Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Class Update: Asthma/COPD Medications

Month/Year of Review: July 2014
PDL Classes: Asthma Controller, Asthma Rescue, COPD
New drug(s): Anoro® Ellipta® (umeclidinium/vilanterol)

Last Oregon Review: May 2012/November 2013
Source Documents: OSU College of Pharmacy
Manufacturer: GSK/Theravance
Dossier Received: Yes

Current Status of PDL Classes:

Chronic Obstructive Pulmonary Disease (COPD):

- **Preferred Agents**: IPRATROPIUM BROMIDE HFA AER AD, IPRATROPIUM BROMIDE SOLUTION, IPRATROPIUM/ALBUTEROL SULFATE AMPUL-NEB, TIOTROPIUM BROMIDE(SPIRIVA®) CAP W/DEV, IPRATROPIUM/ALBUTEROL (COMBIVENT®) RESPIMAT
- **Non-Preferred Agents**: AFORMOTEROL (BROVANA®), FORMOTEROL (PERFOROMIST), ROFLUMILAST (DALIRESP®), INDACATEROL (ARCAPTA®) NEOHALER, ACLIDINIUM (TUDORZA®) PRESSAIR, VILANTEROL/FLUTICASONE (BREO®) ELLIPTA

Asthma Controllers and Asthma Rescue

- **Preferred Agents**: BECLOMETHASONE DIPROPIONATE(QVAR®), BUDESONIDE (PULMICORT FLEXHALER®), BUDESONIDE / FORMOTEROL FUMARATE (SYMBICORT®), FLUTICASONE PROPIONATE(FLOVENT HFA®), FLUTICASONE PROPIONATE(FLOVENT DISKUS®), FLUTICASONE/SALMETEROL(ADVAIR DISKUS®), FLUTICASONE/SALMETEROL(ADVAIR HFA®), FORMOTEROL (FORADIL®) AEROLIZER, MONTELUKAST SODIUM TAB CHEW/TABLET, SALMETEROL XINAFOATE (SEREVENT®), ALBUTEROL SULFATE SOLUTION/VIAL NEBS, PIRBUTEROL ACETATE, PROAIR® HFA, VENTOLIN® HFA
- **Non-preferred Agents**: CICLESONIDE (ALVESCO®), TRIAMCINOLONE ACETONIDE, ZILEUTON, ARFORMOTEROL, FORMOTEROL FUMARATE/EFORMOTEROL, OMALIZUMAB (XOLAIR®), INDACTEROL, MOMETASONE FUROATE (ASMANEX®) MOMETASONE/FORMOTEROL, BUDESONIDE/FORMOTEROL, MOMETASONE/FORMOTEROL (DULERA®), ZAFIRLUKAST

Research Questions:

- Is there new comparative efficacy and effectiveness in the treatment of persistent asthma or COPD?
- Is there any new comparative evidence of a meaningful difference in harms of medications used to treat persistent asthma or COPD?
- Is there any evidence that umeclidinium/vilanterol is more effective or safer than other long acting beta agonist/ long acting muscarinic agonist (LABA/LAMA) combination products in adults with COPD?
- Are there subgroups of patients in which umeclidinium/vilanterol is more effective or safer than other available treatments for the treatment of COPD in adults?

Conclusions:

- Overall findings from the DERP systematic review did not suggest that a single medication within any of the classes evaluated is significantly more effective or harmful than the other medications within the same class in the treatment of persistent asthma or COPD.[1]
- There is moderate quality evidence that ICSs do not differ in their ability to control asthma symptoms, prevent asthma exacerbations, and reduce the need for additional rescue medication at equipotent doses administered through comparable delivery devices. There are no head to head trials comparing ICSs in the treatment of COPD. [1]
- For patients with COPD, results indicated that monotherapy with ICS and LABAs are similarly effective and have similar risk of experiencing any adverse event. However, there was low-strength evidence that treatment with ICS increases the risk of serious pneumonia.[1]
- Umeclidinium demonstrated a statistically and clinically significant increase in mean change from baseline in the change from baseline FEV1 relative to placebo (115 mL; 95% CI 76 to 155). There is insufficient comparative evidence demonstrating superior efficacy or safety of umeclidinium to other available agents.
- There is low quality evidence that mometasone HFA improves change from baseline mean trough FEV1 at 12 weeks versus placebo (mometasone HFA 100mg difference from placebo 0.12 L; 95% CI 0.05 to 0.2). There is insufficient evidence to determine the efficacy and safety of mometasone HFA compared to mometasone Twisthaler.
- There is low quality evidence that flunisolide HFA improves change in baseline FEV1 at 12 weeks compared to placebo (0.3 L for the 160 mcg group, 0.35 L for the 320 mcg group, and 0.14L for placebo). There is insufficient evidence to determine the safety and efficacy of flunisolide HFA compared to flunisolide.
- There is moderate quality evidence that once daily umeclidinium/vilanterol is effective at improving lung function in patients with moderate to severe COPD, as measured by the change from baseline in trough FEV1 compared to placebo (0.17 L; 95% CI 0.13-0.21; $p < 0.001$). Trials have been short-term, and the long-term safety and efficacy of umeclidinium/vilanterol is unknown. There is insufficient evidence to determine the comparative efficacy of umeclidinium/vilanterol. There is insufficient evidence to draw conclusions about the ability of umeclidinium/vilanterol to decrease exacerbations, reduce shortness of breath, or improve quality of life.
- Serious adverse events were similar among treatment groups versus placebo. The most common adverse events are pharyngitis, sinusitis, lower respiratory tract infection, constipation, diarrhea, pain in extremity, muscle spasms, neck pain and chest pain (all ≥1% of patients and more common than with placebo.
- There is insufficient evidence for differences in subpopulations in which umeclidinium/vilanterol is more effective or safer.

Recommendations:

- Due to no evidence demonstrating clinical superiority of umeclidinium/vilanterol over current agents, recommend making it non-preferred.
- Recommend adding prior authorization criteria to umeclidinium/vilanterol to ensure it is being used appropriately and limiting to patients who have COPD (appendix 2).
- Due to no evidence demonstrating clinical superiority of umeclidinium over current agents, recommend making it non-preferred.
- Due to no evidence demonstrating clinical superiority of mometasone HFA over current agents, recommend making it non-preferred.
- Due to no evidence demonstrating clinical superiority of flunisolide HFA over current agents, recommend making it non-preferred.
- Due to no strong comparative effectiveness of superiority between other agents, recommend comparing costs in executive session.
- Reorganize PDL classes as followed:

- Long-acting Bronchodilators
- Short-acting beta agonists
- Anticholinergic inhalers
- Combination Inhalers
- Inhaled Corticosteroids
- Miscellaneous Pulmonary Drugs

Reason for Review:
The Pacific Northwest Evidence-Based Practice Center Drug Effectiveness Review Project (DERP) published a drug class review on drugs to treat asthma and chronic obstructive pulmonary disease (COPD) in April 2014. This update will summarize findings from the DERP class review and identify other new relevant comparative effectiveness evidence, high-quality systematic reviews, or evidence-based guidelines, as well as review the evidence for umeclidinium/vilanterol (Anoro® Ellipta®), a new drug (combination of a long acting anticholinergic and LABA) approved in December 2013 and two new formulations, umeclidinium (Incruse® Ellipta®) and mometasone (Asmanex®) HFA. Changes to the PDL pulmonary drug class classification will also be reviewed. Currently, the classes are "Asthma Controller", "Asthma Rescue" and "COPD". Many medications in these classes are used for both asthma and COPD and the classes do not reflect current use.

Previous P&T Conclusions for Asthma Controllers (May 2012):

- Inhaled corticosteroids (ICS) are recommended for adults and children with persistent asthma. ICS are considered the most potent and effective long-term control treatment. ICS have been shown to reduce the symptoms of asthma severity, improve quality of life, improve lung function, prevent exacerbations, reduce healthcare utilization, and reduce the risk of death due to asthma.
- Long-acting beta-agonists (LABA) are the preferred adjunctive therapy, when combined with an ICS, in adults and children with persistent asthma not controlled with an ICS alone. Systematic reviews and guidelines suggest the addition of LABA improve airway function, quality of life and reduce asthma symptoms and short-acting rescue inhaler use. New safety data recommends that equal consideration should be given to increasing the dose of ICS or adding a LABA in patients with uncontrolled persistent asthma. FDA labeling states that ICS/LABA combination products are indicated for patients not adequately controlled on other asthma controller medications.
- Asthma controller medications that are alternatives, but not preferred options, for patients requiring step 2 care (persistent asthma) include: cromolyn sodium, nedocromil, montelukast, zafirlukast, zileuton and theophylline.
- Anti-IgE therapy, i.e., omalizumab, is recommended for patients whom have a specific sensitivity to a relative allergen and require step 5 or 6 care (persistent asthma on high-dose ICS, LABA or montelukast +/- oral steroids).
- Additional data on the safety of LABA, especially in children, is needed to help delineate the risks and benefits of treatment.

Previous P&T Conclusions for COPD (November 2013):

- There is moderate to high quality evidence based on a very recent Cochrane review that compared to ipratropium, tiotropium results in improved lung function, fewer COPD exacerbations (OR 0.71, 95% CI 0.52 to 0.95), fewer hospital admissions (OR 0.34, 95% CI 0.15 to 0.76) and improved quality of life. There was also moderate quality evidence of no difference in all-cause mortality (OR 1.30, 95% CI 0.44 to 4.39).
- There is low quality evidence of no difference between tiotropium and LABAs in mortality (OR 0.82, 95% CI 0.60 to 1.13), and overall hospitalizations (OR 0.93, 95% CI 0.57-0.93). However, there is moderate quality evidence that tiotropium was associated with fewer COPD exacerbations compared with LABA (OR 0.86, 95% CI 0.79 to 0.93). There was insignificant evidence to conclude whether tiotropium or LABAs result in improved quality of life and insignificant evidence to compare the combination of tiotropium plus LABA with tiotropium alone
- Published trials use the surrogate marker of change in FEV1 to evaluate the efficacy of fluticasone/vilanterol, while mortality remains most desired clinical outcome. There remains insufficient evidence to determine its effects on mortality and other patient-related outcomes.
- There is moderate quality evidence that once daily fluticasone/vilanterol is effective at improving lung function in patients with moderate to severe COPD, as measured by the weighted mean FEV1 (0-4 h post-dose) after 24 weeks of treatment compared to placebo (0.173 L, $p<0.001$). Trials have been short-term, and the long-term safety and efficacy of fluticasone/vilanterol is unknown.
- Serious adverse events were similar among treatment groups versus placebo. The most common adverse events are pneumonia, decrease in bone mineral density, nasopharyngitis, upper respiratory tract infection, oral candidiasis and headache (all seen in ≥5% of patients).
- There is insufficient evidence for differences in subpopulations in which fluticasone/vilanterol is more effective or safer.
- There is moderate quality evidence that fluticasone/vilanterol is non-superior to fluticasone/salmeterol 250/50 ug after 12 weeks of therapy in change in FEV1 after 12 weeks.
- There is no evidence demonstrating clinical superiority of aclidinium bromide over tiotropium, and limited long term effectiveness or safety evidence of aclidinium bromide compared to tiotropium.
- There is insufficient comparative effectiveness evidence between inhaled corticosteroids and long acting agents. Choice of agent should be based on availability, cost of medication and the patient's response.

Background:

Asthma is a chronic lung disease characterized by reversible airway obstruction, inflammation and increased airway responsiveness. As a result of inflammation, individuals with asthma may experience symptoms such as wheezing, difficulty breathing, or coughing. The airway obstruction which occurs with asthma is generally reversible spontaneously or with treatment. The Expert Panel of the National Asthma Education and Prevention Program (NAEPP) asthma categories are intermittent and persistent (subdivided into mild, moderate or severe).

COPD is another chronic lung disease, characterized primarily by persistent airflow limitation. Smoking is the most common risk factor. COPD is more common over the age of 40 and is usually progressive, becoming more severe over time, and is usually associated with an increased inflammatory response to smoke and other airborne particles. Chronic inflammation may destroy lung tissue, causing emphysema, and/or lead to small airway damage and obstruction. However, the current COPD definition from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) does not describe emphysema and chronic bronchitis as COPD subtypes, as has been done in the past. Instead, COPD is defined as a mixture of airflow obstruction, alveolar destruction and chronic inflammation. The GOLD classification was updated to include grades A-D (A being low risk of exacerbations and D being a high risk of exacerbations) based upon a combination of clinical symptoms, most notably dypsnea, FEV1 and number of yearly exacerbations.

Many current medications available to treat persistent asthma target the inflammatory process caused by multiple inflammatory cells and mediators including lymphocytes, mast cells and eosinophils, among others. There are currently two categories of medications used for asthma treatment, controller medications and quick relief (or rescue) medications. All patients with persistent asthma should have a short-acting relief (or rescue) medication for the treatment of exacerbations and a controller medication for long-term control. Inhaled corticosteroids (ICS) are the preferred agents for long-term control in all stages of persistent asthma. Long-acting beta-2 agonists (LABAs) are agents used in combination with ICSs to obtain control in persistent asthma. The NAEPP expert panel advocates for the use of LABAs as the preferred adjunct with an ICS in individuals ≥12 years old for persistent asthma. LABAs may also be used in preventing exercised-induced bronchospasm, but are not approved or recommended for relief of acute asthma symptoms or for use as monotherapy for persistent asthma. Leukotriene modifiers can also be used to help control asthma symptoms.

Pharmacotherapy recommendations for COPD differ from those for asthma, although the drugs used overlap. Either a LABA or a long-acting anticholinergic (also known as a long-acting muscarinic agonist or LAMA) are used as first-line therapy, rather than an ICS. The GOLD guidelines recommend treatment sequencing for patients with disease of increasing severity of (1) LABA or LAMA, (2) ICS/LABA *or* LAMA, and (3) ICS/LABA *and/or* LAMA. They also include roflumilast (a phosphodiesterase-4 [PDE-4] inhibitor) as an option to prevent exacerbations, given in combination with long-acting bronchodilators as an alternative to ICS treatment. LAMA/LABA combination may be considered when symptoms are not improved with a single agent. Long-term treatment with an ICS is recommended for patients with severe and very severe airflow limitations and patients with frequent exacerbations that are not adequately controlled by a LAMA or LABA. The American College of Physicians and collaborating organizations consider evidence for combination therapy weaker than that for monotherapy and state that clinicians may consider combination therapy.

There are many drugs used in both asthma and COPD, but there are a few drugs that are only used in one of these diseases. Tiotropium (a LAMA) and roflumilast (a PDE-4 inhibitor) are approved for the treatment of COPD, but not for asthma. Leukotriene modifiers (leukotriene receptor antagonists and 5-lipoxygenase inhibitors), cromolyn sodium, nedocromil, montelukast, theophylline and omalizumab are used in the treatment of asthma only.

Many trials for asthma and COPD use a surrogate endpoint of change in FEV1 because it is highly reproducible in a majority of patients. However, FEV1 measurements do not always correlate with clinically relevant outcomes such as dyspnea, health status, exercise capacity, quality of life, exacerbations or hospitalization, and changes in lung volume can occur without concomitant changes in FEV1.[2] The American Thoracic Society/European Respiratory Society (ATS/ERS) suggests a minimally important difference of 100-140 ml is an appropriate value, although this value remains poorly defined in COPD patients.[3]

Umeclidinium/vilanterol 62.5/25 mcg is a new combination inhalation product comprised of a LAMA and a LABA and is delivered with the dry powder inhaler Ellipta®. Neither component is currently marketed as a single-ingredient inhalation product, although vilanterol is a component in fluticasone/vilanterol (Breo® Ellipta®), an ICS/LABA combination inhaler approved for use in COPD. This is the first LAMA/LABA combination product that is approved for the treatment of COPD. It is not approved for use in patients with asthma, although it may be used off-label, and carries a safety warning in patients with asthma, as LABAs increase the risk of asthma-related death.[4]

In planning for efficacy studies, the investigators planned a step-down closed statistical testing procedure a priori. This accounts for multiplicity across treatment comparisons and ensures that statistical significance is truly achieved, rather than the appearance of statistical significance through chance. A step-wise statistical testing hierarchy was used whereby (1) the highest combination dose was compared to placebo, (2) the lowest combination product was compared to

placebo, (3) the highest combination was compared to each component and (4) the lowest combination was compared to each component. Each comparison had to be statistically significantly different in order for subsequent tests to have statistical significance.

Methods:
A Medline literature search was conducted for new systematic reviews and randomized controlled trials (RCTs) comparing beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, triamcinolone, mometasone, formoterol, arformoterol, salmeterol, indacaterol, montelukast, zafirlukast, zileuton, phosphodiesterase-4, roflumilast, tiotropium and aclidinium since the date of the literature search included in the DERP report (January 2014). The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Care Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, UpToDate, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches,

Systematic Reviews:
Drug Effectiveness Review Project (DERP) Report

A systematic review as performed to compare the efficacy and safety of ICSs, LABAs, leukotriene modifiers (LMs), long-acting anticholinergics, phosphodiesterase-4 inhibitors, and combination products for people with persistent asthma or COPD. [1] However, as it was a streamlined report, only direct comparisons were included. Placebo controlled trials were excluded from the review. Overall, the authors concluded that the evidence does not suggest that one medication within any of the classes is more effective or harmful than another medication.[1] Results support starting treatment for persistent asthma with an ICS, followed by the addition of a LABA as the next step. [1] In the treatment of COPD, monotherapy with ICS and LABAs are similar in efficacy and have similar risk of adverse events. [1] There is low strength evidence that treatment with ICS increases the risk of serious pneumonia and the evidence for newer medications is of insufficient or low strength for most outcomes. [1]

<u>Inhaled Corticosteroids</u>
Overall, efficacy studies provide moderate quality evidence that ICSs do not differ in their ability to control asthma symptoms, prevent exacerbations, and reduce the need for additional rescue medication at equipotent doses administered through comparable delivery devices. [1] Relatively few studies reported exacerbations, healthcare utilization (hospitalizations, emergency visits) or quality of life outcomes. [1] There was moderate strength of evidence from 2 studies that fluticasone reduces the risk of exacerbations better than beclomethasone.[1] Long-term data (beyond 12 weeks) is lacking for most comparisons. [1] In children, head-to-head trials do not show a difference in health outcomes, but data were only available for 5 comparisons (3 systematic reviews and 7 RCTs): beclomethasone compared with fluticasone, beclomethasone compared with budesonide, budesonide compared with ciclesonide, budesonide compared with fluticasone and ciclesonide compared with fluticasone. [1]

There are no ICS products approved by the FDA for the treatment of COPD. No head-to-head trials comparing ICS with another were identified.[1]

<u>Leukotriene Modifiers</u>

Limited head-to-head evidence from 2 short-term (12 week) studies does not support differences between leukotriene modifiers (montelukast and zafirlukast) in ability to decrease rescue medicine use or improve quality of life in patients with asthma, although symptoms improve slightly more with zileuton than montelukast in patients in India (low quality evidence). [1] There were no head-to-head trials comparing zafirlukast to zileuton identified, or any trials in patients with COPD.[1]

LABAs

Results from 3 efficacy studies provide moderate evidence that LABAs do not differ in their ability to prevent exacerbations, improve quality of life, and prevent hospitalizations or emergency visits in patients ≥ 12 years with persistent asthma not controlled on ICSs alone.[1] In children, direct evidence is limited to 1 fair-quality trial enrolling children and adolescents age 6-17. [1] The trial reported no difference in exacerbations, quality of life, missed work, or missed school in subjects treated with formoterol compared to those treated with salmeterol.[1]

There is low quality evidence that arformoterol and formoterol are associated with similar exacerbation rates and improvements in quality of life in patients with COPD. [1] Nebulized formoterol is similar to formoterol via dry powder inhaler in its effects on exacerbations and quality of life. Formoterol and indacaterol have similar impacts on exacerbations and quality of life (low quality evidence). [1] There was a trend towards improved exacerbation and quality of life outcomes for formoterol versus arformoterol.

ICS/LABA

Overall, results from 4 large trials of up to 6 months duration provide moderate strength evidence that there is no significant difference in efficacy between fixed-dose combination treatment with budesonide/formoterol and fluticasone/salmeterol. [1] There is no statistically significant difference between the risk of exacerbations requiring oral steroids (OR 1.11; 95% CI 0.95 to 1.3) or exacerbations requiring emergency visits or hospital admissions (OR 0.74; 95% CI 0.53 to 1.03). [1] Quality of life measures specific to asthma also found no difference between these treatments.[1] Moderate strength evidence from 2 trials (12 weeks and 52 weeks) indicated no difference in asthma deteriorations (emergency visits, hospitalizations or requiring additional medicine) between mometasone/formoterol and fluticasone/salmeterol at medium doses. [1] Low strength evidence from only the 52-week study also suggests no difference between mometasone/formoterol and fluticasone/salmeterol at high doses. A single study of fluticasone/salmeterol and fluticasone/vilanterol provides low strength evidence of no difference in quality of life between the treatments. [1]

No head-to-head trials comparing 2 or more fixed-dose combination products of ICS/LABA in patients with COPD that reported efficacy or effectiveness outcomes were found. [1]

LAMAs

No reviews or head-to-head RCTs comparing LAMAs in patients with either COPD or asthma were found. [1]

ICS vs Leukotriene Modifiers

No evidence comparing ICSs with leukotriene modifiers in patients with COPD was found. [1] In patients with asthma, efficacy studies up to 56 weeks in duration provide consistent evidence favoring ICSs over LMs for the treatment of asthma as monotherapy for both children and adults for exacerbations and quality of life (high strength evidence).[1] Results for rescue medicine use and asthma symptoms also favored ICSs. [1]

ICSs vs LABAs

Overall, efficacy studies provide consistent evidence favoring ICSs over LABAs for the treatment of asthma monotherapy in children and adults (high strength evidence). [1] Those treated with LABAs had significantly higher odds of experiencing an exacerbation than those treated with ICSs (OR 2.12; 95% CI 1.53-2.95; 7 studies). [1] There was no statistically significant differences in measures of symptoms or rescue medicine use in the meta-analysis, although the majority of individual RCTs included in this review reported no differences or favorable results for those treated with ICSs compared to those treated with LABAs for almost all outcomes.[1] LABAs are not recommended or approved for use as monotherapy for persistent asthma. [1]

In COPD, there is low quality evidence of no difference between ICS and LABA in mortality (OR 1.17; 95% CI 0.97-1.42).[1] There is moderate quality evidence of no difference between ICS and LABA in exacerbations (OR 0.96; 95% CI 0.89-1.02) or in hospitalizations due to exacerbations (RR 1.07; 95% CI 0.91-1.26).[1]

Leukotriene Modifiers vs LABAs

There is insufficient evidence to draw any firm conclusions about the comparative efficacy of leukotriene modifiers and LABAs for uses as monotherapy for persistent asthma. [1] Neither are recommended nor approved for use as monotherapy for persistent asthma. [1]

No head-to-head trials comparing leukotriene modifiers with LABAs in COPD were identified. [1]

LABAs vs LAMAS

There is low strength evidence that step-up therapy with either tiotropium or salmeterol in patients whose asthma was not controlled by ICS alone does not differ in its effects on exacerbations or quality of life. [1] Evidence was insufficient to support conclusions about mortality and hospitalizations. [1]

In COPD, evidence for mortality is insufficient to support any conclusions about the comparative effects of tiotropium and LABAs. [1] Compared with salmeterol, there is moderate strength evidence that tiotropium is associated with fewer patients experiencing 1 or more exacerbations and low strength evidence that tiotropium and salmeterol do not differ in hospitalizations and proportions of patients with clinically significant improvement in quality of life. [1] Compared with indacaterol, there is low strength of evidence that tiotropium was associated with significantly lower proportions of patients with clinically significant improvement in quality of life, but the drugs did not differ in hospitalizations or exacerbations. [1] There is low strength of evidence that tiotropium and formoterol do not differ in exacerbations and insufficient evidence to draw conclusions about hospitalizations and quality of life. [1]

ICS vs PDE-4 Inhibitors

There is low strength of evidence that more patients taking roflumilast experienced exacerbations than did those taking beclomethasone in patients with asthma. [1] There were no trials of this comparison in COPD patients. [1]

ICS/LABA vs Higher Dose ICS

There is high strength of evidence that there is greater efficacy with the addition of a LABA to an ICS than increasing the dose of the ICS for adults and adolescents with persistent asthma. [1] There is insufficient evidence in children with asthma and no trials with this comparison in patients with COPD. [1]

ICS/LABA vs LAMA

There was no evidence of this comparison in patients with asthma.[1]

In patients with COPD, there is low strength evidence that, compared with tiotropium, fluticasone/salmeterol was associated with lower risk of mortality, higher risk of hospitalization and a lower proportion of patients with a clinically significant improvement in quality of life and no difference in effects on exacerbations. [1] There is low strength evidence that tiotropium and fluticasone/vilanterol do not differ in their effects on mortality and insufficient evidence to draw conclusions about how tiotropium and fluticasone/vilanterol compare for hospitalizations, exacerbations and quality of life.[1] For the comparison of umeclidinium bromide/vilanterol vs tiotropium, there is low strength evidence of no statistically significant difference in risk of mortality and insufficient evidence to draw conclusions about other effectiveness outcomes. [1]

ICS/Leukotriene Receptor Antagonist vs ICS

The addition of leukotriene receptor antagonists to ICSs compared to continuing the same dose of ICS in patients with asthma resulted in improvement in rescue medicine use and a non-statistically significant trend toward fewer exacerbations requiring systemic steroids. [1] There is no apparent difference in symptoms, exacerbations, or rescue medicine use between the two groups. [1] There were some conflicting results and further research may alter the results. There was no evidence in patients the COPD for this comparison. [1]

ICS/LABA vs Leukotriene Modifier

The combination of fluticasone/salmeterol is more efficacious than montelukast for the treatment of persistent asthma.[1] No studies in patients with COPD were found for this comparison. [1]

Addition of LABA compared to Leukotriene Receptor Antagonist as Add-On Therapy to ICS

There is high strength evidence that the addition of a LABA to ICS therapy prevents exacerbations in more patients than does the addition of a leukotriene receptor antagonist to ICS therapy for adolescents and adults with persistent asthma.[1] There was high strength of evidence that the choice of a LABA versus a leukotriene receptor antagonist did not affect quality of life.[1]

Addition of LABA to ICS compared to switching ICS

There is low strength of evidence of no difference in exacerbations between fluticasone/vilanterol versus fluticasone propionate in patients with asthma. [1] There were no comparisons in patients with COPD. [1]

Subgroup Analyses-Asthma

Age: See above for specific differences in efficacy or adverse events between children and adolescents or adults. For children under 4 years of age, no head-to-head studies were found, but one study included a subgroup analysis of patients age 2 to 4. This analysis suggested more exacerbations per patient and more patients with serious adverse events for montelukast compared with budesonide, with risk differences greater among the younger patients (low strength).

Elderly: There were no head –to-head studies comparing the safety and efficacy of older adults treated with ICS. One case-control study on older adults found 2-fold increase in serious pneumonia with fluticasone compared to controls with a dose-response relationship. Budesonide had 17% increase in serious pneumonia compared to controls without a dose-response effect (low strength of evidence).

Racial groups: A trial including 63 African American and 375 Caucasian patients with COPD suggested higher risk of serious adverse events and withdrawals due to adverse events among African American patient taking aformoterol compared with formoterol, though there were few events in this small subgroup. These risk differences were not apparent among Caucasians (low strength of evidence).

Gender: One observational study suggested that the effects on montelukast compared with ICSs budesonide or fluticasone on linear growth velocity do not differ between boys and girls (low strength of evidence).

Pregnancy: No head-to-head studies were found. Budesonide is the only ICS labeled pregnancy category B; the other ICSs are category C. LABA and lower dose ICS were not associated with low birth weight, preterm birth or small for gestational age babies. Higher dose ICS increased the risk of having a low birth weight or small for gestational age baby. (Low strength of evidence)

New Guidelines:
An update to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines was published in January 2014.[5] Changes in pharmacologic recommendations focus around medications approved since the GOLD guidelines were first published in 2011. [5] Among long-acting anticholinergics, aclidinium and glycopyrronium appear to have a similar action on lung function and breathlessness as tiotropium but less data are available for other outcomes.[5] Combinations of a long-acting beta2-agonist and a long-acting anticholinergic have shown a significant increase in lung function whereas the impact on patient reported outcomes is still limited. [5] There is still too little evidence to determine if a combination of long-acting bronchodilators is more effective than a long-acting anticholinergic alone for preventing exacerbations. [5] While there were no changes to the treatment algorithm, there is a suggestion of using two short comprehensive symptom measures (COPD Assessment Test, CAT, and COPD Control Questionnaire, CCQ) as one tool to stratify a patient into a Patient Group (A-D) in order to guide the initial pharmacologic management. [5]

New Safety Alerts, Indications:
None

New Formulations:
<u>Umeclidinium (Incruse® Ellipta®)</u>

Umeclidinium was approved in April 2014 for the maintenance treatment of COPD.[6] It is the same strength and in the same delivery device as umeclidinium/vilanterol (Anoro® Ellipta®) (see below).[6] Umeclidinium should be administered as 1 inhalation once daily.[6] FDA approval was based on one 24-week efficacy trial which included 698 patients with a mean age of 63, an average smoking history of 46 pack-years and 50% identified as current smokers.[6] The primary endpoint was change from baseline in trough FEV1 at Day 169 compared to placebo.[6] Umeclidinium demonstrated a statistically and clinically significant increase in mean change from baseline in the change from baseline FEV1 relative to placebo (115 mL; 95% CI 76 to 155).[6] Health-related quality of life was

measured using St. George's Respiratory Questionnaire (SGRQ); umeclidinium demonstrated an improvement in mean SGRQ total score compared with placebo treatment at Day 168: -4.69 (95% CI: -7.07,-2.31).[6] There is insufficient comparative evidence demonstrating superior efficacy or safety to other available agents.

Mometasone (Asmanex®) HFA

Mometasone HFA was approved in April 2014 for the treatment of asthma.[7] It contains slightly different doses than delivered by the Twisthaler® device already on the market at 100 mcg and 200 mcg doses, compared to 110 mcg and 220 mcg contained in the Twisthaler®.[7] The safety and efficacy of mometasone HFA was demonstrated in two randomized, double-blind, placebo- or active-controlled multi-center clinical trials of 12 and 26 weeks' duration, conducted as part of a mometasone/formoterol (Dulera®) 100/5 mcg or 200/5 mcg combination product development program. [7] One trial evaluated 781 patients, of which 192 patients received mometasone HFA 100 mcg and 196 patients received placebo. [7] Patients ranged from 12 to 76 years of age, 59% were female, 72% were Caucasian, and all had persistent asthma and were not controlled on medium dose of inhaled corticosteroids prior to randomization. [7] Mean FEV1 and mean percent predicted FEV1 were similar among all treatment groups (2.33 L, 73%).[7] The change from baseline to week 12 in the mean trough FEV1 was greater among patients receiving mometasone HFA 100 mcg than among those receiving placebo (treatment difference from placebo 0.12 L; 95% CI 0.05 to 0.2).[7]

A second trial evaluated mometasone in combination with formoterol at both doses and did not contain a mometasone-only arm [7] In order to assess the added benefit of a higher dose of mometasone in the 200 mcg mometasone product compared to the lower dose 100 mcg product, trough FEV1 at 12 weeks was compared between the combination mometasone/formoterol 200/5 mcg and 100/5 mcg treatment groups as a secondary endpoint.[7] Improvement in trough FEV1 from baseline to week 12 in patients who received mometasone/formoterol 200/5 mcg was not statistically different than among patients who received mometasone/formoterol 100/5 mcg (treatment difference: 0.05 L; 95% CI -0.02 to 0.10).[7]

Flunisolide (Aerospan®) HFA

Flunisolide HFA was approved in August 2013 for the treatment of asthma. The safety and efficacy of flunisolide HFA was evaluated in two randomized, double blind, placebo- or active-controlled trials of 12 weeks duration in patients with mild to moderate asthma. One trial included 669 adults and adolescents 12 years of age and older. Patients were randomized to flunisolide HFA at doses of 80 mcg, 160 mcg or 320 mcg twice daily, flunisolide CFC (original formulation, AeroBid which is now removed from the market) at doses of 250 mcg, 500 mcg or 1000 mcg twice daily, or placebo for 12 weeks. Compared to placebo, flunisolide HFA 160mcg and 360mcg demonstrated a statistically significant improvement in FEV1, but the 80 mcg dose did not. The study was not powered to show a difference between the active treatment groups, so no head-to-head analysis was conducted. FEV1 efficacy information for the comparison between flunisolide HFA and flunisolide CFC were not reported. Change in FEV1 was 0.3 L for the 160 mcg group, 0.35 L for the 320 mcg group, and 0.14L for placebo.

A second trial evaluated the safety and efficacy of flunisolide HFA in 583 children aged 4-11 for 12 weeks. These data are unpublished. Patients were randomized to flunisolide HFA 80 mcg or 160 mcg, flunisolide CFC 250 mcg or 500 mcg, or placebo. While there was a statistically significant difference in change in FEV1 from baseline for the flunisolide groups compared to placebo, absolute changes in FEV1 were not reported and the clinical significance of this difference cannot be evaluated. Additionally, no head-to-head comparison was reported.

New Drug Evaluation: Anoro Ellipta (umeclidinium/vilanterol)

FDA approved indications: Umeclidinium/viltanterol is a combination of an anticholinergic and LABA, indicated for the long-term, once-daily maintenance treatment of COPD.

Potential Off-label Use: Maintenance treatment of asthma

Clinical Efficacy Data:
The approval of umeclidinium/vilanterol 62.5/25 mcg was based on four 24-week studies.[8–10] The primary endpoint in all 4 studies was the trough FEV1 at day 169, intending to show the benefit of the combination product over both single ingredients. [4] These studies included patients who had a diagnosis of moderate-to-severe COPD. Results of this primary endpoint showed a statistically significant difference between umeclidinium/vilanterol at both the 125/25 mcg and 62.5/25 mcg doses over each of the respective single ingredients, with a statistically significant difference from placebo in the single ingredient arms. However, there was not a statistically significant difference between the two combination doses (0.21 L vs 0.21 L in Decramer Study 2 and 0.22 L vs 0.21 L in Decramer Study 1 for the 125/25 mcg and 62.5/25 mcg doses, respectively).[9] The 62.5/25 mcg dose was the only dose that consistently showed statistically significant differences from placebo and its component parts and was granted FDA approval.[4] Only 3 studies[8,9] included this dose; the fourth study[10] only compared umeclidinium/vilanterol 125/25 mcg to its component parts and placebo.

Donahue et al[8] compared umeclidinium/vilanterol 62.5/25 mcg with placebo and the difference in the primary endpoint (change from baseline in trough FEV1) was 0.17 L (95% CI 0.13-0.21; p <0.001), which is clinically significant. The Decramer et al[9] studies compared umeclidinium/vilanterol 62.5/25 mcg to tiotropium 18 mcg and comparative differences were 0.09 L (95% CI 0.04-0.14; p=0.006) for study 1 and 0.06 L for study 2 (statistical significance for this difference cannot be claimed as a result of the failure of the predefined testing hierarchy in the clinical trial design).[4] Interestingly, a higher-than-approved dose of the LAMA component, umeclidinium 125 mcg, was tested against tiotropium 18 mcg in Celli et al[10] and there was not a statistically significant difference in mean change from baseline in trough FEV1 at day 169 for umeclidinium compared to tiotropium (0.04 L; 95% CI -0.01 to 0.09; p-value = 0.138).

There is insufficient evidence to draw conclusions about the ability of umeclidinium/vilanterol to decrease exacerbations, reduce shortness of breath, or improve quality of life.[4] Data on exacerbation rates are not available in the published trial or on the ClinicalTrials.gov website. The FDA stated that while umeclidinium/vilanterol showed some numerical benefit in improving exacerbations over umeclidinium and vilanterol in some studies, the results were not statistically significant. [4] The FDA also stated that umeclidinium/vilanterol did not show consistent, statistically significant differences from its component parts in reducing shortness of breath based on Shortness of Breath with Daily Activities (SOBDA) scores, a daily patient recording of shortness of breath on 13 activities related to daily living. [4] There was also a lack of data supporting a claim for improvement in St. George's Respiratory Questionnaire (SGRQ), as umeclidinium/vilanterol was only shown to meet the threshold for clinically meaningful improvement (an increase of 4 units) in SGRQ scores from baseline in 1 of the 4 pivotal efficacy trials.[4]

Clinical Safety:

Overall, the most common adverse events seen in trials are pharyngitis, sinusitis, lower respiratory tract infection, constipation, diarrhea, pain in extremity, muscle spasms, neck pain and chest pain (all ≥1% of patients and more common than with placebo).[4] The total incidence of adverse events was comparable across treatment groups and respiratory events were the most commonly reported. [4] Rates of patients discontinuing due to an adverse event was also comparable across treatment groups. [4] There is low quality evidence that of no statistically significant difference in rates of mortality. One unpublished 52 week

trial of umeclidinium/vilanterol 125/25 mcg showed similar adverse reactions as those in the efficacy trials and rates of adverse events were low across all groups. [4]

Due to the LABA component of this combination product, the FDA has issued a safety warning for its use in patients with asthma, as LABAs have been shown to increase asthma exacerbation and asthma-related death. [4] Since COPD is a disease that occurs only in adults, umeclidinium/vilanterol has not been specifically studied in the pediatric population, and as such no safety data for this population is available. [4]

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Mortality
2) Rate of exacerbations
3) Health-related quality of life
4) Dyspnea

Primary Study Endpoint:

1) Mean change from baseline in pre-dose trough FEV1 at day 169

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
Donohue et al[8] R, DB, PC 24-weeks	A: UMEC/VI 62.5/25 mcg U: UMEC 62.5 mcg V: VI 25 mcg P: Placebo Medications allowed: inhaled albuterol as rescue medication, ICS at stable dose	Demographics: Age: 63 70% male 50% current smokers at screening 46 pack-year history Inclusion Criteria: Established COPD ≥40 years old Current/former smoker ≥10 pack-year smoking history Post-albuterol FEV/FVC <0.70 Post-albuterol FEV1 ≤70% pred MMRC score ≥2 Exclusion Criteria: Asthma or other known respiratory disorders (including α-1antitrypsin deficiency, active TB, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary HTN, interstitial lung disease); any clinically significant uncontrolled disease (including CV-related, abnormal clinically significant ECG, or 24-h Holter ECG, abnormal clinical lab finding)	3:3:3:2 randomization ITT: A: 413 U: 418 V: 421 P: 280 Attrition: A: 81 (20%) U: 94 (22%) V: 103 (24%) P: 76 (27%)	LS Mean Change from Baseline in Trough FEV1 at Day 169 (L): **A**: 0.171 VS P: 0.167 (95% CI 0.128-0.207) p-value <0.001 **U**: 0.119 Vs P: 0.115 (95% CI 0.076-0.155) p-value <0.001 **V:** 0.076 Vs P: 0.072 (95% CI 0.032-0.112) p-value <0.001 **P**: 0.004	NA	SAE: A: 21 (5%) U: 27 (6%) V: 24 (6%) P: 9 (3%) Withdrawals due to AE: A: 23 (6%) U: 34 (8%) V: 24 (6%) P: 9 (3%)	NS NS	**Quality Rating: Fair** **Internal Validity: RoB** Selection: Central randomization schedule generated using validated computerized system, patients randomized using automated, interactive telephone-based system Performance: Patients randomized using interactive telephone-based system Detection: FEV1 and FVC were obtained using standard spirometry equipment that met or exceeded the minimal ATS performance recommendations Attrition: high (23.1% overall). Withdrawals similar to other COPD trials. **External Validity:** Recruitment: No details given Patient Characteristics: Baseline characteristics were similar across all groups. Majority of patients (91%) were GOLD stage II and III. Setting: 163 outpatient centers in 10 countries Outcomes: The accepted surrogate outcome of FEV1 was used for efficacy measure. No clinically important outcomes measured, including mortality, hospitalizations, and quality of life.

Decramer 2014[9] Study 1 R, DB, AC 24-weeks	A125: UMEC/VI 62.5/25 mcg U: UMEC 62.5 mcg T: Tiotropium 18 mcg V: VI 25 mcg Medications allowed: inhaled albuterol as rescue medication, ICS at stable dose	Demographics: Age: 63 70% male 50% current smokers at screening 46 pack-year history Inclusion Criteria: Established COPD ≥40 years old Current/former smoker ≥10 pack-year smoking history Post-albuterol FEV/FVC <0.70 Post-albuterol FEV1 ≤70% pred MMRC score ≥2 Exclusion Criteria: Asthma, α-1antitrypsin deficiency, any clinically significant uncontrolled disease, significant ECG or clinical lab finding, lower respiratory tract infection or recent COPD exacerbation	ITT: A125: 214 A62.5: 212 TIO: 208 VI: 209 Attrition: A125: 41 (19%) 62.5: 31 (15%) TIO: 31 (15%) VI: 44 (21%)	<u>LS Mean Change from Baseline in Trough FEV1 at Day 169 (L):</u> **A125**: 0.209 Vs VI: 0.088 (95% CI 0.036 to 0.140) p-value <0.001 Vs TIO: 0.090 (95% CI 0.036 to 0.140) p-value <0.001 **A62.5**: 0.211 Vs VI: 0.088 (95% CI 0.036 to 0.140) p-value <0.001 Vs TIO: 0.090 (95% CI 0.036 to 0.141) p-value <0.001 **TIO:** 0.121 **VI**:0.121	NA	<u>SAE:</u> A125: 5 (2%) A62.5: 7 (3%) TIO: 13 (6%) VI: 15 (7%) Withdrawals due to AE: A125: 15 (7%) A62.5: 10 (5%) TIO: 9 (4%) VI: 10 (5%)	NS NS	**Quality Rating: Poor** **Internal Validity:** <u>Selection:</u> Randomization schedule generated using computer software. Block randomization in groups of 8 were used. Allocation controlled by telephone system. <u>Performance:</u> Double-dummy design used, however tiotropium and placebo were not identical (placebo capsules lacked markings). <u>Detection:</u> Staff involved in safety and efficacy assessments were not present during dosing in clinic. No other details given. Many secondary outcomes were rater-administered with no details on training or standardization of scores given. <u>Attrition:</u> high (17% and 23% overall). **External Validity:** <u>Recruitment:</u> No details given <u>Patient Characteristics:</u> Baseline characteristics were similar across all groups. Most were in their mid-60's, male, GOLD stage II or III, and about half used inhaled corticosteroids. <u>Setting:</u> 91 outpatient centers in 9 countries (study 1); 95 outpatient centers in 10 countries (study 2) <u>Outcomes:</u> The accepted surrogate outcome of FEV1 was used for efficacy measure. No clinically important outcomes measured, including mortality, hospitalizations, and quality of life.

Decramer 2014[9] Study 2 R, DB, AC 24-weeks	A125: UMEC/VI 125/25 mcg A62.5: UMEC/VI 62.5/25 mcg TIO: Tiotropium 18 mcg UMEC: UMEC 62.5 mcg Medications allowed: inhaled albuterol as rescue medication, ICS at stable dose	Demographics: Age: 63 70% male 50% current smokers at screening 46 pack-year history Inclusion Criteria: Established COPD ≥40 years old Current/former smoker ≥10 pack-year smoking history Post-albuterol FEV/FVC <0.70 Post-albuterol FEV1 ≤70% pred MMRC score ≥2 Exclusion Criteria: Asthma, α-1antitrypsin deficiency, any clinically significant uncontrolled disease, significant ECG or clinical lab finding, lower respiratory tract infection or recent COPD exacerbation	A125: 215 A62.5: 217 TIO: 215 UMEC: 222 Attrition: A125: 49 (23%) A62.5: 54 (25%) TIO: 39 (18%) UMEC: 57 (26%)	<u>LS Mean Change from Baseline in Trough FEV1 at Day 169 (L):</u> **A125**: 0.223 Vs UMEC: 0.088 (95% CI 0.036 to 0.140) p-value 0.142 Vs TIO: 0.074 (95% CI 0.025 to 0.123) p-value 0.003 **A62.5**: 0.208 Vs UMEC: 0.022 (95% CI -0.018 to 0.072) p-value 0.377 Vs TIO: 0.060 (95% CI 0.010 to 0.109) p-value 0.018 **TIO:** 0.149 **UMEC**:0.186		<u>SAE:</u> A125: 15 (7%) A62.5: 22 (10%) TIO: 9 (4%) UMEC: 15 (7%) Withdrawals due to AE A125: 15 (7%) A62.5: 20 (9%) TIO: 13 (6%) UMEC: 17 (8%)		**SAME AS ABOVE**

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8. Donohue, J. F. *et al.* Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. *Respiratory Medicine* **107,** 1538–1546 (2013).
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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY[4]

PHARMACOKINETICS

Parameter	Result
Protein Binding	Umeclidinium: 89%, Vilanterol: 94%
Elimination	Urine (vilanterol); feces (umeclidinium and vilanterol)
Half-Life	11 hours
Metabolism	CYP2D6 (umeclidinium) CYP3A4 (vilanterol)

DOSE & AVAILABILITY[4]

STRENGTH	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Umec/VI 62.5/25 mcg	INH	1 inhalation once daily	No adjustment	No adjustment (has not been studied in severe hepatic impairment)	NA	NA	Not for the relief of acute bronchospasm or for asthma treatment Device has to be discarded 6 weeks after it is removed from the foil tray

DRUG SAFETY[4]

Serious (REMS, Black Box Warnings, Contraindications):

Black Box Warning: May cause an increase in asthma-related death, which is considered a class effect of LABA. No study adequate to determine whether the rate of asthma-related death is increased in subjects treated with fluticasone furoate /vilanterol has been conducted.

Contraindications: Patients with severe hypersensitivity to milk proteins or hypersensitivity to umeclidinium, vilanterol or any component of the product.

REMS: none

Warnings and Precautions:

- Should not be initiated in patients during rapidly deteriorating exacerbations.

- Should not be used as a rescue inhaler
- Should not use with any other LABA-containing medication
- Caution should be exercised when considering the coadministration with known strong CYP3A4 inhibitors because vilanterol is a CYP3A4 substrate
- May cause paradoxical bronchospasm
- May produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and cardiac arrhythmias
- May cause worsening of narrow-angle glaucoma
- May cause worsening urinary retention
- May cause increase in serum glucose

Look-alike / Sound-alike (LA/SA) Error Risk Potential:

Anoro Ellipta may be confused with Breo Ellipta, Alora
Ellipta may be confused with Ella®, Ellence®, eletriptan
Umeclidinium may be confused with Umecta®, aclidinium

Appendix 2: Current PA with Proposed Changes

~~LABA/ICS~~Combination Inhalers

Goal(s):

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

Initiative:

- ~~LABA/ICS~~Combination Inhaler Step Therapy

Length of Authorization:

Up to 12 months

Requires PA:

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

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Step Therapy Required Prior to Coverage:

Asthma: oral corticosteroid inhalers (see preferred drug list options at (www.orpdl.org)

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

Approval Criteria		
1. Does patient have asthma or reactive airway disease (ICD-9: 493, 493.0-493.93)?	**Yes:** Go to #2	**No:** Go to #4
2. Is the medication for Breo Ellipta (fluticasone furoate/vilanterol) or Anoro Ellipta (umeclidinium/vilanterol)	**Yes:** Pass to RPH; Deny (Medical appropriateness)	**No:** Go to #3
3. Has patient: • failed an inhaled corticosteroid or other controller medication OR • Had ≥2 exacerbations requiring oral systemic corticosteroids in the past year, OR • Is there documentation of step 3 asthma or higher OR • Is there a hospital admission or ER visit related to asthma or reactive airway disease within last 60 days?	**Yes**: Document the following: Date of trial, drug, reason(s) for failure or contraindications OR chart notes of asthma severity in the PA record Approve for 1 year if this is patient's first prescription for a combination inhaler or if this is a continuation of therapy	**No**: PASS TO RPH DENY (Medical Appropriateness).

	and patient is well controlled on current dose.	
4. Does patient have COPD (ICD-9 496) or Chronic bronchitis (491.1-2.) and/or emphysema (492.xx)?	**Yes:** ~~Approve for 12 months.~~Go to #5	**NO:** PASS TO RPH DENY (Medical Appropriateness). Need a supporting diagnosis. If prescriber believes diagnosis appropriate inform them of the provider reconsideration process for Medical Director Review.
5. Is the medication of Anoro Ellipta (umeclidinium/vilanterol)?	**Yes:** Got to #6	**No:** Approve for 12 months.
6. Has the patient: • failed or have contraindication to an inhaled corticosteroid OR • Is there a documentation of Stage 4 COPD	**Yes:** Approve for 12 months	**No:** PASS TO RPH DENY (Medical Appropriateness).

Appendix 3: Current PA Criteria

Roflumilast

Goal(s):

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

Length of Authorization: 1 year

Covered Alternatives: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the diagnosis an OHP covered diagnosis?	**Yes:** Go to #3.	**No:** Pass to RPh, Deny for OHP Coverage.
3. Does the patient have documented severe or very severe (Stage III or Stage IV) COPD?	**Yes:** Go to #4	**No:** Deny (medical inappropriateness)
4. Does the patient have a history of chronic bronchitis AND Prior COPD exacerbations?	**Yes:** Go to #5	**No:** Deny (medical inappropriateness)
5. Is the patient currently on a long-acting bronchodilator?	**Yes:** Go to #6	**No:** Deny. Recommend trial of preferred long-acting bronchodilators
6. Has the patient tried an inhaled corticosteroid (ICS), and ICS combination, or tiotropium (LAMA)?	**Yes:** Approve up to 1 year	**No:** Deny. Recommend trial of preferred long-acting ICS or LAMA

Appendix 4: Current PA Criteria

Asthma Controller Drugs

Goal(s):

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

Length of Authorization:

Up to 12 months

Requires PA :

- Non-preferred drugs

Covered alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. Is the requested drug montelukast (Singulair®)?	Yes: Go to Leukotriene Inhibitor Criteria	No: Go to #2
2. Is the request for a LABA/ICS combination product?	Yes: Go to LABA/ICS criteria	No: Go to #3
3. What is the diagnosis being treated?	Record ICD-9 Code	
4. Is this an OHP covered diagnosis?	Yes: Go to #5	NO: PASS TO RPH DENY (not covered by OHP)
5. Is this a continuation of current therapy (i.e. filled prescription within prior 90 days)? Verify via pharmacy claims.	Yes: Document prior therapy in PA record. Approve for 1 year.	No: Go to #6
6. Will the provider consider a change to a preferred product? Message: • Preferred products do not require a PA • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T Committee).	Yes: Inform provider of covered alternatives	No: Approve for 1 year or length of prescription, whichever is less.

Author: Amanda Meeker Date: July 2014

Appendix 5: Abstracts of potentially relevant randomized controlled trials and/or systematic reviews

Karabis, A., Lindner, L., Mocarski, M., Huisman, E. & Greening, A. Comparative efficacy of aclidinium versus glycopyrronium and tiotropium, as maintenance treatment of moderate to severe COPD patients: a systematic review and network meta-analysis. *Int J Chron Obstruct Pulmon Dis* **8,** 405–423 (2013).

BACKGROUND: Aclidinium bromide is a new long-acting muscarinic antagonist (LAMA) indicated for maintenance bronchodilator treatment of chronic obstructive pulmonary disease (COPD). The efficacy of aclidinium was compared with tiotropium and glycopyrronium, using a network meta-analysis (NMA) of randomized controlled trials (RCTs) in moderate-to-severe COPD patients.

METHODS: A systematic review was performed to identify RCTs evaluating aclidinium 400 µg twice daily (BID), glycopyrronium 50 µg once daily (OD), tiotropium 18 µg OD, or tiotropium 5 µg OD in adults with moderate-to-severe COPD. The outcomes of interest were: trough forced expiratory volume in 1 second (FEV1); St George's Respiratory Questionnaire (SGRQ) total score and proportion of patients achieving ≥4 unit change; Transition Dyspnea Index (TDI) focal score and proportion of patients achieving ≥1 point change. The results were synthesized by means of a Bayesian NMA.

RESULTS: Twenty-one studies (22,542 patients) were included: aclidinium 400 µg BID (three studies); tiotropium 5 µg OD (three studies); tiotropium 18 µg OD (13 studies); and glycopyrronium 50 µg OD (two studies). Regarding trough FEV1 at 24 weeks, aclidinium demonstrated comparable efficacy to tiotropium 5 µg (difference in change from baseline [CFB]), (0.02 L [95% credible interval CrI -0.05, 0.09]); tiotropium 18 µg (0.02 L [95% CrI -0.05, 0.08]); and glycopyrronium (0.00 L [95% CrI -0.07, 0.07]). Aclidinium resulted in higher improvement in SGRQ score at 24 weeks, compared to tiotropium 5 µg (difference in CFB, -2.44 [95% CrI -4.82, -0.05]); and comparable results to tiotropium 18 µg (-1.80 [95% CrI -4.52, 0.14]) and glycopyrronium (-1.52 [95% CrI -4.08, 1.03]). Improvements in TDI score were comparable for all treatments.

CONCLUSION: Maintenance treatment with aclidinium 400 µg BID is expected to produce similar improvements in lung function, health-related quality of life, and dyspnea compared to tiotropium 5 µg OD; tiotropium 18 µg OD; and glycopyrronium 50 µg OD.