Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Update: Inhalers for Asthma/COPD

Date of Review: December 2022

Date of Last Review: Inhaled anticholinergics (Oct 2021)
Short-acting beta agonists (July 2019)
Other inhalers (Oct 2020)

Dates of Literature Search: 01/01/2020 - 10/03/2022

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

Plain Language Summary:

- This review looks at new evidence for medicines that are inhaled to treat people that have lung diseases called asthma and chronic obstructive pulmonary disease (COPD). These medicines work in several different ways. Groups of medicines that work the same way are put into the same category that are called classes. Classes include:
  - Medicines that help to quickly open up the lungs (called fast-acting beta-agonists [FABA])
  - Medicines that help to reduce swelling to open up the lungs (called an inhaled corticosteroid [ICS])
- New evidence shows that people who used both a FABA and ICS were able to breathe normaly, needed less additional medication to treat their asthma, and went to the hospital or urgent care for treatment less frequently than when people used placebo or other asthma treatments.
- In people with COPD, an inhaled medicine that combines three classes of medicines helped people breathe better than inhalers that contained only two classes of medicines. The product with 3 classes includes the medicines budesonide, glycopyrronium and formoterol fumarate compared to inhalers with only two of these medicines.
- New evidence shows that people with mild COVID-19 symptoms who were not vaccinated and used an ICS inhaler needed to go to the hospital less often than people who did not use an ICS.
- A new study compared 2 different FABA and ICS combination inhalers called formoterol/ICS and salmeterol/ICS. People who took these medicines had similar risk of severe side effects.
- The National Asthma Education Prevention Program Coordinating Committee (NAEPPCC) recommends that people with asthma use the combination of ICS-formoterol if they:
  - require medicine occasionally when they have trouble breathing or
  - have symptoms more often and require daily treatment with medicine.
- The Drug Use Research and Management Group (DURM) recommends no changes to our current policy for inhaled therapies used for people with asthma and COPD.

Author: Kathy Sentena, PharmD

Purpose for Class Update:
The purpose of this update is to review new literature on effectiveness and safety of asthma and COPD inhaled therapies published since the last reviews.

Research Questions:
1. What is the comparative efficacy for asthma and COPD maintenance medications for important outcomes such as symptoms, lung function, hospitalizations and mortality?
2. What is the evidence for harms associated with asthma and COPD maintenance medications?
3. Are there subpopulations of patients based on demographics (e.g., age, racial groups, gender), comorbidities (drug-disease interactions), or other medications (drug-drug interactions) for which treatments for asthma or COPD are better tolerated or more effective?

Conclusions:
- There were 4 high-quality systematic reviews, 3 new guidelines, 2 randomized controlled trials (RCTs) and 4 new formulations identified for this review.
- Evidence for the use of budesonide 182 mcg plus glycopyrronium 8.2 mcg plus formoterol fumarate 5.8 mcg (BGF) in people with COPD was evaluated by the Canadian Agency for Drugs and Technologies in Health (CADTH). There was moderate quality of evidence that BGF reduced the rate of moderate to severe COPD exacerbations compared with glycopyrronium 14.4 mcg plus formoterol fumarate 9.6 mcg (GFF) and budesonide 320 mcg plus formoterol fumarate 9.6 mcg (BFF) at 52 weeks and improved FEV_1 at 24 weeks when compared to GFF and BFF. The changes were Results were not clinically significant for this comparison.[1] There is insufficient direct evidence which compares this product to other triple therapy inhalers; however, indirect comparison suggest similar efficacy and safety.
- A high quality systematic review and meta-analysis evaluated the use of FABA and ICS inhalation in patients with mild asthma. The single combination inhaler of FABA/ICS reduced asthma exacerbations requiring steroids (high quality evidence), hospital admissions or unscheduled healthcare visits (low quality of evidenced), and exposure to systemic corticosteroids compared to FABA, taken as needed (low quality evidence). When compared to ICS, the use of FABA/ICS demonstrated reductions in asthma-related hospital admissions or unscheduled heath care visits (low quality of evidence).[2]
- Patients with mild COVID-19 treated with ICS, in addition to standard of care (e.g., antipyretics and antibiotics if bacterial pneumonia was suspected), had a reduced risk of hospital admission or death up to day 30.[3] Incidence of admission or death was 57 per 1000 people treated with ICS compared to standard of care (incidence 79 per 1000 people treated; relative risk [RR] 0.72; 95% confidence intervals [CI], 0.51 to 0.99) based on moderate quality evidence.[3]
- A high quality systematic review and meta-analysis evaluated risk of death and severe adverse reactions associated with formoterol/ICS compared to salmeterol/ICS.[4] There was insufficient evidence to make conclusions on mortality outcomes due to low incidence of events. Based on data for all-cause non-fatal serious events, there is probably no difference in safety profiles between formoterol/ICS compared to salmeterol/ICS (moderate quality evidence).
- New guidance from the National Asthma Education Prevention Program Coordinating Committee (NAEPPCC) recommends the use of single-inhaler ICS-formoterol both daily and as needed for individuals 4 years and older with moderate persistent asthma.[5] This single inhaler regimen is referred to as "single maintenance and reliever therapy (SMART)". Long acting muscarinic antagonists (LAMAs) are recommended in addition to an ICS in people 12 years and older who have uncontrolled persistent asthma who cannot tolerate ICS-long-acting beta-agonist (LABA).[5] The addition of LAMA is also indicated in individuals using ICS-LABA and still experiencing symptoms.[5]
- The Global Initiative for Asthma (GINA), the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2022 and US Preventative Services Task Force (USPSTF) updates support current policy.[6,7,8]
- There is insufficient evidence for the use of inhaled therapies for asthma and COPD in non-white people and in Medicaid populations.

Recommendations:

- No changes recommended based on the review of the current evidence.
- The prior authorization (PA) criteria will be updated to align with current guideline recommendations. Recommend retiring the ICS/LABA specific criteria and making non-preferred therapies subject to general PA for non-preferred products.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy:

- Literature for inhaled anticholinergics was last evaluated in October 2021. At the time, the NAEPPCC Expert Panel recommended the use of LAMAs in patients with asthma and conditionally recommended adding LAMA to ICS controller therapy instead of continuing the same dose of ICS alone (conditional recommendation; moderate certainty of evidence). After executive session Combivent®, Respimat®, and Incruse Ellipta® were made preferred.
- Evidence for short acting beta agonists (SABA) was reviewed July of 2019. In certain groups with asthma, the use of SABA with anticholinergics may reduce hospitalization rates when presenting to an emergency room compared to SABA use alone. No changes in policy were made.
- A list of preferred therapies are available in **Appendix 1**. All classes have PA criteria for non-preffered therapies. The LABAs require step-therapy prior to coverage of non-preferred LABA and LABA/ICS products for patients with asthma and COPD. There is PA criteria for all LAMA/LABA and LAMA/LABA/ICS products.
- The inhaled therapies for asthma and COPD are comprised of 7 classes: anticholinergics, SABAs, LABAs, ICS, ICS/LABAs, and LAMA/LABA combinations. The inhaled therapies account for a significant cost to the Oregon Health Authortiy. Compliane to the PDL ranges from a low of 25% for the LABA class to 100% for SABAs.

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. Centers for Disease Control and Prevention data from 2018 reports the burden of asthma in Oregon to be over 11%.[9] Asthma is characterized by symptoms of wheezing, cough, dyspnea and chest tightness. Diagnosis is confirmed by spirometry (FEV_1 > 200 mL or ≥ 12% from baseline after SABA use), airway obstruction that is at least partially reversible and exclusion of other potential diagnoses.[6] Asthma is characterized as being intermittent or persistent (and further divided into mild, moderate or severe). The underlying pathophysiology of asthma is multi-factorial and includes several phenotypes: eosinophil predominant, neutrophil predominant, and allergic asthma. In particular, those patients with eosinophil asthma Type 2 (T2)-high, which indicates high levels of T-helper type 2 lymphocytes, respond well to ICS therapy and biologic therapy if asthma remains uncontrolled. Patients with eosinophilic asthma also have high levels of sputum eosinophils, and while a correlation of blood eosinophil levels to sputum eosinophils is not well defined, guidelines typically diagnose eosinophilic asthma when blood eosinophils are greater than or equal to 150 cells/µL.[6] Studies of biologic therapies have evaluated use in patients with eosinophil levels of at least 150 cells/µL to more than 400 cells/µL.

Asthma treatment can be categorized as quick-relief medication and long-term control medications. Asthma treatment is inititated in a stepwise manner based on the severity of asthma symptoms.[6] Evidence demonstrates that even people with mild asthma can be at risk of exacerbations; therefore, several guidelines recommend the use of ICS-formoterol as a controller and reliever therapy, also referred to as SMART (single maintenance and reliever therapy) or MART (maintenance and reliever therapy).[5] ICS, alone or in combination, are the preferred maintenance therapy for all patients with persistent asthma.[5] If additional therapy is required to control asthma symptoms, LABAs are recommended in combination with ICS.[6] Other maintenance therapy options include leukotriene

inhibitors, methylxanthines, cromolyn sodium and nedocromil. Fast-acting beta-agonists, ICS-formoterol, anticholinergics and systemic corticosteroids are recommended for acute symptom management. Biologic asthma treatments are recommended for those patients with severe asthma that is unresponsive to controller-drug therapy.[6]

Outcome measures used in asthma trials are forced expiratory volume in one minute (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 in clinical trials and clinical practice since it is highly reproducible. Research in COPD patients suggest that minimally important FEV_1 changes range from 100-140 mL.[6] Moderate-quality evidence suggests that targeting interventions for asthma based on sputum eosinophil levels in people with severe asthma that is difficult to treat may reduce the number and severity of asthma attacks in adults; however, additional research is needed.[6] The Asthma Control Questionnaire (ACQ) is used to determine symptom control. Scores range from 0-6 with higher scores indicative of worse asthma. The ACQ-5 consists of 5 questions that are averaged for a score. MCID for the ACQ-5 is a change of 0.5 points.[6]

COPD

Chronic obstructive pulmonary disease 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. Chronic bronchitis and emphysema are often associated with COPD.[1] 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.

Chronic cough or sputum production and dyspnea are common symptoms of COPD. The diagnosis and management of COPD is based on spirometry (post-bronchodilator ratio of $FEV_1/FVC < 0.70$), symptom severity, risk of exacerbations and comorbidities.[1] COPD is classified into four stages based on spirometric measurements of FEV_1/FVC: grade 1 (mild), grade 2 (moderate), grade 3 (severe), and grade 4 (very severe). The Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (GOLD) guidelines recommend therapeutic approaches based on disease burden (e.g., breathlessness, exercise limitations, health status and risk of exacerbations) as well as FEV_1. Patients are classified into groups A-D (low to high risk of symptoms and exacerbations).[1] This type of classification system shifts the focus from only FEV_1 measurements as these are not always indicative of COPD status.[7]

Common treatment options for patients with COPD are bronchodilators and antimuscarinic drugs (LABAs and LAMAs). For patients who require additional therapy, the combination of a LABA and LAMA is often used.[1] Triple therapy with a LABA, LAMA and ICS is recommended for those with COPD and sustained symptoms despite dual therapy.[1] Bronchodilators (short and long-acting) have demonstrated improvements in FEV_1 and symptom improvement. Long-acting bronchodilators (LAMAs and LABAs) improve lung function, dyspnea, health status and reduce exacerbation rates. Inhaled corticosteroids/LABAs have been shown to improve health status, reduce exacerbations and improve lung function compared to ICS monotherapy. Conclusive evidence of benefit has not been demonstrated with ICS alone in patients with COPD. Phosphodiesterase-4 inhibitors have a role in COPD management by minimizing airway narrowing and damage due to inflammation. Phosphodiesterase-4 inhibitors are used as add-on therapy for patients with COPD who have persistent symptoms or exacerbations despite optimal treatment with other COPD therapies. There is a lack of conclusive benefit for improved survival rates with any of the inhaled respiratory medications used in the management of COPD, and no medications have shown a preventative effect in the decline of lung function.[7]

Goals of therapy for COPD management are to improve symptoms, reduce frequency of exacerbations, improve exercise tolerance and daily activities and reduce mortality.[1] Important outcomes to access the effectiveness of therapies include: lung function, quality of life (QoL), dyspnea, exacerbation rate and/or severity, mortality and adverse events. FEV_1 is the most common surrogate outcome used in studies to determine therapy effectiveness. The minimal clinically

important difference (MCID) in FEV_1 values for COPD changes have not been clearly defined, but Cochrane reviews recommend a change of 100 mL.[7] Other sources suggest a change in percent predicted FEV_1 of 10.38% or more would correlate with a MCID.[7] The St. George Respiratory Questionnaire (SGRQ) is used to determine the effects of COPD on quality of life with scores ranging from 0-100 and higher scores indicative of more limitations. The MCID for the SGRQ is a change of 4 units.[7] The transitional dyspnea index (TDI) is a measurement of breathlessness in people with COPD. A score change of 1 unit has been shown to be clinically meaningful. Symptom are also accessed by the Modified British Medical Reasearch Council (mMRC) questionnaire which is a scale measuring dyspnea and the COPD Assessment Test (CAT) which evaluates a range of symptoms from cough to energy.[10] Smoking cessation is the only intervention shown to reduce the rate of lung function decline.

Methods:

A Medline literature search for new systematic reviews and 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.

New Systematic Reviews:

<u>CADTH- Budesonide-Glycopyrronium-Formoterol Fumarate Reimbursement Review</u>

CADTH evaluated the clinical efficacy of the combination product budesonide, glycopyrronium and formoterol fumarate (BGF) for long-term maintenance treatment of patients with COPD.[1] A systematic review of the clinical benefits and adverse events of BGF identified 2 RCTs for evaluation (ETHOS and KRONOS).[11,12] Relevant outcomes of significance were COPD exacerbations, symptom relief, and incidence of chronic bronchitis and/or emphysema. Results for exacerbation outcomes are presented in **Table 1**. In the KRONOS study, the primary outcome was FEV_1 area under the curve (AUC) from 0-4 hours for BGF versus BFF, GFF or versus BUD-FOR comparisons. Change from baseline in morning pre-dose trough FEV_1 was higher for BGF compared to GFF and for BGF compared to BUD/FORM.[1] For the secondary outcome of use of rescue medications, the difference was not statistically different in KRONOS between groups but was reduced with the use of BGF in ETHOS when compared to GFF and BFF. Between group difference in SGRQ scores were not clinically significant. In ETHOS, there was a reduced risk of mortality with BGF compared to GFF (HR 0.51; 95% CI, 0.330 to 0.80) with no differences compared to BFF.[1] Mortality was not measured in KRONOS. Adverse events were similar between groups. The most common events were nasopharyngitis, and upper respiratory tract infection. Serious adverse events were reported in approximately 20% of patients treated in ETHOS and 9% treated in KRONOS.[1]

Both studies had high rates of discontinuations due to adverse events (6.1% in ETHOS and 4.25% in KRONOS) and missing data.[1] Additional limitations were under enrollment of females and lower use than expected of the LAMA-LABA combination inhaler (14%) at baseline and the overall magnitude of benefit was small for the use of triple inhalation combination therapy.

Table 1. Description of Randomized Comparative Clinical Trials.[1,11,12]

Study	Comparison	Population	Outcome	Results	Notes/Limitations
ETHOS DB, MC, PG	1. BGF MDI 2. GFF MDI 3. BFF MDI 52 week duration	Patients with moderate to very severe COPD and at least 1 exacerbation in the last year N=8,588	Moderate to severe COPD exacerbations*	Adjusted rate: 1. 1.08 2. 1.42 3. 1.24 <u>BGF vs. GFF</u> RR 0.76 (95% CI, 0.69 to 0.83) <u>BGF vs. BFF</u> RR 0.87 (95% CI, 0.79 to 0.95)	- BGF was more effective than GFF and GFF at reducing COPD exacerbations
			Lung function (FEV_1 $AUC_{0\text{-}4h}$ mL)‡	<u>BGF vs. GFF</u> LSM 22 mL (95% CI, 4 to 39)	- Differences between groups were not clinically meaningful
			Symptoms (based on TDI focal score)	<u>BGF vs. GFF</u> 0.40 units (95% CI, 0.24 to 0.55) <u>BGF vs. BFF</u> 0.31 units (95% CI, 0.15 to 0.46)	- Symptom improvement was higher with BGF compared to GFF and BFF but the difference was not considered clinically meaningful
KRONOS DB, MC, PG	1. BGF MDI 2. GFF MDI 3. BFF MDI 4. BUD-FOR DPI (400 mcg-12 mcg active control) open-label 24 week duration	Symptomatic patients with moderate to very severe COPD N=1,902	Moderate to severe COPD exacerbations	Adjusted rate: 1. 0.46 2. 0.95 3. 0.56 4. 0.55 <u>BGF vs. GFF</u> RR 0.48 (95% CI, 0.37 to 0.64); P<0.0001 <u>BGF vs. BFF</u> RR 0.82 (95% CI, 0.58 to 1.17); P=0.2792 <u>BGF vs. BUD-FOR</u> RR 0.83 (95% CI, 0.59 to 1.18); P=0<0.0001 <u>BGF vs. BUD-FOR</u> RR 0.83 (95% CI, 0.59 to 1.18); P=0.3120	- All comparisons were prespecified superiority analysis with the exception of BFF MDI vs. BUD/FORM DPI which was prespecified as a non-inferiority analysis

			Lung function* (FEV_1 $AUC_{0\text{-}4h}$ mL)	1. 305 mL 2. 288 mL 3. 201 mL 4. 214 mL <u>BGF vs. GFF</u> LSM 16 mL (95% CI, -6 to 38); P=0.1448 <u>BGF vs. BFF</u> LSM 104 mL (95% CI, 77 to 131); P<0.0001 <u>BGF vs. BUD-FORM</u> LSM 91 mL (95% CI, 64 to 117); P<0.0001	- MCID for FEV_1 $AUC_{0\text{-}4h}$ mL is 0.10 L to 0.14 L so results are clinically significant for BGF vs BFF comparison BGF vs. BUD-FORM
			Change from baseline in morning pre-dose trough FEV_1*	1. 293 mL 2. 125 mL 3. 73 mL 4. 88 mL <u>BGF vs. GFF</u> LSM 22 mL (95% CI, 4 to 39); P=0.0139 <u>BGF vs. BFF</u> LSM 74 mL (95% CI, 52 to 95)†; P<0.0001 <u>BGF vs. BUD-FORM</u> LSM -10 mL (95% CI, -36 to 16); P=0.4390	- BGF increased morning pre-dose trough FEV_1 more than GFF and BFF but not more than BUD-FORM
			Symptoms (based on TDI focal score)	<u>BGF vs. GFF</u> 0.177 units (95% CI, -0.071 to 0.426) <u>BGF vs. BFF</u> 0.237 units (95% CI, -0.068 to 0.542) <u>BGF vs. BUD-FOR</u> 0.461 units (95% CI, 0.156 to 0.766)	- None of the comparison differences were clinically significant.

Key: * Primary outcome; † Prespecified secondary endpoint; ‡ Prespecified substudy population

Abbreviations: $AUC_{0\text{-}4h}$ – area under the curve in 0 to 4 hours; BFF – budesonide 320 mcg plus formoterol fumarate 9.6 mcg; BGF – budesonide 182 mcg plus glycopyrronium 8.2 mcg plus formoterol fumarate 5.8 mcg; FEV_1 – forced expiratory flow in 1 second; GFF – glycopyrronium 14.4 mcg plus formoterol fumarate 9.6 mcg; MCID – minimal clinically important difference; MDI – meter-dose inhaler; RR – rate ratio; TDI – Transitional Dyspnea Index (TDI)

Cochrane – Combination Fixed-dose Beta Agonist and Steroid Inhaler as Required for Adults or Children with Mild Asthma

The efficacy and safety of using a single combination therapy inhaler consisting of a FABA plus ICS for the treatment of mild asthma, as needed for symptoms, was evaluated by Cochrane in 2021. Studies that were at least 12 weeks in duration were included.[2] Single fixed-dose FABA/ICS inhaler as needed was compared to placebo, SABA as needed, ICS with SABA as needed, fixed-dose combination ICS/LABA, or fixed-dose combination ICS/FABA with as needed ICS/FABA. Six studies (n=9,656) were included and all studies used budesonide (200 mcg or 320 mcg) and formoterol (6 or 9 mcg) in a single dry powder inhaler.[2] Two-studies were open-label. Active comparators contained fast-acting bronchodilators terbutaline (0.5 mg per puff or 500 mcg) and formoterol (4.5 mcg per puff) or salbutamol (2 puffs of 100 mcg each/not available in the United States). Four studies included adults and 2 studies included people at least 12 years of age. The mean age of enrolled patients was 36 to 43 years. Overall, the studies were found to be at low risk of bias even with the inclusion of 2 open-label studies.

Results for the comparisons are available in **Table 2**. Combination therapy of FABA/ICS demonstrated reductions in asthma exacerbations requiring steroids, hospital admissions or unscheduled healthcare visits, and exposure to systemic corticosteroids in patients with mild asthma compared to FABA as needed. When compared to ICS the use of FABA/ICS demonstrated reductions in asthma-related hospital admissions or unscheduled heath care visits.[2] There were no clinically meaningful changes in perceived symptom control by patients, as measured by the ACQ-5, for any comparison.

Table 2. Results for Comparison of FABA/ICS to Active Comparators in Patients with Mild Asthma[2]

Treatment	Comparator	Outcome	Result	Strength of Evidence	Comments
FABA/ICS as needed (2 RCTs)	FABA as needed	Exacerbations requiring systemic steroids	OR 0.45 (95% CI, 0.34 to 0.60)	High	Equates to 109 people out of 1000 in the FABA group experiencing an exacerbation compared to 52 out of 1000 people taking FABA/ICS
		Asthma-related hospital admission or emergency-department or urgent care visit	OR 0.35 (95% CI, 0.20 to 0.60)	Low	Results favored FABA/ICS
		Asthma control (based on ACQ-5)*	MD -0.15 points (95% CI, -0.20 to -0.10)	Moderate	Results favored FABA/ICS but did not meet the MCID threshold of a difference of 0.5.
		Inhaled steroid dose	MD 76.50 mcg beclomethasone (the mean ICS dose was 18.7 mcg in the FABA as needed group)	Moderate	Patients treated with a combined therapy containing ICS have a higher daily inhaled steroid dose than those treated with FABA alone
		Total systemic steroid dose	MD 9.90 mg prednisolone lower in FABA/ICS group (the mean total dose in the FABA as needed group was 17.4 mg prednisolone)	Low	Similar between groups since both groups utilized small doses of systemic steroids

		Adverse Events	OR 0.82 (95% CI, 0.71 to 0.95)	Moderate	Fewer adverse events in those taking FABA/ICS as needed
FABA/ICS as needed (4 RCTs)	Maintenance ICS plus as needed FABA	Exacerbations requiring systemic steroids	OR 0.79 (95% CI, 0.59 to 1.07)	Low	Results favored as needed FABA/ICS but was not statistically significant
		Asthma-related hospital admission or emergency-department or urgent care visit	OR 0.63 (95% CI, 0.44 to 0.91)	Low	Results favored as needed FABA/ICS
		Asthma control (based on ACQ-5)*	MD 0.12 points higher	High	Results favored maintenance ICS but change from baseline was not clinically significant
		Inhaled steroid dose	MD 154.51 mcg lower in FABA/ICS group	Moderate	Results favored lower inhaled steroid doses in FABA/ICS group
		Total systemic steroid dose	MD 7 mg prednisolone lower in FABA/ICS group (the mean total dose in the FABA as needed group was 20.97 mg prednisolone)	Moderate	Similar between groups since both groups utilized small doses of systemic steroids
		Adverse Events	OR 0.96 (0.82 to 1.14)	Moderate	Incidence was similar between groups

Key: * Lower scores indicate better asthma control

Abbreviations: ACQ-5 – asthma control questionnaire-5; CI – confidence interval; FABA – fast-acting beta-agonist; ICS – inhaled corticosteroid; MD – mean difference; OR – odds ratio; RCTs – randomized controlled trials

Cochrane – Inhaled Corticosteroids for the Treatment of COVID-19

A 2022 Cochrane review evaluated the safety and efficacy of ICS use for the treatment of COVID-19.[3] Three RCTs, including 3,607 participants, evaluated people with confirmed mild COVID-19. The majority of participants were adults and those over 50 years of age had comorbidities such as hypertension, diabetes, or lung disease. Inhaled corticosteroids studied were budesonide (1600 mcg/day) and ciclesonide (640 mcg/day) and given in addition to usual care. Comparisons were made to standard of care (e.g., antipyretics and antibiotics if bacterial pneumonia was suspected).[3]

The most robust evidence was for the outcomes of hospital admission or death and symptom reduction (all initial symptoms resolved). The use of ICS resulted in a reduced risk of admission to the hospital or death up to day 30 by 57 per 1000 people treated compared to standard of care with 79 per 1000 people treated (RR 0.72; 95% CI, 0.51 to 0.99; moderate-quality evidence).[3] There was moderate-quality evidence that symptom resolution (all initial syptoms resolved) at day 14 occurred in 553 people per 1000 in those using an ICS compared to 465 per 1000 people treated with standard of care (RR 1.19; 95% CI, 1.09 to 1.30).[3] There was low-quality evidence that there was little difference in all-cause mortality and in duration (time) to symptom resolution upon comparison of ICS and standard of care.[3]

Results are mostly applicable to people with mild COVID-19. Studies were completed before the introduction of COVID vaccines so applicability of these results to vaccinated populations is unclear. There is insufficient evidence on adverse reactions, quality of life, and use in people with moderate to severe COVID.

Cochrane – Regular Treatment with Formoterol and an Inhaled Corticosteroid versus Regular Treatment with Salmeterol and an Inhaled Corticosteroid for Chronic Asthma: Serious Adverse Events

A systematic review and meta-analysis published in 2021 evaluated 11,572 adults and 723 children and adolescents with chronic asthma to evaluate formoterol or salmeterol, with an ICS, on mortality and non-fatal serious adverse events.[4] Included studies were at least 12 weeks in duration and randomized patients to either formoterol/budesonide, salmeterol/fluticasone, formoterol/extra-fine beclomethasone, formoterol/mometasone, or salmeterol/budesonide. Most of the included studies had low risk of bias.

There was insufficient evidence to make conclusions on mortality, as the rate of death was low in all studies. Forty-six adults experienced asthma-related severe adverse events.[4] Moderate quality evidence demonstrated no difference between formoterol/ICS versus salmeterol/ICS for the outcomes of all-cause non-fatal serious events in studies lasting 18 to 26 weeks.[4] The specific findings for all-cause non-fatal serious adverse events comparison were:

- formoterol/budesonide versus salmeterol/fluticasone odds ratio (OR) 1.14 (95% CI, 0.82 to 1.59);
- formoterol/beclomethasone versus salmeterol/fluticasone OR 0.94 (95% CI, 0.43 to 2.08) and
- formoterol/mometasone versus formoterol/salmeterol OR 1.02 (95% CI, 0.47 to 2.20).[4]

Limitations include a low number of serious adverse events related to asthma, making it difficult to have high confidence in comparative findings for patients treated with formoterol/ICS and salmeterol/ICS.

After review, nine systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[13–21]

New Guidelines:

High Quality Guidelines:

NAEPPCC – Update on the Asthma Management Guidelines

Guidance for the management of asthma was updated in 2020 by the NAEPPCC.[5] Recommendations were formulated by an Expert Panel using the GRADE framework in conjunction with a methodology team. A systematic review was completed by the Agency for Healthcare Research and Quality Evidence-Based Practice Center. Conflicts of interest (COI) were disclosed and those with a high level of COI were excluded from the Expert Panel. Priority topics were identified and those pertaining to inhaled treatments will be presented.[5]

The intermittent use of ICS and LAMAs for asthma was one of the priority topics included in this update.[5] Recommendations are presented in **Table 3**. A change from previous guidance is the use of ICS-formoterol as a controller and reliever therapy, based on evidence that the combination therapy reduces asthma exacerbations.[5]

Table 3. NAEPP Recommendations for Asthma Management Inhaled Therapies[5]

Recommendation	Age Group	Strength of Recommendation
Recommendations for use of Intermittent ICS for Asthma		
Children that have recurrent wheezing triggered by respiratory tract infections and no wheezing between infections should receive a short course of daily ICS at the onset of a respiratory tract	0-4 years of age	Conditional recommendation, high strength of evidence

infection with an as-needed SABA for quick-relief therapy compared to an as needed SABA only for quick-relief therapy		
Individuals with mild persistent asthma should receive either of the following treatments as part of Step 2 therapy for worsening asthma: 1. Daily low-dose ICS and as-needed SABA for quick-relief therapy OR 2. Intermittent* as-needed SABA and an ICS used concomitantly	Ages 12 years and older	Conditional recommendation, moderate strength of evidence
Individuals with mild to moderate persistent asthma who are likely to be adherent to daily ICS, short-term increases in the ICS dose for increased symptoms or decreased peak flow are NOT recommended	Ages 4 years and older	Conditional recommendation, low strength of evidence
Individuals with moderate to severe persistent asthma should receive ICS-formoterol in a single inhaler‡ used as both daily controller and reliever therapy† compared to either a higher-dose ICS as daily controller therapy and SABA for quick-relief therapy or the same-dose ICS-LABA as daily controller therapy and SABA for quick-relief therapy	Ages 4 years and older	High certainty of evidence for ages 12 years and older, moderate certainty of evidence for ages 4 to 11 years
Individuals with moderate to severe persistent asthma should receive ICS-formoterol‡ in a single inhaler used as both daily controller and reliever therapy compared to higher-dose ICS-LABA as daily controller therapy and SABA for quick relief therapy	Ages 12 years and older	Conditional recommendation, high strength of evidence
Recommendations for the use of LAMAs for Asthma		
In individuals with uncontrolled persistent asthma, it is not recommended to add LAMA to ICS compared to adding LABA to ICS	Ages 12 years and older	Conditional recommendation, moderate strength of evidence
In individuals not using LABA for uncontrolled persistent asthma, adding a LAMA to ICS controller therapy is recommended over continuing the same dose of ICS	Ages 12 years and older	Conditional recommendation, moderate strength of evidence
In individuals with uncontrolled persistent asthma, adding LAMA to ICS-LABA compared to continuing the same dose of ICS-LABA is recommended	Ages 12 years and older	Conditional recommendation, moderate certainty of evidence

Key: * intermittent therapy is defined as temporary use of ICS in those not regularly using ICS controller therapy; † Single-inhaler ICS-formoterol both daily and as needed is referred to as "single maintenance and reliever therapy (SMART)"; ‡ The maximum recommended formoterol dose is 12 puffs (54 mcgs) for those 12 years and older and 8 puffs (36 mcgs) for children 4 to 11 years.

GINA – Global Strategy for Asthma Management and Prevention

The Global Initiative for Asthma published an update in 2022 for the management of asthma. GINA updates their recommendations on an annual basis to guide diagnosis and management of asthma in adults and adolescents.[6] Guidelines are based on a systematic search of the literature and publications are reviewed for acceptance by at least two committee members that are without conflicts of interest. Evidence is graded based on criteria developed by the National Heart Lung and Blood Institute which ranks the level of evidence from A to D (**Table 4**) .[6] Guideline limitations included to the guidelines were lack of reporting for conflicts of interest and limited discussion on barriers to implementing ecommendations.[6]

Table 4. GINA Guidance Levels of Evidence[6]

Evidence Categories	Sources of Evidence	Definition
A	• Randomized controlled trials (RCTs)	Evidence from well designed RCTs

	• High quality evidence without significant limitations	
B	• Randomized controlled trials with important limitations • Limited body of evidence	Evidence from RCTs that include only a limited number of patients, post-hoc, or subgroup analyses of RCTs or meta-analyses of RCTs
C	• Non-randomized trials • Observational studies	Evidence is from outcomes of uncontrolled or non-randomized tirlas or from observational studies
D	• Panel consensus judgement	Provision of guidance is deemed valuable but clinical literature on the subject matter is insufficient

Pharmacotherapy used to treat people with asthma is based off of asthma severity (**Table 5**). A substantial change in treatment recommendations is that monotherapy with SABAs in adults and adolescents is no longer recommended for asthma management. GINA guidelines recommend that all adults and adolescents with asthma receive an ICS-containing controller treatment.[6] Therapy can be given as a regular daily treatment for people with persistent symptoms or as-needed in people with mild asthma for symptom relief. Recommendations are divided into treatment tracks based on *the choice of reliever therapy*: Track 1 and Track 2.

- Track 1: Low dose ICS -formoterol. Preferred option due to exacerbation reduction compared to SABA monotherapy.
- Track 2: SABA for reliever therapy

Initial treatment recommendations for adults and adolescents with asthma are presented in **Table 6**. Track 1 is the preferred treatment option. Recommendations for children 6-11 years old are in **Table 7**.

Table 5. Asthma Severity Directing Therapy[6]

Mild Asthma	*Step 1* – Symptoms less than twice a month
	Step 2 – Symptoms twice a month or more, but less than daily
Moderate Asthma	*Step 3* – Symptoms most days or waking with asthma once a week or more
Severe Asthma	*Step 4* – Symptoms most days or waking with asthma once a week or more or low lung function
	Step 5 – Severely uncontrolled asthma

Table 6. GINA Recommendations for Starting Treatment in Adults and Adolescents with Asthma[6]

STEP	Treatment Recommendation Track 1*	Treatment Recommendation Track 2†
STEP 1	-As-needed low dose ICS-formoterol	-Low dose ICS whenever a SABA is taken
STEP 2	-As-needed low dose ICS-formoterol	-Low dose maintenance ICS
STEP 3	-Low dose maintenance ICS-formoterol (MART)	-Low dose maintenance ICS/LABA
STEP 4	-Medium dose maintenance ICS-formoterol (MART)	-Medium/high dose maintenance ICS/LABA
STEP 5	-Add-on LAMA -Refer for phonotypic assessment -Consider high dose maintenance ICS-formoterol +/- other pharmacotherapy	-Add-on LAMA -Refer for phonotypic assessment -Consider high dose maintenance ICS-LABA +/- other pharmacotherapy

Key: * Reliever is as-needed low-dose ICS-formoterol; † Reliever is as-needed SABA
Abbreviations: ICS – inhaled corticosteroid; LABA – long-acting beta agonist; LAMA = long-acting muscarinic antagonist; MART – maintenance and reliever therapy with ICS-formoterol; SABA – short-acting beta agonist

Table 7. GINA Recommendations for Starting Treatment in Children 6-11 years with Asthma[6]

STEP	Preferred Controller Therapy *	Alternate Controller Therapy Options*
STEP 1	- Low dose ICS whenever a SABA is taken	- Consider low dose daily ICS
STEP 2	- Daily low dose ICS	- Daily LTRA *or* - Low dose ICS taken whenever a SABA is used
STEP 3	- Low dose ICS-LABA *or* - Medium dose ICS *or* - Very low dose ICS-formoterol maintenance and reliever (MART)	- Low dose ICS + LTRA
STEP 4	- Medium dose ICS-LABA *or* - Low dose ICS-formoterol maintenance and reliever therapy (MART)	- Add tiotropium *or* - Add LTRA
STEP 5	- Refer for phonotypic assessment *+/-* - Higher dose ICS-LABA *or* - Other add-on pharmacotherapy	- Add-on anti-IL5 *or* - As a last resort, consider add-on low dose OCS but consider side effects
Key: *As-needed SABA (or low dose ICS-formoterol reliever for MART) Abbreviations: ICS – inhaled corticosteroid; LABA – long-acting beta agonist; IL-5 – interleukin 5; LTRA - leukotriene receptor antagonist; MART – maintenance and reliever therapy with ICS-formoterol; OCS – oral corticosticosteroids; SABA – short-acting beta agonist		

GOLD – Global Strategy for Diagnosis, Management, and Prevention of COPD

The Global Initiative for Chronic Obstructive Lung Disease updated recommendations for managing COPD in 2022.[7] A systematic review was undertaken to evaluate new literature. Guidelines are based on a systematic search of the literature and publications are reviewed for acceptance by at least two committee members that are without conflicts of interest. Evidence is graded based on criteria developed by the National Heart Lung and Blood Institute which ranks the level of evidence from A to D (**Table 8**) . Conflict of interest were documented for 76% of the committee. Other limitations include no discussion on resource implications/barriers to implementation of recommendations.

Table 8. GOLD Guidance Levels of Evidence

Evidence Categories	Sources of Evidence	Definition
A	• Randomized controlled trials (RCTs) • High quality evidence without significant limitations	Evidence from well designed RCTs
B	• Randomized controlled trials with important limitations • Limited body of evidence	Evidence from RCTs that include only a limited number of patients, post-hoc, or subgroup analyses of RCTs or meta-analyses of RCTs
C	• Non-randomized trials • Observational studies	Evidence is from outcomes of uncontrolled or non-randomized tirlas or from observational studies
D	• Panel consensus judgement	Provision of guidance is deemed valuable but clinical literature on thee subject matter is insufficient

COPD is classified based on FEV_1 and symptoms/risk of exacerbations as described in **Table 9 and Table 10**.[7] Exacerbations are also an important component of managing symptoms in people that have COPD. Exacerbations are defined as an acute worsening of respiratory symptoms that result in additional therapy. Mild exacerbations are those that require treatment with SABA only, moderate require treatment with SABA and antibiotics and/or oral corticosteroids, and severe exacerbations are those that require the patient be hospitalized or visits the ER. The combination of symptomatic assessment, spirometry, and risk of exacerbations helps to determine the impact of COPD on the patient.

Table 9. Classification of Airflow Limitation for Patients wit COPD Based on 2022 GOLD Guidelines*[7]

Classification	Severity	Post-Bronchodilator FEV_1
GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4	Very severe	$FEV_1 < 30\%$ predicted

* For patients with a FEV1/FVC < 0.70

Table 10. Classification of Symptoms/Exacerbation Risk for Patients wit COPD Based on 2022 GOLD Guidelines[7]

Classification	Assessment Test	Exacerbations
GOLD Category A	mMRC 0-1 or CAT <10	History of 0-1 moderate to severe exacerbations*
GOLD Category B	mMRC ≥2 or CAT ≥10	History of 0-1 moderate to severe exacerbations*
GOLD Category C	mMRC 0-1 or CAT <10	History of ≥2 moderate/severe exacerbations or ≥1 exacerbation (leading to hospital admission)
GOLD Category D	mMRC ≥2 or CAT ≥10	History of ≥2 moderate/severe exacerbations or ≥1 exacerbation (leading to hospital admission)

Key: * Not leading to hospital admission
Abbreviations: CAT – COPD Assessment Test; MRC – modified Medical Research Counsel questionnaire

Inhaled bronchodilators are recommended for regular use in people with COPD for the prevention and reduction of symptoms. Specific evidence related to their use is presented in **Table 11**.[7] Generally long-acting bronchodilators are preferred to short-acting therapies. Inhaled anti-inflammatory use is also an important component in the management of COPD (**Table 12**).[7] The use of ICS is not recommended in patients with COPD that have repeated pneumonia, blood eosinophils <100 cells/microliter or history of mycobacterial infection. Long-term ICS monotherapy is not recommended; however, long-term ICS with LABAs may be appropriate in people with a history of exacerbations despite appropriate treatment with long-acting bronchodilators.[7] There is some evidence to suggest the use of LABA/LAMA combination may have beneficial mortality effect in people with symptomatic COPD and a history of frequent or severe exacerbations.

Table 11. Evidence for the Use of Bronchodilators in COPD[7]

Recommendation	Evidence level
Regular and as-needed use of SABA or SAMA improves FEV_1 and symptoms	A
Combination of SABA and SAMA are superior compared to either medication alone in improving FEV_1 and symptoms	A
LABAs and LAMAs significantly improve lung function, dyspnea, health status and reduce exacerbations rates	A
LAMAs have greater effect on exacerbation reduction* and decreased hospitalizations† compared with LABAs	A* and B†
Combination treatment with a LABA and LAMA increases FEV_1 and reduces symptoms compared to monotherapy	A
Combination treatment with LABA/LAMA reduces exacerbations compared to monotherapy	B
Tiotropium improves the effectiveness of pulmonary rehabilitation in increasing exercise performance	B

Table 12. Evidence for the Use of Inhaled Anti-inflammatory Therapies in COPD[7]

Recommendation	Evidence level
The combination of an ICS and LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to severe COPD	A
Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease	A
Triple inhaled therapy of LABA/LAMA/ICS improves lung function symptoms, improves health status, and reduces exacerbations compared to LABA/ICS, LABA/LAMA, or LAMA monotherapy	A

Treatments for COPD should be initiated in people based on symptoms and exacerbation risk. There is no high quality evidence to guide initial therapy; however, **Figure 1** recommends treatment options based on available evidence.

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

US Preventative Services Task Force – COPD Updated Evidence Report and Systematic Review

In 2022 the USPSTF updated treatment recommendations for the screening and management of COPD.[8] The guidance was based off of a systematic review and meta-analysis done by the Agency for Heatlhcare Research and Quality (AHRQ).[10] There were 3 new trials (n=20,058) included in the updated analysis on the use of pharmacological therapies for the treatment of COPD.[8]

There was moderate quality of evidence that the use of LABA, LAMA, ICS or LABA/ICS reduces the risk of exacerbations in people with moderate COPD.[8] Tiotropium demonstrated reduction in deterioration in people with moderate COPD and exacerbations in people with minimally symptoms and moderate airflow obstruction. Harms data from new evidence is consistent with previous findings from trials that show no serious adverse reactions from the use of LAMA, LABAs or ICS.[8] Data from observations trials suggest that there may be a increased risk of cardiovascular disease with LABA use and long-term use of ICS may affect bone health negatively.

After review, no guidelines were excluded due to poor quality.

New Formulations or Indications:

Breztri Aerosphere (budesonide 160 mcg, glycopyrrolate 9 mcg, and formoterol fumarate 4.8 mcg inhalation aerosol) – In July of 2020 a triple combination product of budesonide, glycopyrrolate, and formoterol was approved for the maintenance treatment of patients with COPD.[22] The approved dose is 2 inhalations twice daily. Two studies evaluated the use of Breztri in patients with COPD and history of previous LAMA, LABA and ICS use. Breztri reduced COPD exacerbation more than combination therapy with 2 agents over 52 weeks in trial 1 and over 24 weeks in trial 2 (**Table 13**).[22]

Table 13. Rate of Moderate to Severe Exacerbations[22]

Treatment	Mean Annual Rate	Rate Ratio vs. Comparator
Trial 1 (52 weeks, n=6388)		
Breztri Aerosphere*	1.08	N/A
GFF MDI	1.42	RR 0.76 (95% CI, 0.69 to 0.83); p<0.0001
BFF MDI	1.24	RR 0.87 (95% CI, 0.79 to 0.95); p=0.0027
Trial 2 (24 weeks, n=1,896)		
Breztri Aerosphere	NR	
GFF MDI	NR	RR 0.48 (95% CI, 0.37 to 0.64); p<0.05
BFF MDI	NR	RR 0.82 (95% CI, 0.58 to 1.17); p>0.05

Key: * budesonide 320 mcg/glycopyrrolate 18 mcg/formoterol fumarate 9.6 mcg

Abbreviations: BFF – budesonide/formoterol fumarate 320 mcg/9.6 mcg; GFF – glycopyrrolate/formoterol fumarate 18 mcg/9.6 mcg; MDI – meter dose inhaler; NR – not reported; RR – rate ratio.

ArmonAir Respiclick (fluticasone propionate) – Prescribing information for Armonair Respiclick® formulation of fluticasone was updated in April of 2022 to include the addition of a new 30 mcg strength.[23]

ArmonAir Respiclick (fluticasone propionate) – In July of 2021, ArmonAir Respiclick® received the approval for use as maintenance treatment for asthma as prophylactic therapy in pediatric patients ages 4 to 11 years.[23]

Trelegy Ellipta (fluticasone furoate-umeclidinium-vilanterol) – In September of 2022, Trelegy Ellipta® received an expanded indication from the FDA for maintenance treatment in people 18 years and older with asthma. A new dosage form of fluticasone furoate 200 mcg-umeclidinium 62.5 mcg-vilanterol 25 mcg was approved.[24]

New FDA Safety Alerts:
No new FDA safety alerts identified.

Randomized Controlled Trials:
A total of 160 citations were manually reviewed from the initial literature search. After further review, 158 citations were excluded because of wrong study design (e.g., observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining two trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 14. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Papi, et al[25] DB, MC, Phase 3, RCT	1. Albuterol 180 mcg -budesonide 160 mcg as needed 2. Albuterol 180 mcg -budesonide 80 mcg as needed 3. Albuterol 180 mcg as needed	Patients (4 years and older) with uncontrolled moderate to severe asthma receiving inhaled glucocorticoid-containing maintenance therapy N=3132	The first event of severe asthma exacerbation in a time-to-event analysis	Annualized Rate Ratio: 1. 0.43 2. 0.48 3. 0.59 Albuterol 180 mcg/budesonide 160 mcg vs. Albuterol 180 mcg: HR 0.74 (95% CI, 0.62 to 0.89); P=0.001 Albuterol 180 mcg/budesonide 80 mcg vs. Albuterol 180 mcg: HR 0.84 (95% CI, 0.71 to 1.0); P=0.052	As needed albuterol 180 mcg/budesonide 160 mcg was more effective than albuterol 180 mcg in reducing the risk of severe asthma exacerbations. A majority of patients were white (81.1%) and 25.9% were Latinx or Hispanic.
Clemency, et al[26] DB, MC, Phase 3, RCT	1. Ciclesonide 320 mcg 2. Placebo 30 days	Non-hospitalized participants with symptomatic COVID-19 infection N=413	Time to alleviation of all COVID-19-related symptoms by day 30	1. 19.0 days 2. 19.0 days OR 1.28 days (95% CI, 0.84 to 1.97)	There was no difference between ciclesonide and placebo in reducing symptoms of COVID-19

Abbreviations: CI = confidence intervals; DB = double-blind; HR = hazard ratio; MC = multicenter; OR = odds ratio; RCT = randomized clinical trial.

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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
ipratropium/albuterol sulfate	IPRATROPIUM-ALBUTEROL	AMPUL-NEB	Y
ipratropium/albuterol sulfate	COMBIVENT RESPIMAT	MIST INHAL	Y
tiotropium bromide	SPIRIVA HANDIHALER	CAP W/DEV	Y
umeclidinium bromide	INCRUSE ELLIPTA	BLST W/DEV	Y
aclidinium bromide	TUDORZA PRESSAIR	AER POW BA	N
glycopyrrol/nebulizer/accessor	LONHALA MAGNAIR STARTER	VIAL-NEB	N
glycopyrrolate/neb.accessories	LONHALA MAGNAIR REFILL	VIAL-NEB	N
revefenacin	YUPELRI	VIAL-NEB	N
tiotropium bromide	SPIRIVA RESPIMAT	MIST INHAL	N

Beta agonists, Inhaled Long-acting

Generic	Brand	Form	PDL
salmeterol xinafoate	SEREVENT DISKUS	BLST W/DEV	Y
arformoterol tartrate	ARFORMOTEROL TARTRATE	VIAL-NEB	N
arformoterol tartrate	BROVANA	VIAL-NEB	N
formoterol fumarate	FORMOTEROL FUMARATE	VIAL-NEB	N
formoterol fumarate	PERFOROMIST	VIAL-NEB	N
olodaterol HCl	STRIVERDI RESPIMAT	MIST INHAL	N

Beta-agonists, Inhaled Short-acting

Generic	Brand	Form	PDL
albuterol sulfate	ALBUTEROL SULFATE HFA	HFA AER AD	Y
albuterol sulfate	PROAIR HFA	HFA AER AD	Y
albuterol sulfate	PROVENTIL HFA	HFA AER AD	Y
albuterol sulfate	VENTOLIN HFA	HFA AER AD	Y
albuterol sulfate	ALBUTEROL SULFATE	SOLUTION	Y

albuterol sulfate	ALBUTEROL SULFATE	VIAL-NEB	Y
albuterol	ALBUTEROL	AER REFILL	N
albuterol sulfate	PROAIR RESPICLICK	AER POW BA	N
albuterol sulfate	PROAIR DIGIHALER	AER PW BAS	N
levalbuterol HCl	LEVALBUTEROL CONCENTRATE	VIAL-NEB	N
levalbuterol HCl	LEVALBUTEROL HCL	VIAL-NEB	N
levalbuterol HCl	XOPENEX	VIAL-NEB	N
levalbuterol HCl	XOPENEX CONCENTRATE	VIAL-NEB	N
levalbuterol tartrate	LEVALBUTEROL TARTRATE HFA	HFA AER AD	N
levalbuterol tartrate	XOPENEX HFA	HFA AER AD	N

Corticosteroids, Inhaled

Generic	Brand	Form	PDL
budesonide	PULMICORT FLEXHALER	AER POW BA	Y
fluticasone propionate	FLOVENT HFA	AER W/ADAP	Y
fluticasone propionate	FLUTICASONE PROPIONATE HFA	AER W/ADAP	Y
fluticasone propionate	FLOVENT DISKUS	BLST W/DEV	Y
mometasone furoate	ASMANEX	AER POW BA	Y
beclomethasone dipropionate	QVAR REDIHALER	HFA AEROBA	N
budesonide	BUDESONIDE	AMPUL-NEB	N
budesonide	PULMICORT	AMPUL-NEB	N
ciclesonide	ALVESCO	HFA AER AD	N
fluticasone furoate	ARNUITY ELLIPTA	BLST W/DEV	N
fluticasone propionate	ARMONAIR DIGIHALER	AER PW BAS	N
mometasone furoate	ASMANEX HFA	HFA AER AD	N

Corticosteroid/LABA Combination Inhalers

Generic	Brand	Form	PDL
budesonide/formoterol fumarate	BUDESONIDE-FORMOTEROL FUMARATE	HFA AER AD	Y
budesonide/formoterol fumarate	SYMBICORT	HFA AER AD	Y
fluticasone propion/salmeterol	AIRDUO RESPICLICK	AER POW BA	Y
fluticasone propion/salmeterol	FLUTICASONE-SALMETEROL	AER POW BA	Y
fluticasone propion/salmeterol	ADVAIR DISKUS	BLST W/DEV	Y
fluticasone propion/salmeterol	FLUTICASONE-SALMETEROL	BLST W/DEV	Y
fluticasone propion/salmeterol	WIXELA INHUB	BLST W/DEV	Y
fluticasone propion/salmeterol	ADVAIR HFA	HFA AER AD	Y
mometasone/formoterol	DULERA	HFA AER AD	Y
fluticasone propion/salmeterol	AIRDUO DIGIHALER	AER PW BAS	N
fluticasone/vilanterol	BREO ELLIPTA	BLST W/DEV	N
fluticasone/vilanterol	FLUTICASONE-VILANTEROL	BLST W/DEV	N

LAMA/LABA Combination Inhalers

Generic	Brand	Form	PDL
tiotropium Br/olodaterol HCl	STIOLTO RESPIMAT	MIST INHAL	Y
umeclidinium brm/vilanterol tr	ANORO ELLIPTA	BLST W/DEV	Y
aclidinium brom/formoterol fum	DUAKLIR PRESSAIR	AER POW BA	N
budesonide/glycopyr/formoterol	BREZTRI AEROSPHERE	HFA AER AD	N
fluticasone/umeclidin/vilanter	TRELEGY ELLIPTA	BLST W/DEV	N
glycopyrrolate/formoterol fum	BEVESPI AEROSPHERE	HFA AER AD	N

Appendix 2: Abstracts of Comparative Clinical Trials

Efficacy of Inhaled Ciclesonide for Outpatient Treatment of Adolescents and Adults With Symptomatic COVID-19: A Randomized Clinical Trial

Objective: To determine the efficacy of the inhaled steroid ciclesonide in reducing the time to alleviation of all COVID-19-related symptoms among nonhospitalized participants with symptomatic COVID-19 infection.

Design, setting, and participants: This phase 3, multicenter, double-blind, randomized clinical trial was conducted at 10 centers throughout the US and assessed the safety and efficacy of a ciclesonide metered-dose inhaler (MDI) for treating nonhospitalized participants with symptomatic COVID-19 infection who were screened from June 11, 2020, to November 3, 2020.

Interventions: Participants were randomly assigned to receive ciclesonide MDI, 160 µg per actuation, for a total of 2 actuations twice a day (total daily dose, 640 µg) or placebo for 30 days.

Main outcomes and measures: The primary end point was time to alleviation of all COVID-19-related symptoms (cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell) by day 30. Secondary end points included subsequent emergency department visits or hospital admissions for reasons attributable to COVID-19.

Results: A total of 413 participants were screened and 400 (96.9%) were enrolled and randomized (197 [49.3%] in the ciclesonide arm and 203 [50.7%] in the placebo arm; mean [SD] age, 43.3 [16.9] years; 221 [55.3%] female; 2 [0.5%] Asian, 47 [11.8%] Black or African American, 3 [0.8%] Native Hawaiian or other Pacific Islander, 345 [86.3%] White, and 1 multiracial individuals [0.3%]; 172 Hispanic or Latino individuals [43.0%]). The median time to alleviation of all COVID-19-related symptoms was 19.0 days (95% CI, 14.0-21.0) in the ciclesonide arm and 19.0 days (95% CI, 16.0-23.0) in the placebo arm. There was no difference in resolution of all symptoms by day 30 (odds ratio, 1.28; 95% CI, 0.84-1.97). Participants who were treated with ciclesonide had fewer subsequent emergency department visits or hospital admissions for reasons related to COVID-19 (odds ratio, 0.18; 95% CI, 0.04-0.85). No participants died during the study.

Conclusions and relevance: The results of this randomized clinical trial demonstrated that ciclesonide did not achieve the primary efficacy end point of reduced time to alleviation of all COVID-19-related symptoms.

Albuterol-Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma

Alberto Papi , Bradley E Chipps , Richard Beasley, Reynold A Panettieri Jr, Elliot Israel , Mark Cooper , Lynn Dunsire , Allison Jeynes-Ellis , Eva Johnsson , Robert Rees , Christy Cappelletti , Frank C Albers

Background: As asthma symptoms worsen, patients typically rely on short-acting β_2-agonist (SABA) rescue therapy, but SABAs do not address worsening inflammation, which leaves patients at risk for severe asthma exacerbations. The use of a fixed-dose combination of albuterol and budesonide, as compared with albuterol alone, as rescue medication might reduce the risk of severe asthma exacerbation.

Methods: We conducted a multinational, phase 3, double-blind, randomized, event-driven trial to evaluate the efficacy and safety of albuterol-budesonide, as compared with albuterol alone, as rescue medication in patients with uncontrolled moderate-to-severe asthma who were receiving inhaled glucocorticoid-containing maintenance therapies, which were continued throughout the trial. Adults and adolescents (≥12 years of age) were randomly assigned in a 1:1:1 ratio to one of three trial groups: a fixed-dose combination of 180 µg of albuterol and 160 µg of budesonide (with each dose consisting of two actuations of 90 µg and 80 µg, respectively [the higher-dose combination group]), a fixed-dose combination of 180 µg of albuterol and 80 µg of budesonide (with each dose consisting of two actuations of 90 µg and 40 µg, respectively [the lower-dose combination group]), or 180 µg of albuterol (with each dose consisting of two actuations of 90 µg [the albuterol-alone group]). Children 4 to 11 years of age were randomly assigned to only the lower-dose combination group or the albuterol-alone group. The primary efficacy end point was the first event of severe asthma exacerbation in a time-to-event analysis, which was performed in the intention-to-treat population.

Results: A total of 3132 patients underwent randomization, among whom 97% were 12 years of age or older. The risk of severe asthma exacerbation was significantly lower, by 26%, in the higher-dose combination group than in the albuterol-alone group (hazard ratio, 0.74; 95% confidence interval [CI], 0.62 to 0.89; P = 0.001). The hazard ratio in the lower-dose combination group, as compared with the albuterol-alone group, was 0.84 (95% CI, 0.71 to 1.00; P = 0.052). The incidence of adverse events was similar in the three trial groups.

Conclusions: The risk of severe asthma exacerbation was significantly lower with as-needed use of a fixed-dose combination of 180 µg of albuterol and 160 µg of budesonide than with as-needed use of albuterol alone among patients with uncontrolled moderate-to-severe asthma who were receiving a wide range of inhaled glucocorticoid-containing maintenance therapies. (Funded by Avillion; MANDALA ClinicalTrials.gov number, NCT03769090.).

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to October 03, 2022
Search Strategy:

#	Searches	Results
1	Ipratropium/ or ipratropium.mp.	2660
2	tiotropium.mp. or Tiotropium Bromide/	1986
3	umeclidinium.mp.	309
4	glycopyrrolate.mp. or Glycopyrrolate/	1674
5	revefenacin.mp.	41
6	salmeterol.mp. or Salmeterol Xinafoate/	3153
7	arformoterol.mp. or Formoterol Fumarate/	1910
8	formoterol.mp. or Formoterol Fumarate/	2878
9	olodaterol.mp.	252
10	albuterol.mp. or Albuterol/	11071
11	levalbuterol.mp. or Levalbuterol/	156
12	Budesonide/ or budesonide.mp.	6988
13	Fluticasone/ or fluticasone.mp.	5025
14	mometasone.mp. or Mometasone Furoate/	1309
15	beclomethasone.mp. or Beclomethasone/	3952
16	Budesonide/ or budesonide.mp.	6988
17	ciclesonide.mp.	458
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	30459
19	limit 18 to (english language and humans and yr="2020 -Current")	1721
20	limit 19 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	160

Appendix 4: Key Inclusion Criteria

Population	People with asthma and chronic obstructive pulmonary disease (COPD)
Intervention	Inhaled therapies for people with asthma or COPD
Comparator	Active therapies or placebo
Outcomes	Lung function, symptoms, hospitalizations and mortality
Timing	NA
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

Long-acting Beta-agonists (LABA)

Goals:

- To optimize the safe and effective use of LABA therapy in patients with asthma and COPD.

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?	**Yes:** Go to #5	**No:** Go to #4
4. Does the patient have a diagnosis of COPD, mucopurulent chronic bronchitis and/or emphysema?	**Yes:** Approve for up to 12 months	**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
5. Does the patient have an active prescription for an inhaled corticosteroid (ICS) or an alternative asthma controller medication?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: *10/22 (KS), 10/20 (KS), 5/19 (KS); 1/18; 9/16; 9/15); 5/12; 9/09; 5/09*
Implementation: *3/1/18; 10/9/15; 8/12; 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 asthma and COPD.
- Step-therapy required prior to coverage:
  - Asthma and COPD: short-acting bronchodilator and previous trial of two drug combination therapy (ICS/LABA, LABA/LAMA or ICS/LAMA). Preferred monotherapy inhaler 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 without COPD?	**Yes:** Go to #8	**No:** Go to #4

Approval Criteria		
4. Does the patient have a diagnosis of COPD, mucopurulent chronic bronchitis and/or emphysema?	**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.
5. Is the request for a LAMA/LABA combination product?	**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:** Go to #6
6. Is the request for a 3 drug ICS/LABA/LAMA combination product and is there a documented trial of a LAMA and LABA, or ICS and LABA or ICS and LAMA?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is there documentation that the prescriber is willing to stop coverage of all other LAMA, LABA, and ICS inhaler combination products?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA, LABA and ICS inhalers.	**No:** Pass to RPh. Deny; medical appropriateness.
8. Does the patient have an active prescription for an on-demand short-acting acting beta-agonist (SABA) and/or for ICS-formoterol?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
9. Is the request for Trelegy Ellipta (ICS/LAMA/LABA) combination product and is there a documented trial of an ICS/LABA?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA, LABA and ICS inhalers (with the exception of ICS-formoterol which may be continued)	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *10/22 (KS), 10/21 (SF); 12/20 (KS), 10/20, 5/19; 1/18; 9/16; 11/15; 9/15; 11/14; 11/13; 5/12; 9/09; 2/06*
Implementation: *1/1/21; 3/1/18; 10/13/16; 1/1/16; 1/15; 1/14; 9/12; 1/10*

Inhaled Corticosteroids (ICS)

Goals:
- To optimize the safe and effective use of ICS therapy in patients with asthma and COPD.

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?	**Yes:** Go to #6	**No:** Go to #4
4. Is the request for treatment of COPD, mucopurulent chronic bronchitis and/or emphysema?	**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.
5. 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.
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:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: *10/22 (KS), 10/20 (KS), 5/19 (KS), 1/18; 9/16; 9/15*
Implementation: *3/1/18; 10/13/16; 10/9/15*