meta-analysis reviewed the efficacy of using ICS/LABA as controller and quick relief therapy (SMART) compared to ICS with or without LABA controller therapy and SABA for relief therapy in individuals with persistent asthma.[3] Studies included 22,524 patients that were twelve years of age and older and 341 children ages 4-11 years old. Trials were divided by comparative ICS dose and comparators as follows: SMART versus same dose ICS alone, SMART versus higher dose ICS, SMART versus same dose of ICS and LABA, or SMART versus higher dose of ICS and LABA. All trials but one used budesonide and formoterol for SMART. Included studies were evaluated for risk of bias and the strength of evidence was graded. Main outcomes of interest are asthma exacerbations, use of steroids, hospitalizations, emergency department visits, asthma quality of life, asthma-specific mortality and trough FEV1. Results with moderate or high strength of evidence are reported in **Table 3**. Overall the use of SMART was associated with a lower incidence of exacerbations compared to ICS, with or without LABA, and use of SABA as reliever therapy.

Table 3. SMART versus Other Controller Therapy for Patients with Persistent Asthma 12 years and older[3]

Comparison	Outcome	Results	Strength of Evidence
SMART **Vs.** **Same dose ICS**	Asthma exacerbations*	SMART: 137 (14%) ICS: 212 (22%) ARD -8.1% (95% CI, -11.5 to -4.5) RR 0.64 (95% 0.53 to 0.78) *Favors SMART therapy*	Moderate
	FEV1	SMART: 2.54 L ICS: 2.44 L MD 0.10 L (95% CI, 0.07 to 0.13) *Favors SMART therapy*	Moderate
SMART **Vs.** **Same dose ICS and LABA**	Asthma exacerbations*	SMART: 263 (6%) ICS/LABA: 385 (9%) ARD -6.4% (95% CI, -10.2 to -2.6) RR 0.68 (95% CI, 0.58 to 0.80) *Favors SMART therapy*	High
	Death	SMART: 2 (0.06%) ICS/LABA: 5 (0.15%) ARD -6.4% (95% CI, -10.2 to -2.6) OR 0.43 (95% CI, 0.04 to 4.49) *No difference between treatments*	Moderate
	Patient Response Rate (ACQ-5)†	SMART: 587 (56%)	Moderate

		ICS/LABA: 511 (49%) ARD 6.9% (95% CI, 2.6 to 11.2) RR 1.14 (1.05 to 1.24) *Favors SMART therapy*	
SMART **Vs.** **Higher dose ICS and LABA**	Asthma exacerbations*	SMART: 202 (9%) High ICS/LABA: 394 (12%) ARD: -2.8% (95% CI, -5.2 to -0.3) RR: 0.77 (95% CI, 0.60 to 0.98) *Favors SMART therapy*	High
	Death	SMART: 3 (0.13%) High ICS/LABA: 1 (0.03%) OR 5.19 (95% CI, 0.32 to 85.45) *No difference between treatments*	Moderate
	Asthma control (ACQ-5)	SMART: 1.84 High ICS/LABA: 1.89 MD -0.02 (95% CI, -0.07 to 0.04) *No difference between treatments*	High
	FEV1	SMART: 2.69 L High ICS/LABA: 2.66 L MD 0.01 (-0.3 to 0.04) *No difference between treatments*	Moderate
	Rescue medication use (puffs/day)	SMART: 0.95 High ICS/LABA: 1.01 MD: -0.04 (95% CI, -0.12 to 0.04)	High
Abbreviations: ACQ-5 = Asthma Control Questionnaire; ARD= absolute risk difference; ED = emergency department; ICS = inhaled corticosteroid; LABA = long-acting beta agonist; MD = mean difference, OR = odds ration; RR = risk ratio; SMART = single maintenance and reliever therapy Key: * Required use of systemic corticosteroids, hospitalizations or ED visit, † ACQ-5 responders – patient response was defined as a reduction of 0.5 points or greater			

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

New Guidelines:

High Quality Guidelines:

NICE – Asthma Diagnosis, Monitoring and Chronic Asthma Management

A 2017 NICE guidance updated the management of chronic asthma in children, young people and adults.[1] The pharmacological recommendations will be presented and discussed. Patients who have asthma that is well controlled on their current regimen should not have their treatment changed despite new guideline recommendations. In general, new guidance recommendations mirror previous statements of using SABA first line, followed by an ICS for first-line

maintenance therapy (**Table 4, Table 5 and Table 6**). The addition of an LTRA in children 5 and older and in adults as second-line maintenance therapy, instead of a LABA, is one of the changes to the treatment recommendations.

NICE recommends self-management and titration of ICS doses, up to quadruple the dose if maximum manufacture recommended dose is not exceeded, in adults who use a single inhaler when their asthma symptoms escalate and control deteriorates.[1] Recommendations are the same for children and young people with the exception of limiting the days of increased dose of ICS to 7 days. Maintenance therapy should be accessed and potential decreases in therapy should be considered after at least 3 months of asthma control. Discontinuation of ICS maintenance therapy should only be considered in patients who are symptom free on low dose ICS monotherapy.

Table 4. Pharmacotherapy for Adults (17 years and older) with Newly Diagnosed or Uncontrolled Asthma [1]
Offer a SABA for reliever therapy: SABA monotherapy can be considered for adults who have infrequent, short-lived wheeze and normal lung function.
First-line maintenance therapy is a low dose ICS with the following characteristics: - Symptoms at presentation consistent with need for maintenance therapy (e.g., asthma symptoms 3 or more times a week or causing waking at night) or asthma that is uncontrolled with SABA alone. - In patients with uncontrolled asthma on low dose ICS, offer a leukotriene receptor antagonist (LTRA) in addition to ICS and reevaluate in 4 to 8 weeks. - In patients with uncontrolled asthma on low dose ICS and LTRA, offer a LABA in combination with the ICS, review LTRA therapy to determine response to treatment, and discuss with patient if therapy should be continued.
Patients with uncontrolled asthma on low dose ICS and a LABA, with or without an LTRA, offer a switch the ICS and LABA maintenance therapy to a MART* with low dose maintenance ICS. - If asthma is uncontrolled on MART* regimen with a low dose ICS, with or without LTRA, consider increasing the ICS to a moderate maintenance dose (MART regimen can be continued or switched to a fixed-dose ICS/LABA combination with a SABA as a reliever therapy).
In patients, whose asthma remains uncontrolled on moderate maintenance ICS dose with a LABA (with MART or fixed-dose regimen) with or without a LTRA, consider the following: - Increasing the ICS to high maintenance dose (offered as part of a fixed-dose regimen, with a SABA used as reliever therapy) or a trial of an additional drug (e.g., a LAMA or theophylline) or consultation with asthma expert.
* MART – maintenance and reliever therapy which is a combination of an ICS and fast-acting LABA which is used for daily maintenance treatment and symptom relief.

Table 5. Pharmacotherapy for Children and Young People (5 to 16 year olds) with Newly Diagnosed or Uncontrolled Asthma[1]
SABA should be offered to children and young people with newly diagnosed asthma
SABA monotherapy can be considered for infrequent, short-lived wheeze and normal lung function.
Offer pediatric low dose ICS as first-line maintenance therapy for the following: - Symptoms at presentation consistent with need for maintenance therapy (e.g., asthma symptoms 3 or more times a week or causing waking at night) or asthma that is uncontrolled with SABA alone. - In patients whose asthma remains uncontrolled on a pediatric low dose of an ICS as maintenance therapy, consider an LTRA in addition to the ICS and reevaluate in 4 to 8 weeks.

If asthma remains uncontrolled on pediatric low dose ICS and an LTRA, consider stopping the LTRA and starting a LABA in combination with the ICS.
In patients with uncontrolled asthma on pediatric low dose ICS and LABA, consider changing the regimen to MART* with a pediatric low maintenance ICS dose.
If asthma is uncontrolled on a MART* regimen with a pediatric low maintenance dose ICS, consider increasing the ICS to pediatric moderate maintenance dose (either on a MART regimen or changing to a fixed-dose of an ICS and a LABA, with a SABA as reliever therapy).
If the patient's asthma remains uncontrolled on a pediatric moderate maintenance ICS dose with LABA (either as MART or a fixed-dose regimen) consider seeking advice from an asthma expert or increasing the ICS dose to pediatric high maintenance dose (as part of a fixed-dose regimen, with a SABA used as reliever therapy) or trial of an additional drug (theophylline).
* MART – maintenance and reliever therapy which is a combination of an ICS and fast-acting LABA which is used for daily maintenance treatment and symptom relief.

Table 6. Pharmacotherapy for Children Under 5 with Suspected or Confirmed Asthma.[1]
A SABA should be offered to children with suspected asthma for symptom relief and alongside maintenance therapy.
An 8-week trial of pediatric moderate dose ICS should be considered in children with the following: - Symptoms at presentation consistent with need for maintenance therapy (e.g., asthma symptoms 3 or more times a week or causing waking at night) or asthma that is uncontrolled with SABA alone. - ICS treatment should be stopped after 8-weeks and child's symptoms should be monitored. - Consider an alternative diagnosis if symptoms did not resolve during trial period.
If symptoms resolved but reoccurred within 4 weeks of stopping ICS, then restart pediatric low dose ICS as first-line maintenance therapy.
If symptoms resolved but reoccurred after 4 weeks of stopping ICS, repeat 8-week trial of pediatric moderate dose ICS.
If pediatric low dose ICS maintenance therapy fails to control symptoms in children with suspected asthma, consider an LTRA in addition to an ICS.
If children with suspected asthma remain uncontrolled on pediatric low dose ICS and LTRA maintenance therapy, discontinue LTRA and refer the child to an asthma specialist.

NICE – Chronic Obstructive Pulmonary Disease: Diagnosis and Management

A March 2018 review evaluated the effectiveness of LAMAs, LABAs and ICSs for managing patients with stable COPD.[6] Included patient were over 35 years of age with a baseline FEV1 of less than 80% predicted. The majority of participants were also using an ICS. The main outcomes of interest were: COPD exacerbations, SGRQ scores, transition dyspnea index (TDI), mortality, trough FEV1, pneumonia, dropouts due to adverse events, and serious adverse events. Exacerbations were divided into moderate and severe. The definition of a moderate exacerbation was worsening of respiratory status that requires treatment with systemic corticosteroids and/or antibiotics. Severe exacerbations were defined as those with rapid deterioration requiring hospitalization. FEV1 and TDI were analyzed at 3, 6 and 12 months and all other outcomes were collected at the final time point. Minimal clinically important differences were determined for the following outcomes: total change in SGRQ score (4 points), trough FEV1 (100 ml), change in TDI (1 point). Outcomes with moderate to high strength of evidence will be presented.[6] Network meta-analysis (NMA) comparisons were also done, but results are not included due to the inherent methodological issues with NMAs.

LABA/LAMA versus LABA/ICS

- LABA/LAMA demonstrated a lower risk of pneumonia compared to those patients taking LABA/ICS based on moderate quality evidence.
- Trough FEV1 was improved at 3 and 6 months (but not at 12 months) in more patients taking LAMA/LABA compared to LABA/ICS based on very low to moderate quality evidence, but the differences were not clinically different.
- Other outcomes found no meaningful differences between LABA/LAMA and LABA/ICS.

LABA/LAMA versus LAMA

- No meaningful differences between LABA/LAMA and LAMA were demonstrated based on moderate or high quality evidence.

LABA/LAMA versus LABA

- There was no moderate or high-quality evidence demonstrating differences in outcomes for LABA/LAMA versus LABA.

LABA/ICS versus LAMA

- Low to moderate quality of evidence found reduced incidence of all-cause mortality and cardiac severe adverse reaction associated with LABA/ICS compared to LAMA. Incidence of pneumonia was higher in patients treated with LABA/ICS compared to LAMA based on low to moderate evidence.
- There was low to moderate quality evidence of no meaningful difference in other outcomes.

LABA/ICS versus LABA

- The risk of pneumonia was increased in patients taking LABA/ICS compared to LABA alone based on high quality evidence.
- There was low to high quality evidence of no meaningful difference in other outcomes.

LAMA versus LABA

- A reduction in the number of patients with severe exacerbations and severe adverse events (COPD related) was less in patients taking LAMA compared to LABA; however, these differences did not meet the threshold for being clinically meaningful.
- There was low to moderate quality evidence of no meaningful difference in other outcomes.

LAMA monotherapy (tiotropium, aclidinium, glycopyrronium, or umeclidinium) versus placebo

- ***Tiotropium 5-18 mcg***: In studies evaluating tiotropium to placebo, tiotropium was found to improve trough FEV1 (121 – 134 mL), TDI (1.05-1.10) and number of SGRQ responders (RR 1.33; CI, 1.25 to 1.42; $p<0.00001$) (moderate strength of evidence). Improvements met the threshold for minimal clinically important differences (MCID). Moderate strength of evidence found no differences in the incidence of severe exacerbations or serious adverse events between the groups.
- ***Aclidinium bromide 400 mcg (twice daily)***: Compared to placebo, aclidinium improved TDI and SGRQ scores based on low to high quality of evidence; however, scores did not meet the threshold for being MCID.
- ***Glycopyrronium bromide 50 mcg***: Compared to placebo, glycopyrronium improved trough FEV1 and SGRQ at 3 months (but had no meaningful difference in the number of responders) and reduced moderate to severe exacerbations based on low to moderate evidence.
- ***Umeclidinium bromide 62.5 mcg***: TDI, SGRQ scores, SGRQ responders and trough FEV1 were improved when umeclidinium was compared to placebo (low to high quality evidence).

Additional Guidelines for Clinical Context:

Global Initiative for Chronic Obstructive Lung Disease – 2019

The GOLD guidelines are produced on an annual basis to provide strategies for diagnosis, management and prevention of COPD.[7] The guidelines are funded by sales of documents and resources. Seventy-six percent of GOLD board of directors and science committee have ties to industry, suggesting a high risk for publication bias. Other limitations to the guideline include the absence of the following: diversity in representation from professional groups, patient and public input, external review by experts in the field, and discussion on resource implications/barriers of recommendations. Therefore, guideline recommendations for pharmaceutical management will be provided for clinical context but not relied upon for decisions regarding the PDL.

For initial pharmacological treatment of COPD, GOLD recommendations are outlined in **Figure 1**.[7] There is a lack of high-quality evidence to guide initial drug therapy. There is insufficient evidence to recommend one bronchodilator over another for symptom relief (Group B). Patients in Group B may also be candidates for initiation with two bronchodilators if severe breathlessness is present. Use of the modified Medical Research Council (mMRC) dyspnea questionnaire and COPD assessment test (CAT) are used to predict exacerbations which allows for categorization of patients into groups and assists in initial therapy recommendations.

A higher incidence of pneumonia was demonstrated with ICS use in patients with COPD, requiring consideration of clinical benefit versus risk before initiating. For patients experiencing dyspnea (breathlessness or exercise limitation) on one long-acting bronchodilator, a second bronchodilator should be added and if the patient is on LABA/ICS, a LABA can be added as triple therapy.[7] If patients experience exacerbations on long-acting bronchodilator monotherapy, LABA/LAMA or LABA/ICS is recommended. Consideration of add-on ICS therapy should be based on a peripheral blood level of more than 300 eosinophils/microliter, as these patients are more likely to respond to therapy. Patients with 100 eosinophils/microliter or more may be candidates for LABA/ICS if they have had 2 or more moderate exacerbations per year or a least one severe exacerbation requiring hospitalization in the prior year.[7] Patients taking LABA/LAMAs who are experiencing exacerbations should be considered for LABA/LAMA/ICS (a greater response is expected with a higher eosinophil count, approximately 100 cells/microliter or greater). If patients are unlikely to respond based on low eosinophil count, the addition of roflumilast or azithromycin should be considered. Patients taking LABA/ICS who are experiencing exacerbations can be considered for the addition of a LAMA or switched to a LABA/LAMA. Pharmacotherapy for patients with stable COPD are presented in **Table 7**.

Figure 1. Initial Pharmacological Management of COPD[7]

≥ 2 moderate exacerbations or ≥ 1 leading to a hospitalization	**Group C** LAMA	**Group D** LAMA or LAMA + LABA* or ICS + LABA** * Consider if highly symptomatic (e.g., CAT > 20) ** Consider if eos ≥ 300

0 or 1 moderate exacerbations (not leading to hospital admission)	**Group A** A Bronchodilator (short or long-acting) mMRC 0-1 CAT <10	**Group B** A Long Acting Bronchodilator (LABA or LAMA) mMRC ≥ 2 CAT ≥ 10

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

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. 2019 Report. Available at: [14]. Accessed February 20, 2019.

Table 7. GOLD Guidance on the use of Pharmacological Therapies in Stable COPD[7]

Pharmacotherapy	Recommendations	Evidence level
Bronchodilators		
LABAs and LAMAs	Long-acting bronchodilators are preferred over short-acting agents except for patients with occasional dyspnea and for immediate relief of symptoms in patients already on long-acting bronchodilators for maintenance therapy Evidence to show improved lung function, dyspnea, health status and reduction in exacerbation rates LAMAs > LABAs for exacerbation reduction and decreased risk of hospitalizations (Evidence B) Combination therapy increases FEV1 and reduces symptoms more than monotherapy Combination therapy reduces exacerbations more than monotherapy (Evidence B)	Evidence A
Long-acting bronchodilator	Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy Two bronchodilators should be used in patients with persistent dyspnea on only one bronchodilator	Evidence A
Bronchodilators	Inhaled bronchodilators are recommended over oral bronchodilators	Evidence A
Tiotropium	Improves the effectiveness of pulmonary rehabilitation in increasing exercise performance	Evidence B
Theophylline	Not recommended unless other bronchodilators are not available or not affordable	Evidence B
Anti-inflammatory Therapies		
Monotherapy with ICS	Long-term therapy not recommended	Evidence A
LABA + ICS	Long-term therapy may be considered in patients with a history of exacerbations despite appropriate treatment with long-acting bronchodilators LABA/ICS is more effective than individual components for lung function improvements and health status and exacerbation reduction in patients with moderate to very severe COPD Increased risk of pneumonia especially in those with severe disease	Evidence A
Triple Therapy		
LABA + ICS + LAMA	Improves lung function, symptoms and health status and reduces exacerbations compared to ICS/LABA, LABA/LAMA or LAMA monotherapy	Evidence A
Abbreviations: ICS – inhaled corticosteroids; LABA – long-acting beta-agonists, LAMA – long-acting muscarinic antagonist		

The GOLD guidelines recommend escalation or de-escalation based on patient specific responses. If patients experience a lack of clinical benefit, have adverse reactions, or have some improvement of symptoms, de-escalation should be considered. If patients continue to have dyspnea when on a LABA or LAMA or LABA + ICS, recommendations are to consider combination LABA + LAMA or LABA + LAMA + ICS. If patients are experiencing exacerbations on a LABA or LAMA then a LABA + LAMA or LABA + ICS should be considered. In patients with an eosinophil count greater than 100, consider LABA + LAMA + ICS. In patients with eosinophil counts less than 100, consider roflumilast or azithromycin. Roflumilast and azithromycin should also be considered in patients with high eosinophil counts that are on triple therapy and continue to have exacerbations.

New Formulations or Indications:

Formulations

3/2019 – The combination product aclidinium bromide and formoterol fumarate (Duaklir Pressair) was approved as a twice daily maintenance treatment for patients with COPD (**Table 9**).[15]

1/2019 – The first generic of Advair Diskus, Wixela Inhub (fluticasone propionate/salmeterol inhalation powder), was recently approved for the maintenance treatment of airflow obstruction and reducing exacerbations in patients with COPD and for the treatment of asthma in patients 4 and older.[16]

12/2017 – A new nebulized formulation of glycopyrrolate, Lonhala Magnair, was approved by the FDA for the long-term maintenance treatment of airflow obstruction in patients with COPD (**Table 9**).[17]

Indications

12/2017 - Budesnonide/formoterol (Symbicort) received an indication for the treatment of asthma in patients 6 and older (**Table 9**).[18, 28]

4/2018 – The three-drug combination, fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta), had the indication section changed to long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD and for reduction in exacerbations of COPD in patients with a history of exacerbations.[19]

5/2018- Approval of fluticasone furoate (Arnuity Ellipta) for the use as a maintenance treatment for pediatric asthma patients aged 5 to 11 years.[20]

10/2018 - Tiotropium bromide and olodaterol (Stiolto Respimat) received an expanded indication to treat patients with COPD, including bronchitis and/or emphysema.[21]

New FDA Safety Alerts:

Table 8. Description of New FDA Safety Alerts/Updates

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Long-acting beta agonists[5]	NA	12/2017	Removal of boxed warning from combination LABA/ICS products	FDA review finds no significant increase in risk of serious asthma outcomes used in combination with inhaled corticosteroids.

Mometasone[22]	Asmanex	3/2018	Warnings	Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Risk of increased systemic corticosteroid effects. Exercise caution when used with mometasone.

Randomized Controlled Trials:

A total of one hundred citations were manually reviewed from the initial literature search. After further review, 85 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 seven trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 9. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Busse, et al[23] **MC, PG, DB, RCT, NI**	Safety analysis of LABA/ICS vs. ICS 26 weeks	Adolescents (10%) and adults (90%) with persistent asthma n=36,010	Composite of asthma-related intubation or death	LABA/ICS: 119 (0.66%) ICS: 108 (0.60%) RR 1.09 (95% CI, 0.83 to 1.43; P=0.55) *No difference in serious asthma-related events*
Kerwin, et al[24] **(GOLDEN 3)** **MC, DD, DB, RCT, phase 3**	Glycopyrrolate 25 mcg nebulized solution twice daily and Glycopyrrolate 50 mcg nebulized solution twice daily vs. Placebo 12 weeks	Adult patients with moderate to very severe COPD N = 653	Change from baseline in trough FEV1	Glycopyrrolate 25 mcg: 0.105 L Glycopyrrolate 50 mcg: 0.126 L Placebo: - 0.022 L *Favors glycopyrrolate*
Kerwin, et al[24] **(GOLDEN 4)** **MC, DD, DB, RCT, phase 3**	Glycopyrrolate 25 mcg nebulized solution twice daily and Glycopyrrolate 50 mcg nebulized solution twice daily vs. Placebo 12 weeks	Adult patients with moderate to very severe COPD N = 641	Change from baseline in trough FEV1	Glycopyrrolate 25 mcg: 0.084 L Glycopyrrolate 50 mcg: 0.082 L Placebo: 0.007 L *Favors glycopyrrolate*
Lipson, et al[25] **(IMPACT)**	Fluticasone furoate 100 mcg/umeclidinium 62.5 mcg/vilanterol 25 mcg (FUV) vs.	Adult patients with moderate (47%) to severe COPD	Annual rate of moderate or severe COPD exacerbations during treatment	FUV: 0.91/year FV: 1.07/year UV: 1.21/year

MC, PG, DB, RCT, phase 3	Fluticasone furoate 100 mcg/vilanterol 25 mcg (FV) vs. Umeclidinium 62.5 mcg/vilanterol 25 mcg (UV) 52 weeks	N= 10,355		FUV vs. FV RR 0.85 (95% CI, 0.80 to 0.90) P<0.001 *Favors triple therapy over FV* FUV vs. UV RR 0.75 (95% CI, 0.70 to 0.81) P<0.001 *Favors triple therapy over UV*
Lipson, et al[26] **(FULFIL)** **MC, DD, DB, RCT, phase 3**	Fluticasone furoate 100 mcg/umeclidinium 62.5 mcg/vilanterol 25 mcg once daily (FUV) Vs. Budesonide 400 mcg/ formoterol 12 mcg twice daily (BF) 24 weeks	Adults 40 years and older with COPD N= 1,810	Coprimary endpoints change in baseline trough FEV1 and St. George's Respiratory Questionnaire total score at week 24	Trough FEV1 FUV: 142 ml BF: -29 ml MD 171 ml (95% CI, 148 to 194) P<0.001 *Triple therapy is superior to combination therapy* SGRQ FUV: -6.6 units BF: -4.4 units MD −2.2 (95% CI, −3.5 to −1.0) P<0.001 *Triple therapy is superior to combination therapy*
O'Byrne, et al[27] **MC, PG, DB, RCT, phase 3**	Terbutaline 6 mcg as needed + placebo twice daily (T) vs. Budesonide 200 mcg/formoterol 6 mcg as needed + placebo twice daily (BF) vs. Budesonide 200 mcg twice daily + terbutaline as needed (BP) 52 weeks	Patients 12 years and older with mild asthma N=3,849	Number of weeks of well-controlled asthma	T: 31.1% BF: 34.4% BP: 44.4% BF vs. T OR 1.14 (95% CI, 1.00 to 1.3) P = 0.046 *As needed budesonide/formoterol superior to terbutaline as needed* BF vs. BP OR 0.64 (95% CI, 0.57 to 0.73) *As needed budesonide/formoterol inferior to maintenance budesonide*

Pearlman, et al[28] **MC, PG, DB, RCT, phase 3**	Budesonide/formoterol 80/4.5 mcg twice daily vs. Budesonide/formoterol 80/2.25 mcg twice daily vs. Budesonide 80 mcg twice daily 12 weeks	Patients 6 to up to 12 years of age with asthma and previously receiving a medium-dose ICS or ICS/LABA N=279	Change in FEV1 from baseline to 1 hour after dosing	Budesonide/formoterol 80/4.5 mcg: 0.28 L Budesonide/formoterol 80/2.25 mcg: 0.24 L Budesonide 80 mcg: 0.17 L <u>Budesonide/formoterol 80/4.5 mcg vs. budesonide 80 mcg:</u> TD 0.12 L (95% CI, 0.03 to 0.20); P = 0.006 *Budesonide/formoterol 80/4.5 mcg was statistically and moderately clinically superior to budesonide* <u>Budesonide/formoterol 80/2.25 mcg vs. budesonide 80 mcg:</u> TD 0.08 (95% CI, 0.00 to 0.16); P=0.063 *Budesonide/formoterol 80/2.25 mcg twice daily was not clinically or statistically more effective than budesonide alone*
Sethi, et al[29] **(AMPLIFY)** **MC, PG, DB, RCT, phase 3** **NI comparison for aclidinium vs. tiotropium**	Aclidinium/formoterol fumarate 400mcg/12mcg twice daily vs. Aclidinium 400 mcg twice daily vs. Formoterol fumarate 12 mcg twice daily And Aclidinium 400mcg twice daily vs. Tiotropium 18 mcg once daily 24-week	Adult patients with moderate to very symptomatic COPD N=1,594	Co-primary endpoints were change from baseline at week 24 in 1-hour morning post-dose FEV1 (aclidinium/formoterol) vs. aclidinium) and trough FEV1 (aclidinium vs. formoterol) And Change from baseline in trough FEV1 for aclidinium vs. tiotropium	Change in post-dose FEV1: Aclidinium/formoterol fumarate 400mcg/12mcg: 84 mL Aclidinium: 84 mL Formoterol: 92 mL <u>Aclidinium/formoterol vs. formoterol*:</u> 55 mL; P<0.001 <u>Aclidinium/formoterol vs. aclidinium*:</u> 14 mL (NS) <u>Aclidinium/formoterol vs. tiotropium*:</u> 19 mL (NS) Change from baseline trough FEV1: <u>Aclidinium vs. tiotropium*:</u> LS MD 7 mL (95% CI: -21 mL to 35 mL; P=0.6377) *Aclidinium/formoterol was more effective than formoterol for the outcome of trough FEV1 change from baseline.* *Aclidinium was noninferior to tiotropium*

Key: * No confidence intervals provided.
Abbreviations: DB = double blind; DD = double dummy; CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV1= forced expiratory volume in one second; LS = least squares; MC = multi-center; MD = mean difference; NI= noninferiority; NS = not significant; OR = odds ratio; PG = parallel group; RCT = randomized control trial; RR = rate ratio; SGRQ = St. George's Respiratory Questionnaire; TD = treatment difference

NEW DRUG EVALUATION: Revefenacin

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

There are no published studies available to evaluate the safety and efficacy of revefenacin, therefore, risk of bias could not be accessed. Manufacturer dossier and prescribing material provided evidence for the efficacy summary. Two, 12-week clinical trials were used for the FDA- approval of revefenacin nebulization solution for the maintenance treatment of COPD.[8] Revefenacin was given as a 175 microgram once-daily inhalation solution and compared to placebo in a total of 812 patients. Revefenacin nebulized solution is delivered via a standard jet nebulizer. Both trials were randomized, double-blind, placebo-controlled, parallel-group trials in adult patients 40 year and older (mean age of 64 years) with a history of smoking greater than or equal to 10-pack years. Patients were diagnosed with moderate to very severe COPD, had an FEV1/FVC ratio of 0.7 or less, and 48% were current smokers. Concomitant therapy, if on a stable dose 30 days prior to screening, was allowed and 37% of patients were taking LABA or ICS/LABA. The primary endpoint was change from baseline trough FEV1 at day 85 (mITT population) and secondary endpoint of number of SGRQ responders (an improvement of 4 or more). Revefenacin increased FEV1 more than placebo in both studies with a LS mean difference of 146 mL and 147 mL, in trials 1 and 2, respectively (**Table 10**).[8,30] Changes were considered statistically and clinically significant. FDA review suggests a greater clinical benefit in patients with very severe COPD. Changes in SGRQ scores were higher with revefenacin but considered statistically significant in only the first study, OR 2.11 (95% CI, 1.14 to 3.92).

Table 10. Results from Trials of Revefenacin[8,30,31]

Study	Comparators	Outcome	Result
Placebo-controlled Study	Revefenacin 88mcg daily and Revefenacin 175 mcg daily Vs. Placebo	Trough FEV^1 at day 85	Placebo adjusted change: Revefenacin 88 mcg: 79 mL Revefenacin 175 mcg: 146 mL
Placebo-controlled study	Revefenacin 88mcg daily and Revefenacin 175 mcg daily Vs. Placebo	Trough FEV^1 at day 85	Placebo adjusted change: Revefenacin 88 mcg: 155 mL Revefenacin 175 mcg: 142 mL
Abbreviations: FEV^1= forced expiratory flow volume; mcg = microgram; mL = milliliter			

Limitations to the data include lack of published trials to be evaluated for bias; however, data from the FDA summary suggests low risk of selection and performance bias.[29] The evidence that is available is from short term, 12-week, trials in patients with previous use or current smoking history. Lack of active treatment comparison limits ability to determine role of revefenacin in the management of COPD. Improvements in FEV1 border on clinical significance, which is a trough FEV1 change of 100-140 mL. There is insufficient evidence for use with other LAMAs.

Clinical Safety:

Safety data comes from 1,798 patients with revefenacin exposure of 12-52 weeks.[31] Common adverse reactions were similar to other LAMA products and include cough, nasopharyngitis, upper respiratory tract infection, headache and back pain. No severe adverse events were reported in either group except for COPD exacerbations. Drug discontinuations from adverse events were similar in with revefenacin and placebo, 13% and 19%, respectively.[31]

Table 11. Pharmacology and Pharmacokinetic Properties.[8]

Parameter	
Mechanism of Action	Revefenacin is a long-acting muscarinic antagonist (i.e., anticholinergic)
Oral Bioavailability	NA
Distribution and Protein Binding	218 L Active metabolite: 71% Human plasma: 42%
Elimination	54% feces and 27% urine
Half-Life	22-70 hours
Metabolism	Hydrolysis

Abbreviations: NA = Not applicable

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Appendix 1: Current Preferred Drug List

Anticholinergics, Inhaled

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

Beta-Agonists, Inhaled Long Acting

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

Corticosteroids, Inhaled

Generic	Brand	Form	PDL
budesonide	PULMICORT FLEXHALER	AER POW BA	Y
fluticasone propionate	FLOVENT HFA	AER W/ADAP	Y
beclomethasone dipropionate	QVAR	AER W/ADAP	Y
fluticasone propionate	FLOVENT DISKUS	BLST W/DEV	Y
fluticasone propionate	ARMONAIR RESPICLICK	AER POW BA	N
mometasone furoate	ASMANEX	AER POW BA	N

budesonide	BUDESONIDE	AMPUL-NEB	N
budesonide	PULMICORT	AMPUL-NEB	N
fluticasone furoate	ARNUITY ELLIPTA	BLST W/DEV	N
flunisolide	AEROSPAN	HFA AER AD	N
ciclesonide	ALVESCO	HFA AER AD	N
mometasone furoate	ASMANEX HFA	HFA AER AD	N
beclomethasone dipropionate	QVAR REDIHALER	HFA AEROBA	N

Corticosteroids/LABA Combination, Inhaled

Generic	Brand	Form	PDL
fluticasone/salmeterol	ADVAIR DISKUS	BLST W/DEV	Y
fluticasone/salmeterol	ADVAIR HFA	HFA AER AD	Y
budesonide/formoterol fumarate	SYMBICORT	HFA AER AD	Y
fluticasone/salmeterol	AIRDUO RESPICLICK	AER POW BA	N
fluticasone/salmeterol	FLUTICASONE-SALMETEROL	AER POW BA	N
fluticasone/vilanterol	BREO ELLIPTA	BLST W/DEV	N
mometasone/formoterol	DULERA	HFA AER AD	N

LAMA/LABA Combination, Inhalers

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

Appendix 2: Abstracts of Comparative Clinical Trials

Combined Analysis of Asthma Safety Trials of Long-Acting β_2-Agonists.

Busse WW, Bateman ED, Caplan AL, Kelly HW, O'Byrne PM, Rabe KF, Chinchilli VM.

BACKGROUND: Safety concerns regarding long-acting β_2-agonists (LABAs) in asthma management were initially identified in a large postmarketing trial in which the risk of death was increased. In 2010, the Food and Drug Administration (FDA) mandated that the four companies marketing LABAs for asthma perform prospective, randomized, controlled trials comparing the safety of combination therapy with a LABA plus an inhaled glucocorticoid with that of an inhaled glucocorticoid alone in adolescents (12 to 17 years of age) and adults. In conjunction with the FDA, the manufacturers harmonized their trial methods to allow an independent joint oversight committee to provide a final combined analysis of the four trials.

METHODS: As members of the joint oversight committee, we performed a combined analysis of the four trials comparing an inhaled glucocorticoid plus a LABA (combination therapy) with an inhaled glucocorticoid alone. The primary outcome was a composite of asthma-related intubation or death. Post hoc secondary outcomes included serious asthma-related events and asthma exacerbations.
RESULTS: Among the 36,010 patients in the intention-to-treat study, there were three asthma-related intubations (two in the inhaled-glucocorticoid group and one in the combination-therapy group) and two asthma-related deaths (both in the combination-therapy group) in 4 patients. In the secondary analysis of serious asthma-related events (a composite of hospitalization, intubation, or death), 108 of 18,006 patients (0.60%) in the inhaled-glucocorticoid group and 119 of 18,004 patients (0.66%) in the combination-therapy group had at least one composite event (relative risk in the combination-therapy group, 1.09; 95% confidence interval [CI], 0.83 to 1.43; P=0.55); 2100 patients in the inhaled-glucocorticoid group (11.7%) and 1768 in the combination-therapy group (9.8%) had at least one asthma exacerbation (relative risk, 0.83; 95% CI, 0.78 to 0.89; P<0.001).
CONCLUSIONS:
Combination therapy with a LABA plus an inhaled glucocorticoid did not result in a significantly higher risk of serious asthma-related events than treatment with an inhaled glucocorticoid alone but resulted in significantly fewer asthma exacerbations.

Effect of background long-acting beta$_2$-agonist therapy on the efficacy and safety of a novel, nebulized glycopyrrolate in subjects with moderate-to-very-severe COPD.
Kerwin EM, Tosiello R, Price B, Sanjar S, Goodin T.
BACKGROUND: Phase III studies demonstrated efficacy and safety of nebulized glycopyrrolate inhalation solution (GLY) in subjects with COPD. Secondary analyses were performed to examine the effect of background long-acting beta$_2$-agonist (LABA) use on the efficacy and safety of nebulized GLY.
METHODS :In two 12-week placebo-controlled studies (GOLDEN 3 and GOLDEN 4) and one 48-week, open-label active-controlled study (GOLDEN 5), a total of 2,379 subjects were stratified by background LABA use (LABA-yes: n=861; LABA-no: n=1,518) and randomized to placebo vs GLY 25 or 50 µg twice daily, or GLY 50 µg twice daily vs tiotropium (TIO) 18 µg once daily. Lung function, patient-reported outcomes, exacerbations, and safety were assessed.
RESULTS: Compared with placebo, pooled data from the 12-week studies showed significant improvements from baseline with GLY 25 and 50 µg across LABA subgroups in trough FEV_1 (LABA-yes: 0.101 and 0.110 L; LABA-no: 0.092 and 0.101 L, respectively; P<0.001) and St George's Respiratory Questionnaire total score (SGRQ; LABA-yes: -2.957 and -3.888; LABA-no: -3.301 and -2.073, respectively; P<0.05). Incidence of treatment-emergent adverse events (TEAEs) was similar in LABA subgroups, and lower in GLY 25 µg vs placebo. In the 48-week active-controlled study, GLY and TIO both showed improvement from baseline across LABA subgroups in FEV_1 (LABA-yes: 0.106 and 0.092 L; LABA-no: 0.096 and 0.096 L, respectively) and in SGRQ total score (LABA-yes: -5.190 and -3.094; LABA-no: -4.368 and -4.821, respectively). Incidence of TEAEs was similar between GLY and TIO, and across LABA subgroups. Exacerbation rates were similar across treatments and LABA subgroups, and cardiovascular events of special interest were more frequent in the LABA-no subgroup. Nebulized GLY, combined with LABA, did not generate any additional safety signals.
CONCLUSION: Nebulized GLY demonstrated efficacy and was well tolerated up to 48 weeks in subjects with COPD with/without background LABA.

Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD.
Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, Dransfield MT, Halpin DMG, Han MK, Jones CE, Kilbride S, Lange P, Lomas DA, Martinez FJ, Singh D, Tabberer M, Wise RA, Pascoe SJ; IMPACT Investigators.
BACKGROUND: The benefits of triple therapy for chronic obstructive pulmonary disease (COPD) with an inhaled glucocorticoid, a long-acting muscarinic antagonist (LAMA), and a long-acting β_2-agonist (LABA), as compared with dual therapy (either inhaled glucocorticoid-LABA or LAMA-LABA), are uncertain.
METHODS: In this randomized trial involving 10,355 patients with COPD, we compared 52 weeks of a once-daily combination of fluticasone furoate (an inhaled glucocorticoid) at a dose of 100 µg, umeclidinium (a LAMA) at a dose of 62.5 µg, and vilanterol (a LABA) at a dose of 25 µg (triple therapy) with fluticasone furoate-vilanterol (at doses of 100 µg and 25 µg, respectively) and umeclidinium-vilanterol (at doses of 62.5 µg and 25 µg, respectively). Each regimen was administered in a single Ellipta inhaler. The primary outcome was the annual rate of moderate or severe COPD exacerbations during treatment.
RESULTS: The rate of moderate or severe exacerbations in the triple-therapy group was 0.91 per year, as compared with 1.07 per year in the fluticasone furoate-vilanterol group (rate ratio with triple therapy, 0.85; 95% confidence interval [CI], 0.80 to 0.90; 15% difference; P<0.001) and 1.21 per year in the umeclidinium-vilanterol group (rate ratio with triple therapy, 0.75; 95% CI, 0.70 to 0.81; 25% difference; P<0.001). The annual rate of severe exacerbations resulting in hospitalization in the triple-therapy group was 0.13, as compared with 0.19 in the umeclidinium-vilanterol group (rate ratio, 0.66; 95% CI, 0.56 to 0.78; 34% difference; P<0.001). There was a higher incidence of pneumonia in the

inhaled-glucocorticoid groups than in the umeclidinium-vilanterol group, and the risk of clinician-diagnosed pneumonia was significantly higher with triple therapy than with umeclidinium-vilanterol, as assessed in a time-to-first-event analysis (hazard ratio, 1.53; 95% CI, 1.22 to 1.92; P<0.001).
CONCLUSIONS: Triple therapy with fluticasone furoate, umeclidinium, and vilanterol resulted in a lower rate of moderate or severe COPD exacerbations than fluticasone furoate-vilanterol or umeclidinium-vilanterol in this population. Triple therapy also resulted in a lower rate of hospitalization due to COPD than umeclidinium-vilanterol. (Funded by GlaxoSmithKline; IMPACT ClinicalTrials.gov number, NCT02164513 .).

FULFIL Trial: Once-Daily Triple Therapy for Patients with Chronic Obstructive Pulmonary Disease.
Lipson DA, Barnacle H, Birk R, Brealey N, Locantore N, Lomas DA, Ludwig-Sengpiel A, Mohindra R, Tabberer M, Zhu CQ, Pascoe SJ.
RATIONALE: Randomized data comparing triple therapy with dual inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA) therapy in patients with chronic obstructive pulmonary disease (COPD) are limited.
OBJECTIVES: We compared the effects of once-daily triple therapy on lung function and health-related quality of life with twice-daily ICS/LABA therapy in patients with COPD.
METHODS: The FULFIL (Lung Function and Quality of Life Assessment in Chronic Obstructive Pulmonary Disease with Closed Triple Therapy) trial was a randomized, double-blind, double-dummy study comparing 24 weeks of once-daily triple therapy (fluticasone furoate/umeclidinium/vilanterol 100 μg/62.5 μg/25 μg; ELLIPTA inhaler) with twice-daily ICS/LABA therapy (budesonide/formoterol 400 μg/12 μg; Turbuhaler). A patient subgroup remained on blinded treatment for up to 52 weeks. Co-primary endpoints were change from baseline in trough FEV_1 and in St. George's Respiratory Questionnaire (SGRQ) total score at Week 24.
MEASUREMENTS AND MAIN RESULTS: In the intent-to-treat population (n = 1,810) at Week 24 for triple therapy (n = 911) and ICS/LABA therapy (n = 899), mean changes from baseline in FEV_1 were 142 ml (95% confidence interval [CI], 126 to 158) and -29 ml (95% CI, -46 to -13), respectively, and mean changes from baseline in SGRQ scores were -6.6 units (95% CI, -7.4 to -5.7) and -4.3 units (95% CI, -5.2 to -3.4), respectively. For both endpoints, the between-group differences were statistically significant (P < 0.001). There was a statistically significant reduction in moderate/severe exacerbation rate with triple therapy versus dual ICS/LABA therapy (35% reduction; 95% CI, 14-51; P = 0.002). The safety profile of triple therapy reflected the known profiles of the components.
CONCLUSIONS: These results support the benefits of single-inhaler triple therapy compared with ICS/LABA therapy in patients with advanced COPD. Clinical trial registered with www.clinicaltrials.gov (NCT02345161).

Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma.
O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, Jorup C, Lamarca R, Ivanov S, Reddel HK.
BACKGROUND: In patients with mild asthma, as-needed use of an inhaled glucocorticoid plus a fast-acting β_2-agonist may be an alternative to conventional treatment strategies.
METHODS: We conducted a 52-week, double-blind trial involving patients 12 years of age or older with mild asthma. Patients were randomly assigned to one of three regimens: twice-daily placebo plus terbutaline (0.5 mg) used as needed (terbutaline group), twice-daily placebo plus budesonide-formoterol (200 μg of budesonide and 6 μg of formoterol) used as needed (budesonide-formoterol group), or twice-daily budesonide (200 μg) plus terbutaline used as needed (budesonide maintenance group). The primary objective was to investigate the superiority of as-needed budesonide-formoterol to as-needed terbutaline with regard to electronically recorded weeks with well-controlled asthma.
RESULTS: A total of 3849 patients underwent randomization, and 3836 (1277 in the terbutaline group, 1277 in the budesonide-formoterol group, and 1282 in the budesonide maintenance group) were included in the full analysis and safety data sets. With respect to the mean percentage of weeks with well-controlled asthma per patient, budesonide-formoterol was superior to terbutaline (34.4% vs. 31.1% of weeks; odds ratio, 1.14; 95% confidence interval [CI], 1.00 to 1.30; P=0.046) but inferior to budesonide maintenance therapy (34.4% and 44.4%, respectively; odds ratio, 0.64; 95% CI, 0.57 to 0.73). The annual rate of severe exacerbations was 0.20 with terbutaline, 0.07 with budesonide-formoterol, and 0.09 with budesonide maintenance therapy; the rate ratio was 0.36 (95% CI, 0.27 to 0.49) for budesonide-formoterol versus terbutaline and 0.83 (95% CI, 0.59 to 1.16) for budesonide-formoterol versus budesonide maintenance therapy. The rate of adherence in the budesonide maintenance group was 78.9%. The median metered daily dose of inhaled glucocorticoid in the budesonide-formoterol group (57 μg) was 17% of the dose in the budesonide maintenance group (340 μg).
CONCLUSIONS: In patients with mild asthma, as-needed budesonide-formoterol provided superior asthma-symptom control to as-needed terbutaline, assessed according to electronically recorded weeks with well-controlled asthma, but was inferior to budesonide maintenance therapy. Exacerbation rates with the two budesonide-containing regimens were similar and were lower than the rate with terbutaline. Budesonide-formoterol used as needed resulted in substantially lower glucocorticoid exposure than budesonide maintenance therapy. (Funded by AstraZeneca; SYGMA 1 ClinicalTrials.gov number, NCT02149199 .).

Efficacy and safety of budesonide/formoterol pMDI vs budesonide pMDI in asthmatic children (6-<12 years).

Pearlman DS, Eckerwall G, McLaren J, Lamarca R, Puu M, Gilbert I, Jorup C, Sandin K, Lanz MJ

BACKGROUND: The efficacy and safety of budesonide/formoterol pressurized metered-dose inhaler (pMDI) have been demonstrated in patients with asthma at least 12 years old.

OBJECTIVE: To evaluate the efficacy of 2 formoterol doses added to budesonide as fixed combinations vs budesonidealone in children 6 to younger than 12 years with asthma.

METHODS: This randomized, double-blinded, parallel-group, multicenter study (NCT02091986; CHASE 3) included children 6 to younger than 12 years with asthma previously receiving a medium-dose inhaled corticosteroid (ICS) or an ICS plus a long-acting β_2-agonist. Children symptomatic during a 7-28-day run-in on low-dose ICS, 1 inhalation of budesonide dry powder inhaler 90 µg twice daily (BID), were randomized to receive 2 inhalations of budesonide/formoterol pMDI 80/4.5 µg (160/9 µg) BID (n = 92), budesonide/formoterol pMDI 80/2.25 µg (160/4.5 µg) BID (n = 95), or budesonide pMDI 80 µg (160 µg) BID (n = 92) for 12 weeks.

RESULTS: Change in forced expiratory volume in 1 second from baseline to 1 hour after dosing (primary end point), change in forced expiratory volume in 1 second 15 minutes after dosing, and peak expiratory flow 1 hour after dosing at week 12 were statistically significantly greater for budesonide/formoterol 160/9 µg vs budesonide ($P \leq .015$ for all comparisons), but not for budesonide/formoterol 160/4.5 µg vs budesonide. Bronchodilator effects, evident 15 minutes after the dose on day 1, were maintained at week 12. Incidence of protocol-defined asthma exacerbations and improvements in asthma symptom-related and quality-of-life outcomes were similar across treatments. There were no notable safety differences among treatments.

CONCLUSION: Budesonide/formoterol pMDI 160/9 µg showed statistically significant and clinically meaningful lung function improvements vs budesonide pMDI 160 µg, demonstrating appropriateness as a therapeutic option for children 6 to younger than 12 years with asthma symptomatic on ICS alone.

AMPLIFY: a randomized, Phase III study evaluating the efficacy and safety of aclidinium/formoterol vs monocomponents and tiotropium in patients with moderate-to-very severe symptomatic COPD.

Sethi S, Kerwin E, Watz H, Ferguson GT, Mroz RM, Segarra R, Molins E, Jarreta D, Garcia Gil E.

BACKGROUND: AMPLIFY assessed the efficacy and safety of aclidinium bromide/formoterol fumarate (AB/FF) vs its monocomponents and tiotropium (TIO) in patients with moderate-to-very severe symptomatic COPD (NCT02796677).

METHODS: In this 24-week, Phase III, double-dummy, active-controlled study, symptomatic patients (COPD Assessment Test score ≥10) were randomized to twice-daily AB/FF 400/12 µg, AB 400 µg, or FF 12 µg, or once-daily TIO 18 µg. Co-primary endpoints were change from baseline at week 24 in 1-hour morning post-dose FEV1 (AB/FF vs AB) and in pre-dose (trough) FEV1 (AB/FF vs FF). Non-inferiority of AB vs TIO in pre-dose FEV1 was also an objective. Normalized area under the curve (AUC)0-3/3 h FEV1 and nighttime and early morning symptoms were also assessed. A subgroup participated in a 24-hour serial spirometry sub-study.

RESULTS: A total of 1,594 patients were randomized; 566 entered the sub-study. At week 24, 1-hour post-dose FEV1 significantly improved with AB/FF vs AB, FF, and TIO (84, 84, and 92 mL; all $P<0.0001$). AB/FF significantly improved trough FEV1 vs FF (55 mL, $P<0.001$) and AB was non-inferior to TIO. AB/FF significantly improved AUC0-3/3 h FEV1 vs all comparators ($P<0.0001$) and provided significant improvements in early morning symptoms vs TIO. The 24-hour spirometry demonstrated significantly greater improvements with AB/FF in AUC12-24/12 h vs all comparators, and in AUC0-24/24 h vs FF or TIO at week 24. CONCLUSION: In patients with moderate-to-very severe symptomatic COPD, twice-daily AB/FF significantly improved lung function vs monocomponents and TIO, and early morning symptom control vs TIO.

Appendix 3: Medline Search Strategy

Search Strategy:

#	Searches	Results
1	Ipratropium/ or ipratropium.mp.	2425
2	tiotropium.mp. or Tiotropium Bromide/	1439
3	aclidinium bromide.mp.	137
4	umeclidinium.mp.	139
5	glycopyrrolate.mp. or Glycopyrrolate/	1232
6	salmeterol.mp. or Salmeterol Xinafoate/	2723
7	aformoterol.mp.	1
8	formoterol.mp. or Formoterol Fumarate/	2149
9	indacterol.mp.	2
10	olodaterol.mp.	127
11	Budesonide/ or budesonide.mp.	5389
12	Fluticasone/ or fluticasone.mp.	3964
13	beclomethasone.mp. or Beclomethasone/	3634
14	mometasone.mp. or Mometasone Furoate/	901
15	Budesonide/ or budesonide.mp.	5389
16	flunisolide.mp.	360
17	ciclesonide.mp.	315
18	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	18754
19	limit 18 to (english language and humans)	14898
20	limit 19 to (yr="2017 -Current" and (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review"))	100

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use YUPELRI™ (revefenacin) inhalation solution safely and effectively. See full prescribing information for YUPELRI (revefenacin) inhalation solution.

YUPELRI (revefenacin) inhalation solution, for oral inhalation
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------

YUPELRI (revefenacin) inhalation solution is an anticholinergic indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

----------DOSAGE AND ADMINISTRATION----------

For oral inhalation use only. Do not swallow YUPELRI.

- One 175 mcg vial (3 mL) once daily. (2)
- For use with a standard jet nebulizer with a mouthpiece connected to an air compressor. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Inhalation solution in a unit-dose vial for nebulization. Each vial contains 175 mcg/3 mL solution. (3)

----------CONTRAINDICATIONS----------

YUPELRI is contraindicated in patients with hypersensitivity to revefenacin or any component of this product. (4)

----------WARNINGS AND PRECAUTIONS----------

- Do not initiate YUPELRI in acutely deteriorating COPD or to treat acute symptoms. (5.1)
- If paradoxical bronchospasm occurs, discontinue YUPELRI and institute alternative therapy. (5.2)
- Worsening of narrow-angle glaucoma may occur. Use with caution in patients with narrow-angle glaucoma and instruct patients to contact a healthcare provider immediately if symptoms occur. (5.3)
- Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction and instruct patients to contact a healthcare provider immediately if symptoms occur. (5.4)
- Immediate hypersensitivity reactions may occur. If such a reaction occurs, therapy with YUPELRI should be stopped at once and alternative treatments should be considered. (5.5)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence greater than or equal to 2% and more common than placebo) include cough, nasopharyngitis, upper respiratory tract infection, headache, and back pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or [24].

----------DRUG INTERACTIONS----------

- Anticholinergics: May interact additively with concomitantly used anticholinergic medications. Avoid administration of YUPELRI with other anticholinergic-containing drugs. (7.1)
- Transporter-related drug interactions: Coadministration of YUPELRI with OATP1B1 and OATP1B3 inhibitors (e.g. rifampicin, cyclosporine, etc.) may lead to an increase in exposure of the active metabolite. Therefore, coadministration with YUPELRI is not recommended. (7.2., 12.3)

----------USE IN SPECIFIC POPULATION----------

Hepatic impairment: Avoid use of YUPELRI in patients with hepatic impairment. (8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/20

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Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
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Appendix 5: Key Inclusion Criteria

Population	Patients with asthma or COPD
Intervention	Maintenance therapy with anticholinergics, LABA, ICS and/or combinations of these products
Comparator	Therapies listed above
Outcomes	Exacerbations, spirometry, dyspnea, requirement of oral corticosteroid therapy, hospitalizations, emergency department visits, mortality
Timing	Presentation of symptoms
Setting	Outpatient management

Long-acting Beta-agonists (LABA)

Goals:

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

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred LABA products

Covered Alternatives:

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

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

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

Implementation: *3/1/18; 10/9/15; 8/12; 1/10*

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

Goals:

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

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred LABA/ICS products

Covered Alternatives:

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

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

Approval Criteria		
2. Will the provider consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of covered alternatives in class	**No:** Go to #3
3. Does the patient have a diagnosis of asthma or reactive airway disease ~~(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

Approval Criteria		
8. Is there a documented trial of an inhaled corticosteroid (ICS) or does the patient have moderate or ~~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: *5/19 (KS), 1/18 (KS); 9/16; 11/15; 9/15; 11/14; 11/13; 5/12; 9/09; 2/06*
Implementation: *3/1/18; 10/13/16; 1/1/16; 1/15; 1/14; 9/12; 1/10*

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

Goals:

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

Length of Authorization:

- Up to 12 months

Requires PA:

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

Covered Alternatives:

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

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

Approval Criteria		
6. Is the request for a LAMA/LABA combination product?	**Yes:** Go to #7	**No:** Go to #8
7. Is there a documented trial of a LAMA or LABA, or alternatively a trial of a fixed dose combination short-acting anticholinergic with beta-agonist (SAMA/SABA) (i.e., ipratropium/albuterol), or ≥ 2 moderate exacerbations or ≥ 1 leading to a hospitalization?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA and LABA inhalers or scheduled SAMA/SABA inhalers (PRN SABA or SAMA permitted).	**No:** Pass to RPh. Deny; medical appropriateness.
~~6.~~8. Is the request for a ~~the~~ 3 drug ICS/LABA/LAMA combination product ~~fluticasone furoate, umeclidinium and vilanterol (Trelegy Ellipta)~~ and is there a documented trial of a LAMA and LABA, or ICS and LABA or ICS and LAMA? ~~?~~	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA, LABA and ICS inhalers.~~Go to #7~~	**No:** Pass to RPh. Deny; medical appropriateness.~~**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.~~
~~• 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~~
~~• 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.~~

Inhaled Corticosteroids (ICS)

Goals:

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

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred ICS products

Covered Alternatives:

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

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

Approval Criteria		
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Is the request for treatment of asthma or reactive airway disease ~~(ICD10 J45.20-J45.22, J45.901-45.998)~~?	**Yes:** Go to #7	**No:** Go to #4
4. Is the request for treatment 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