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Drug Class Update: Inhalers for Asthma and COPD

Date of Review: February 2024

Date of Last Review: December 2022
Dates of Literature Search: 01/01/2022 – 10/25/2023

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

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 Pharmacy and Therapeutics (P &T) Committee review at the December 2022 meeting.

Plain Language Summary:

- Asthma and chronic obstructive pulmonary disease (COPD) are lung conditions that make it hard to breathe. Asthma is a condition in which the airways narrow and swell and may be blocked by extra mucus in the lungs. COPD is usually caused by damage to the lungs from cigarette smoke or other air pollutants. For both conditions, inhaled medicine can improve symptoms.
- Several types of inhaled medicines are available. Generally, quick relief (or short-acting inhalers) relax the airways to help people breathe easier when they are short of breath. Long-acting inhalers prevent shortness of breath, coughing and chest tightness over time. Long-acting inhalers need to be taken every day, even when people feel well and don't have trouble breathing or other symptoms.
- The 2023 Global Initiative for Asthma report recommends that people with asthma use 2 medicines called a corticosteroid and formoterol if they:
    - require medicine occasionally when they have trouble breathing or
    - require daily treatment with medicine to control more frequent symptoms.
- In many people with COPD, inhalers that combine 2 or 3 types of medicines help people breathe better than inhalers that contain only one type of medicine.
- Oregon Health Plan will pay for a corticosteroid (i.e., mometasone, budesonide, and fluticasone), short acting-beta agonist (albuterol), a long-acting beta agonist (salmeterol), and long-acting muscarinic antagonist (i.e., umeclidinium, tiotropium) inhaler without requiring prior authorization. Combination inhalers with a corticosteroid and salmeterol or formoterol (i.e., ADVAIR, DULERA, SYMBICORT) will also pay without requiring prior authorization. Providers must explain to the Oregon Health Authority why someone needs certain combination inhaler products (i.e., ANORO ELLIPTA, STILOTO RESPIMAT, TRELEGY, DUAKLIR PRESSAIR, and BEVESPI AEROSPHERE) before the Oregon Health Plan will pay for it.

Research Questions:

- What is the comparative efficacy for asthma and COPD inhaler medications for important outcomes such as symptoms, lung function, hospitalizations and mortality?
- What is the evidence for harms associated with asthma and COPD inhaler medications?
- 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:

- Since the last P & T Committee review of inhalers for asthma and COPD in December 2022, 3 high-quality systematic reviews[1-3] and 2 high-quality guidelines[4,5] have been published.
- In December 2022, the Drug Effectiveness Review Project (DERP) published a report focused on effectiveness and safety of single-inhaler triple therapies for management of asthma and COPD compared with monotherapy, dual therapy, or multiple-inhaler triple therapies.[1] No significant differences were observed between triple and dual therapy in the annualized rate of severe asthma exacerbations.[1] Compared with monotherapy or dual therapies, triple therapy demonstrated improvements in frequency of COPD exacerbations, symptom control, and health-related quality of life in people with COPD.[1] Adverse events occurred in similar proportions across treatments in both asthma and COPD populations.[1] Death and early withdrawal from studies due to adverse events were rare.[1]
- A December 2022 Cochrane review assessed dual corticosteroid-long-acting beta-agonists (ICS-LABA) inhaler treatment and triple ICS-LABA-long-acting muscarinic antagonist (LAMA) inhaler treatment compared with each other and medium- to high-dose ICS monotherapy in adolescents and adults with uncontrolled asthma.[2] Compared to medium-dose dual ICS-LABA therapy, medium-dose and high-dose ICS triple inhaler therapies reduce asthma exacerbations, but not asthma-related hospitalizations (high-certainty evidence).[2] High-dose ICS triple therapy is likely superior to medium-dose ICS triple therapy in reducing asthma exacerbations (moderate-certainty evidence).[2] Compared to medium-dose ICS-LABA therapy, high-dose ICS triple therapy, but not medium-dose ICS triple therapy, results in a reduction in all-cause adverse effects (AEs; high-certainty evidence).[2] Compared to dual ICS-LABA therapy, triple therapy does not reduce all-cause serious adverse effects (SAEs; high-certainty evidence).[2] The evidence that any specific formulation would be better than the others within the same group in any outcomes is uncertain due to the scarcity of data and resulting imprecision of estimates.[2]
- A 2023 Cochrane review assessed the safety and efficacy of adding a LABA or LAMA to ICS therapy compared to increasing the ICS dose in adolescents and adults with asthma not well controlled on medium-dose ICS.[3] The findings from this review suggest that compared to medium-dose ICS monotherapy, medium- or high-dose ICS-LABA and medium-dose ICS-LAMA reduce moderate-to-severe asthma exacerbations (moderate-certainty evidence).[3] Medium-dose ICS-LAMA likely reduces all-cause AEs and results in a slight reduction in treatment discontinuation due to AEs compared to medium-dose ICS (moderate-certainty evidence).[3]
- The updated Global Initiative for Asthma (GINA) guidance for management of asthma was published July 2023.[4] Key changes in this report include clarification of terminology for asthma medications and addition of as-needed ICS-SABA reliever therapy to track 2 of alternative treatment options.[4] The specific recommendations for treatment of adults and adolescents (aged 12 years and older) are summarized as Steps 1 through 4 in **Table 5.** Guidance for asthma treatment in children aged 6 to 11 years of age is presented in **Table 6**. Treatment recommendations are based upon the following evidence:
    - SABAs are highly effective for quick relief of asthma symptoms, but patients treated with SABAs alone are at risk of asthma-related death and urgent asthma-related health care use, even if there is good symptom control (high-quality evidence).[4]
    - Regular or frequent LABA use alone is not recommended without ICS due to risk of asthma exacerbations (high-quality evidence).[4]

- In step 4, in patients with persistently uncontrolled asthma despite medium- or high-dose ICS-LABA, consider adding on a LAMA as a separate inhaler (for age ≥ 6 years) or as combination triple therapy inhaler (for age ≥ 18 years).[4] Evidence shows:
  - this strategy may modestly improve lung function but not symptoms (high-quality evidence) and
  - in patients having exacerbations with low-dose ICS-LABA, ICS dose should be increased to medium or higher, or treatment switched to maintenance and reliever therapy with ICS-formoterol before adding LAMA (high-quality evidence).[4]

- The 2023 Global Initiative for COPD (GOLD) report contains several important revisions and updates including: a new definition of COPD; a revision of the COPD patient classification system; a new definition of COPD exacerbation; and updated evidence on therapeutic interventions to reduce COPD mortality.[5] Strong recommendations include:
  - The treatment of patients in Group A remains the same as previous reports: a bronchodilator (i.e., SABA, SAMA, LABA, or LAMA) with a long-acting bronchodilator preferred unless very occasional dyspnea is present (Strong Recommendation).[5]
  - For patients in Group B, a LAMA-LABA inhaler is now recommended since dual therapy is more effective than monotherapy, with similar side effects (Strong Recommendation).[5]
  - For patients in Group E (formerly categorized in groups C and D), LAMA-LABA is also the recommended initial therapy (Strong Recommendation).[5]
- A new ICS-SABA product, albuterol 90 mcg and budesonide 80 mcg (AIRSUPRA) received FDA approval in January 2023. This is the first ICS/SABA inhaler approved in the United States (US). In the MANDALA trial, albuterol-budesonide showed a statistically significant reduction in time to first severe asthma exacerbation compared with albuterol monotherapy.[6] Inhaled albuterol-budesonide is indicated for as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma 18 years of age and older.[7] Details of the pivotal trials that led to FDA-approval are presented in **Table 10.**
- In April 2023, a new formulation of budesonide 160 mcg and formoterol 4.8 mcg (SYMBICORT AEROSPHERE) received FDA approval as maintenance treatment of patients with COPD.[8] It is not indicated for relief of acute bronchospasm or for treatment of asthma.[8] The original budesonide-formoterol (SYMBICORT) products contain formoterol 4.5 mcg and 80 to 160 mcg of budesonide. Compared with formoterol monotherapy, combination budesonide-formoterol improved time to first and rate of moderate- to severe-COPD exacerbations. Details of the pivotal trials that led to FDA-approval are presented in **Table 10.**
- There was insufficient evidence in subgroup populations with asthma or COPD to establish meaningful conclusions on efficacy or harms.

Recommendations:

- Based on 2023 GOLD guidance which recommends a LAMA-LABA inhaler as initial therapy for 2 patient groups (B and E), have at least one LAMA-LABA inhaler preferred without PA on the Preferred Drug List (PDL).
- Modify combination LAMA-LABA and LAMA-LABA-ICS Inhaler PA criteria to remove PA from preferred products.
- Maintain albuterol-budesonide (AIRSUPRA) and budesonide 160 mcg-formoterol 4.8 mcg (SYMBICORT AEROSPHERE) as non-preferred inhalers on the PDL.
- After evaluation of costs in executive session, fluticasone furoate (ARNUITY ELLIPTA) was made preferred on the PDL.

Summary of Prior Reviews and Current Policy:

- The inhaled therapies for asthma and COPD are comprised of 5 classes: short-acting beta-agonists (SABAs), LABAs, short-acting muscarinic antagonists (SAMAs), LAMAs, and ICS. For ease of administration, these drug classes are combined into single inhalers in the following iterations: ICS/LABA, LAMA/LABA, and LAMA/LABA/ICS.

- Previous reviews have found low- to moderate-quality evidence of no within-class differences in efficacy or harms for long-acting products (i.e., LABAs, LAMAs or ICS) for patients with asthma or COPD.
- Preferred therapies for asthma and COPD maintenance inhalers on the Oregon Health Plan (OHP) include:
    a. SAMA, SAMA/SABA combination: ipratropium (aerosol and solution) and ipratropium/albuterol (nebulized solution)
    b. LAMAs: tiotropium, umeclidinium
    c. SABA: albuterol (aerosol and nebulized solution)
    d. LABA: salmeterol
    e. ICS: budesonide, fluticasone propionate, mometasone
    f. ICS-LABA combinations: budesonide/formoterol, fluticasone/salmeterol, mometasone/formoterol
    g. LAMA-LABA combinations: tiotropium/olodaterol, umeclidinium/vilanterol
    h. LAMA-LABA-ICS combinations: no preferred options for triple therapy
- The complete list of inhaled products and their status on the Preferred Drug List (PDL) is presented in **Appendix 1**. There are specific prior authorization (PA) criteria for all non-preferred ICS and LABA inhalers. In addition, all LAMA-LABA and LAMA-LABA-ICS combination products require PA.
- After review at the December 2022 meeting, the Pharmacy and Therapeutics (P & T) Committee agreed to revise inhaler PA criteria to align with recently updated guidance from the 2022 GINA, 2022 GOLD and US Preventative Services Task Force (USPSTF) reports. The specific PA criteria for ICS-LABA inhalers were retired, which made non-preferred therapies subject to general PA for non-preferred products.
- 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).
- The American Rescue Plan (ARP) Act of 2021 included a provision that eliminates the statutory cap on rebates paid to Medicaid by drug manufacturers. Beginning January 1st, 2024, rebates will no longer be capped at 100% of the quarterly average manufacturer price (AMP). This cap previously reduced the amount of rebates paid, particularly for drugs with significant price increases over time. This "AMP CAP" removal has the potential to significantly affect drug rebate amounts. Significant price fluctuations are anticipated in response to this provision, particularly in certain drug classes, including inhalers, which have seen large prices increases over time.
- The inhaled therapies account for a significant cost to the Oregon Health Authority. Compliance to the PDL ranges from a low of 38% for the LABA class to 100% for SABA and LAMAs, as of the third quarter in 2023 (July 1 to September 30).

Background:

Asthma

Asthma is a heterogeneous disease, characterized by chronic, reversible, airway inflammation which results in bronchial hyper-responsiveness. It is defined in the GINA guidance by the history of respiratory symptoms such as wheezing, shortness of breath, chest tightness and cough. Symptom severity can vary over time and be associated with changes in expiratory volume.[9] In 2019 the Centers for Disease Control and Prevention (CDC) estimated 25 million Americans, including 5 million children had asthma.[10] In the United States (U.S.), asthma is more than twice as common among Black children as among White children (13.5% and 6.4% respectively).[10] It is estimated about 5 to 10% of the total asthma population have severe asthma, but the exact prevalence is unknown due to the heterogeneous presentation of the disease.[11] Although the prevalence of severe asthma is relatively low, it accounts for 50% of the health care costs associated with management of asthma exacerbations.[12]

Diagnosis is confirmed by spirometry (improvement in forced expiratory volume in one second [FEV_1] > 200 mL or ≥ 12% from baseline after SABA use), which demonstrates airway obstruction that is at least partially reversible.[13] Asthma is characterized as mild, moderate or severe.[13] The underlying pathophysiology of asthma is multi-factorial and includes several phenotypes: eosinophil predominant, neutrophil predominant, and allergic asthma.[13] In particular, those patients with eosinophilic asthma Type 2-high, which indicates high levels of T-helper type 2 lymphocytes, respond well to ICS therapy and biologic therapy if asthma remains uncontrolled.[13] Patients with eosinophilic asthma also have high levels of sputum eosinophils. While 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.[13]

The GINA guidelines based initial pharmacotherapy on assessment of the frequency and severity of asthma symptoms.[9] The long-term goals of asthma management are to achieve good symptom control, reduce exacerbations, and minimize future risk of asthma-related mortality.[9] Asthma treatment is initiated in a stepwise manner based on the severity of asthma symptoms.[13] For Step 1 and 2 therapy, the 2022 GINA guideline recommends use of a combination low-dose ICS and the fast-acting LABA (formoterol) taken as needed for symptom relief.[13] Formoterol has both a rapid onset and long duration of action (up to 12 hours of bronchodilation).[13] For moderate asthma (Step 3), the preferred controller therapy is a combination low-dose ICS and LABA as maintenance therapy. Because of the rapid onset of action of formoterol, a combination budesonide-formoterol inhaler can be used both for daily controller therapy and for quick relief of symptoms.[13] It is likely that a combination mometasone-formoterol inhaler can be used in the same way (for both maintenance therapy and for acute relief of symptoms), but fewer data are available with this combination.[13] For severe asthma, the preferred controller treatments are medium (Step 4) or high (Step 5) doses of an ICS in combination with a LABA. Medium to high doses of inhaled glucocorticoids require more careful monitoring for adverse effects. As in moderate asthma, the use of a SABA together with an ICS for acute relief of symptoms in patients with severe persistent asthma may improve asthma control and reduce the frequency of asthma exacerbations compared with SABA alone.[14,15] The different inhalers stratified by class are presented in **Table 1**.

Table 1. Classes of Inhaler Medications Presented as Generic (BRAND)

Inhaled Corticosteroids (ICS)	
Beclomethasone (QVAR REDIHALER) Budesonide (PULMICORT FLEXHALER) Ciclesonide (ALVESCO)	Fluticasone Furoate (ARNUITY ELLIPTA) Fluticasone Propionate (FLOVENT) Mometasone (ASMANEX)
Short-Acting Beta-Agonists (SABAs)	
Albuterol (PROAIR, PROVENTIL, VENTOLIN)	Levalbuterol (XOPENEX)
Long-Acting Beta-Agonists (LABAs)	
Arformoterol (BROVANA) Formoterol (FORADIL) Indacaterol (ARCAPTA)	Olodaterol (STRIVERDI) Salmeterol (SEREVENT) Vilanterol (only available in combination)
Short-Acting Muscarinic Antagonist (SAMAs)	
Ipratropium (ATROVENT)	
Long-Acting Muscarinic Antagonists (LAMAs)	
Aclidinium (TUDORZA PRESSAIR) Glycopyrrolate (only available in combination) Revefenacin (YUPELRI)	Tiotropium (SPIRIVA) Umeclidinium (INCRUSE ELLIPTA)

Combination Short-Acting Beta-Agonist/Corticosteroid (SABA/ICS)	
Albuterol/Budesonide (AIRSUPRA)	
Combination Short-Acting Beta-Agonist/Short-Acting Muscarinic Antagonist (SABA/SAMA)	
Albuterol/Ipratropium (COMBIVENT RESPIMAT)	
Combination Long-Acting Muscarinic Antagonist/Long-Acting Beta-Agonists (LAMA/LABA)	
Aclidinium/Formoterol (DUAKLIR PRESSAIR) Glycopyrrolate/Formoterol (BEVESPI AEROSPHERE)	Tiotropium/Olodaterol (STIOLTO RESPIMAT) Umeclidinium/Vilanterol (ANORO ELLIPTA)
Combination Corticosteroid/Long-Acting Beta-Agonists (ICS/LABA)	
Budesonide/Formoterol (SYMBICORT, BREYNA) Mometasone/Formoterol (DULERA)	Fluticasone Propionate/Salmeterol (ADVAIR DISKUS, WIXELA INHUB, AIRDUO) Fluticasone Furoate/Vilanterol (BREO ELLIPTA)
Triple Therapy Inhalers (ICS/LAMA/LABA)	
Budesonide/Glycopyrrolate/Formoterol (BREZTRI AEROSPHERE)	Fluticasone/Umeclidinium/Vilanterol (TRELEGY ELLIPTA)

Outcome measures used in asthma trials include FEV_1, asthma exacerbations, hospitalizations, emergency department (ED) 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.[13] A decline in lung function is observed when FEV_1 is 60% or less of predicted values or peak expiratory flow shows a 30% or greater decrease from baseline.[16] The Asthma Control Questionnaire (ACQ) is a questionnaire that assesses asthma symptoms and rescue inhaler use in the preceding week.[17] Scores range from 0 (totally controlled) to 6 (severely uncontrolled), with a change in score of 0.5 units documented as a minimal clinically important difference (MCID).[17] An ACQ score consistently greater than 1.5 indicates poor symptom control.[17] The Asthma Quality of Life Questionnaire (AQLQ-12) contains 32 items assessing disease-specific, health-related quality-of-life that include domains of activity limitations, symptoms, emotional function, and environmental stimuli in patients aged 12 years and older.[16] The scale ranges from 1 (severely impaired) to 7 (not impaired at all). Total and domain scores are calculated by taking the mean of all questions overall or for each domain.[16] The MCID for this tool is 0.5 points for each item.[16] The St. George's Respiratory Questionnaire (SGRQ) was developed to measure health in chronic health airflow limitation.[18] The questionnaire is a 50 or 76 item assessment (depending on version) that includes 2 domains: frequency and severity of symptoms and impact on activities, which can be used with a 1-month, 3-month, or 12-month recall.[16] The scale ranges from 0 (no symptoms/limitations) to 100 (severe symptoms/limitations).[16] Scoring varies by item and item scores are converted into a domain score and an overall score, both reported on the same scale.[16] The MCID for the SGRQ is 4 points.[16] The Asthma Control Test (ACT) contains 5 self-reported items related to symptoms and daily functioning over past 4 weeks used in patients aged 12 years and older.[16] Assessments include shortness of breath and general asthma symptoms, use of rescue medications, effect of asthma on daily functioning, and overall self-assessment of asthma control.[16] The scale ranges from 5 (poor control) to 25 (complete control) with scores of 19 and greater indicating well-controlled asthma.[16] Each item is scored on 5-point Likert scale and the sum of scores across all items yields the total score.[16] The MCID for the ACT score is 3 points.[16] A summary of the outcomes commonly used in clinical trials for asthma treatment is presented in **Table 2.**

Table 2. Summary of Outcome Measures for Asthma Symptoms[16]

Measure	Scale	Minimal Clinically Important Difference (MCID)
Asthma Control Questionnaire (ACQ)	0 (totally controlled) to 6 (severely uncontrolled)	0.5 points
Asthma Control Test (ACT)	5 (poor control) to 25 (complete control)	3 points
Asthma Quality of Life Questionnaire (AQLQ-12)	1 (severely impaired) to 7 (not impaired at all)	0.5 points

St. George's Respiratory Questionnaire (SGRQ)	0 (no symptoms/limitations) to 100 (severe symptoms/limitations)	4 points

Chronic Obstructive Pulmonary Disease

The 2023 GOLD report updated the definition of COPD as "a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, expectoration, exacerbations) due to abnormalities of the airway (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction".[5] Chronic bronchitis and emphysema are often associated with COPD.[19] The most common cause of COPD is airway irritation, usually from cigarette smoking, although exposure to other environmental pollutants can contribute to the condition.[5] Approximately 10% of individuals aged 40 years or older have COPD, although the prevalence varies between countries and increases with age.[20] In the US, COPD is consistently ranked among the top causes of death, with mortality rates of more than 120,000 individuals each year.[21] As a result, COPD has high healthcare utilization with frequent clinician office visits, multiple hospitalizations due to acute exacerbations, and the need for chronic therapy.[22]

The diagnosis and management of COPD are based on spirometry post-bronchodilation results (i.e., FEV_1/forced vital capacity [FVC]) <0.70), symptom severity, risk of exacerbations and comorbidities.[5] In the GOLD 2023 report, COPD is classified into four stages (mild to very severe) based on spirometric measurements of FEV_1 of after bronchodilator administration for people with COPD (FEV_1/FVC <0.7) as presented in **Table 3**.[5]

Table 3. GOLD 2023 Assessment of Airflow Obstruction for Patients with COPD (FEV_1/FVC <0.7) [5]

Grade	Severity	Post-Bronchodilator FEV_1 (% predicted)
GOLD 1	Mild	≥ 80%
GOLD 2	Moderate	50 to 79
GOLD 3	Severe	30 to 49
GOLD 4	Very severe	< 30
Abbreviations: COPD = Chronic Obstructive Disease: FEV_1 = Forced Expiratory Volume in one second: FVC = Forced Vital Capacity; GOLD = Global Initiative for COPD		

Goals of therapy for COPD management are to improve symptoms, reduce frequency and severity of exacerbations, and improve exercise tolerance and daily activities.[19] Initial treatment options for patients with COPD are inhaled bronchodilators (i.e., SABAs, SAMAs, LABAs or LAMAs).[19] Use of SABAs on a regular basis is generally not recommended due to the risk of AEs.[19] For patients who require additional therapy, the combination of a LABA and LAMA is often used.[19] Triple inhaler therapy with a LABA, LAMA and ICS is recommended for those with COPD and sustained symptoms despite dual therapy.[19] Long-acting bronchodilators (LAMAs and LABAs) improve lung function, dyspnea, health status and reduce exacerbation rates.[19] Compared to ICS monotherapy, ICS-LABA combinations have been shown to improve health status, reduce exacerbations and improve lung function.[19] Conclusive evidence of benefit has not been demonstrated with ICS alone in patients with COPD.[19] No medications have shown a preventative effect in the decline of lung function in COPD.[19] Smoking cessation is the only intervention shown to reduce the rate of lung function decline.[19]

Important outcomes to access the effectiveness of COPD therapies include: lung function, quality of life (QoL), dyspnea, exacerbation rate and/or severity, and AEs. The most common surrogate outcome used in studies to determine therapy effectiveness is FEV_1.[13] The minimal clinically important difference (MCID) in FEV_1 values for COPD changes have not been clearly defined, but research in COPD patients suggest that minimally important FEV_1 changes range from 100-140

mL.[13] The St. George Respiratory Questionnaire (SGRQ) is used to determine the effects of COPD on QoL with scores ranging from 0 to 100 with higher scores indicative of more limitations.[18] In the GOLD guidelines, symptoms are assessed by the modified Medical Research Council (mMRC) dyspnea questionnaire.[5,23] The patient-reported questionnaire assesses extent of breathlessness on a scale of 0 (breathlessness only with exercise) to 4 (breathlessness when dressing).[5] The GOLD report also recommends using the COPD Assessment Test (CAT) to evaluate health status in patients with COPD.[5,24] The 8-item questionnaire ranges in score from 0 (best) to 40 (worst) points and correlates very closely with the SGRQ.[5]

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

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

New Systematic Reviews:
Drug Effectiveness Review Project: Triple Inhaler Therapies for Asthma and COPD
In December 2022, DERP published a report focused on effectiveness and safety of single-inhaler triple therapies (SITT) for management of asthma and COPD compared with monotherapy, dual therapy, or multiple-inhaler triple therapies (MITT).[1] Two of the SITT products are FDA-approved (budesonide-glycopyrrolate-formoterol [BREZTRI] and fluticasone-umeclidinium-vilanterol [TRELEGY]), while the third product (beclomethasone-glycopyrronium-formoterol [TRIMBOW]) is currently being investigated in clinical trials and is not yet FDA-approved. For the purposes of this summary, only evidence for FDA-approved products will be reviewed.

Literature for the DERP report was searched through September 2022.[1] Twelve RCTs met inclusion criteria.[1] One RCT with a moderate risk of bias compared fluticasone-umeclidinium-vilanterol with fluticasone-vilanterol in adults with asthma.[1] Eleven RCTs were identified that evaluated SITT in adults with COPD (7 RCTs with moderate risk of bias and 4 RCTs with high risk of bias).[1] Two RCTs evaluated BREZTRI, 7 evaluated TRELEGY, and 2 evaluated TRIMBOW versus single, dual or triple therapies.[1] The comparators included tiotropium monotherapy, dual therapy with fluticasone-vilanterol, glycopyrrolate-budesonide, or budesonide-formoterol or MITT with tiotropium or umeclidinium monotherapy in combination with fluticasone-vilanterol or budesonide-formoterol dual inhaler therapy.[1] Most participants in the COPD RCTs were white, male and former smokers.[1]

Asthma Findings
In the moderate-quality RCT (n=2,436) conducted in patients with inadequately controlled asthma, fluticasone-umeclidinium-vilanterol (TRELEGY) was compared with fluticasone-vilanterol (BREO) over 24 weeks.[1] The majority of participants in this RCT were white and female.[1] No significant differences were observed between triple and dual therapy in the primary outcome, annualized rate of severe asthma exacerbations.[1] Significant improvements were observed with triple therapy versus dual therapy in secondary outcomes including trough FEV_1 (62.5mcg dose: mean difference [MD] 101 ml; 95% CI 70 to 132; $p<0.001$) and QoL as

measured by the ACQ-7 score (62.5 mcg dose: MD -0.9; 95% CI -0.16 to -0.02; p=0.008).[1] The number of participants experiencing any AE, SAE, or withdrawal from the study due to an AE was similar across all treatment groups.[1]

COPD Findings

One low-quality RCT (n=8,588) evaluated budesonide-glycopyrrolate-formoterol (BREZTRI) with glycopyrrolate-formoterol (LAMA-LABA) or budesonide-formoterol (ICS-LABA) in patients with COPD over 52 weeks.[1] This study had a high attrition rate (20% in the triple therapy arm and 25% in the dual therapy arms) which contributed to the high risk of bias.[1] Another moderate-quality RCT (n=1,902) compared budesonide-glycopyrrolate-formoterol with glycopyrrolate-formoterol or budesonide-formoterol over 24 weeks.[1] Significant improvements in favor of triple therapy versus dual therapy were observed in frequency of moderate to severe COPD exacerbations (see **Table 4**).[1] Secondary outcomes were also improved with triple therapy compared to dual therapy and included: trough FEV_1 (p<0.01); frequency and volume of rescue medication use (p<0.04); and quality of life as measured by the SGRQ (p<0.03).[1] The proportion of individuals experiencing any AE or SAE was similar between treatments for both RCTs.[1] Specific RCT results, which were presented at the December 2022 P&T Committee meeting, are summarized in **Table 4.**[25]

Table 4. Description of Randomized Comparative Clinical Trials for Triple Inhaler Therapy Versus Dual Inhaler Therapy[25]

Study	Comparison	Population	Primary Outcome	Results	Interpretation
Rabe, et al[26] ETHOS 52-week, phase 3, DB, MC, PG, RCT	1) Budesonide 320 µg/ Glycopyrrolate 18 µg/ Formoterol fumarate 9.6 µg inhaled twice daily Vs. 2) Budesonide 160 µg/ Glycopyrrolate 18 µg/ Formoterol fumarate 9.6 µg inhaled twice daily Vs. 3) Glycopyrrolate 18 µg/ Formoterol fumarate 9.6 µg inhaled twice daily Vs. 4) Budesonide 320 µg/ Formoterol fumarate 9.6 µg inhaled twice daily	Patients with moderate to very severe COPD and at least one exacerbation in the last year (n=8509)	The annual rate (estimated mean number per patient per year) of moderate or severe COPD exacerbations	1) 1.08 2) 1.07 3) 1.42 4) 1.24 1 vs. 3 RR 0.76 (95% CI, 0.69 to 0.83) P<0.001 1 vs. 4 RR 0.87 (95% CI, 0.79 to 0.95); P = 0.003 2 vs. 3 RR 0.75 (95% CI, 0.69 to 0.83) P<0.001 2 vs. 4 RR 0.86 (95% CI, 0.79 to 0.95) P=0.002	*Triple therapy with budesonide/glycopyrrolate/ formoterol (low [160 µg budesonide dose] and high [320 µg budesonide dose]) was more effective than glycopyrrolate/formoterol and budesonide/formoterol for reducing the rate of COPD exacerbations. The absolute reduction in exacerbations was less than 1 exacerbation per patient per year.*
Ferguson, et al[27] KRONOS	1) Budesonide 320 µg/ Glycopyrrolate 18 µg/ Formoterol fumarate 9.6 µg inhaled twice daily Vs.	Patients with moderate to severe COPD without a requirement for a history of exacerbations	FEV_1 area under the curve from 0-4 hours (AUC_{0-4}) for	FEV_1 AUC_{0-4}mL 1) 305 mL 2) 288 mL 3) 201 mL	*There was no difference between triple therapy (budesonide/glycopyrrolate/formoterol fumarate) and glycopyrrolate/formoterol*

24-week, phase 3, DB, MC, PG, RCT	2) Glycopyrrolate 18 µg/ Formoterol fumarate 9.6 µg inhaled twice daily Vs. 3) Budesonide 320 µg/ Formoterol fumarate 9.6 µg inhaled twice daily 4) Budesonide 400 µg/ Formoterol fumarate 12 µg inhaled twice daily (open-label)	(n = 3047)	1) versus 3) and 1) versus 4) Analysis of change from baseline in morning pre-dose trough FEV_1 for 1) versus 2) and non-inferiority analysis of 3) versus 4) (non-inferiority analysis of -50 mL from lower bound of 95% CI)	4) 214 mL 1 vs. 2 LSM 16 mL (95% CI, -6 to 38) P=0.1448 1 vs. 3 LSM 104 mL (95% CI, 77 to 131) P<0.0001 1 vs. 4 91 (95% CI, 64 to 117) P<0.0001 Change from baseline in morning pre-dose trough FEV_1 1) 147 mL 2) 125 mL 3) 73 mL 4) 88 mL 1 vs. 2 22 mL (95% CI, 4 to 39) P=0.0139 1 vs. 3 (prespecified secondary endpoint) 74 mL (95% CI, 52 to 95) P<0.0001 1 vs. 4 59 mL (95% CI, 38 to 80) P<0.0001	*fumarate in changes in FEV_1 AUC_{0-4} mL. Triple therapy was more effective in increasing FEV_1 AUC_{0-4}mL compared to budesonide/formoterol fumarate.* *Increases in baseline morning pre-dose trough FEV_1 were larger for budesonide/glycopyrrolate/formoterol fumarate compared to glycopyrrolate/formoterol fumarate and budesonide/formoterol fumarate.* *Differences between groups in lung function for both groups were small and unlikely to be clinically significant.*
Abbreviations: COPD = chronic obstructive pulmonary disease; DB = double-blind; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; LABA = long-acting Beta 2 agonist; LSM = least squares mean; MCID = minimal clinically important difference; MD = mean difference; PC = placebo-controlled; PG = parallel group; RCT = randomized controlled trial; RR = rate ratio					

Seven RCTs compared fluticasone-umeclidinium-vilanterol (TRELEGY) with monotherapy (tiotropium), dual therapy of ICS-LAMA, or MITT (risk of bias was moderate for 4 RCTS and high for 3 RCTs).[1] No statistically significant difference for any outcomes of interest were observed when SITT (fluticasone-umeclidinium-vilanterol) was compared to MITT (budesonide-formoterol plus tiotropium or fluticasone-vilanterol plus umeclidinium) over 24 weeks.[1] When triple therapy was compared to dual therapy (budesonide-formoterol, fluticasone-vilanterol, or umeclidinium-vilanterol), significant improvements in favor of triple therapy were observed in the following outcomes: trough FEV_1 (p<0.001), frequency and volume of rescue medication use (p<0.02), and quality of life

($p<0.001$).[1] When triple therapy was compared with tiotropium monotherapy, trough FEV_1 was significantly improved with triple therapy.[1] The number of participants experiencing any AE, SAE, or withdrawal from the study due to an AE was similar across all treatment groups.[1]

In summary, compared with monotherapy or dual therapies, triple therapy demonstrated improvements in frequency of COPD exacerbations, lung function (trough FEV_1), symptom control, and health-related QoL.[1] Adverse events occurred in similar proportions across treatments in both asthma and COPD populations.[1] Early withdrawal from studies due to AEs were rare, as were deaths.[1]

Cochrane: Effectiveness And Tolerability Of Dual And Triple Combination Inhaler Therapies In People With Asthma

A December 2022 Cochrane review assessed the evidence for the safety and effectiveness of dual ICS-LABA and triple ICS-LABA-LAMA inhaler treatment compared with each other and with medium- to high-dose ICS monotherapy in adolescents (12 years and older) and adults with uncontrolled asthma using pair-wise meta-analysis and network meta-analysis (NMA).[2] Authors conducted a literature search through February 2022 to identify RCTs that included patients treated with combination medium- or high-dose ICS plus LABA therapy compared to triple inhaler therapy for at least 12 weeks.[2] It is not clear if high-dose ICS increases AEs compared with medium-dose ICS. Most studies comparing dual and triple combination therapies did not consider ICS doses (i.e. low- medium- and high-doses) in their combinations.[2] Therefore, this review also analyzed the impact of high-dose versus medium-dose ICS within the dual and triple combination therapies.[2]

Seventeen RCTs (n=17,161) met inclusion criteria with a median duration of 26 weeks, in people with a mean age of 49.1 years, 81% were white, and 40% were male.[2] Current smokers were excluded in all RCTs.[2] All RCTs were multi-center and industry-funded.[2] Most RCTs had a low risk of bias; some outcomes were limited by high attrition rates.[2] The 17 studies evaluated the following ICS-LABA combinations: beclomethasone-formoterol, budesonide-formoterol, ciclesonide-formoterol, fluticasone-formoterol, mometasone-formoterol, mometasone-indacaterol, fluticasone-salmeterol, and fluticasone-vilanterol.[2] Triple therapy included ICS-LABA-LAMA combination inhalers (i.e., fluticasone furoate-vilanterol-umeclidinium and mometasone-glycopyrronium-indacaterol) or an ICS-LABA fixed combination plus a LAMA as a single inhaler (i.e., aclidinium, glycopyrronium, tiotropium, and umeclidinium).[2] RCTs for triple combination therapies included only adults.[2] The primary outcome of interest was number of moderate asthma exacerbations (defined as requiring a short course of oral corticosteroids) and number of severe exacerbations (defined as resulting in hospitalization, mechanical ventilation, or death).[2] Secondary outcome measures included asthma control using the ACQ, QoL using the AQLQ, and AEs.[2]

The pairwise meta-analysis of 6 RCTs (n=5542) suggests:

- There is little or no difference in moderate to severe asthma exacerbations between high-dose ICS-LABA and medium-dose ICS-LABA inhalers over 3 to 12 months (RR 0.93, 95% CI, 0.82 to 1.05; $I^2=0$; high certainty of evidence).[2]
- Compared with dual therapy, triple therapy reduces moderate to severe exacerbations (RR 0.85; 95% CI, 0.78 to 0.92; 5 RCTs; n=8173; high-certainty evidence).[2]
- High-dose ICS triple inhaler therapy likely results in a slight reduction in moderate to severe exacerbations compared to medium-dose ICS triple therapy (RR 0.85; 95% CI 0.72 to 1.01; 3 RCTs, n=3470; $I^2 = 0\%$; moderate certainty of evidence).[2]

In the NMA, each pair of treatments was compared by estimating a hazard ratio (HR) for time-to-event outcomes (e.g., asthma exacerbations), a mean difference for continuous outcomes, and an odds ratio (OR) for dichotomous outcomes, along with their 95% credible intervals (CrIs).[2] Results from the NMA suggest:

- High-dose ICS triple therapy reduces the hazards of moderate-severe exacerbations compared to medium-dose and high-dose ICS/LABA therapy (HR 0.69; 95% CrI 0.58 to 0.82 and HR 0.93; 95% CrI 0.79 to 0.88, respectively; high-certainty evidence), but not asthma-related hospitalizations compared to medium-dose ICS-LABA therapy.[2]
- There is marginal evidence to suggest that medium-dose ICS triple inhaler therapy reduces the hazards of moderate to severe asthma exacerbations compared to medium-dose ICS-LABA therapy (HR 0.84; 95% CrI 0.71 to 0.99; moderate-certainty evidence).[2]
- High-dose ICS triple inhaler therapy reduces the hazards of moderate to severe exacerbations compared to medium-dose ICS triple inhaler therapy (HR 0.83; 95% CrI 0.69 to 0.96; moderate-certainty evidence).[2]

There is insufficient evidence to suggest that there is a clinically meaningful change in ACQ or AQLQ scores at 6 and 12 months for any of the treatment comparisons.[2] The certainty of evidence ranges from low to moderate.[2] There was no difference in the results between fixed-effect and random-effects meta-analysis models.[2] These results are qualitatively similar to those of the NMA.[2]

For all-cause AEs, 12 trials (n=12,915) comparing 4 treatment groups were included in the NMA.[2] The NMA results suggested treatment with high-dose ICS triple therapy reduces the odds of all-cause AEs compared to medium-dose ICS dual therapy and high-dose ICS dual therapy (OR 0.79; 95% CrI 0.69 to 0.90 and OR 0.79; 95% CrI 0.70 to 0.88, respectively).[2] Evidence from the pairwise analysis suggests triple therapy results in a reduction in all-cause AEs compared to dual therapy (RR 0.93; 95% CI 0.90 to 0.96; 6 RCTs; high-certainty evidence).[2] The evidence from both the pairwise meta-analysis and NMA suggests there is no or little difference in all-cause SAEs for any of the treatment comparisons (moderate- to high-certainty evidence).[2]

In summary, medium-dose and high-dose ICS triple inhaler therapies reduce asthma exacerbations, but not asthma-related hospitalizations, compared to medium-dose ICS-LABA therapy (high-certainty evidence).[2] High-dose ICS triple therapy is likely superior to medium-dose ICS triple therapy in reducing asthma exacerbations (moderate-certainty evidence).[2] High-dose ICS triple therapy, but not medium-dose ICS triple therapy, results in a reduction in all-cause AEs (high-certainty evidence) compared with ICS dual therapy.[2] Triple therapy results in little to no difference in all-cause SAEs compared to ICS-LABA therapy (high-certainty evidence).[2] The evidence that any specific formulation would be better than the others within the same group in any outcomes is uncertain due to the scarcity of data and resulting imprecision of estimates.[2]

Cochrane: Adding LABA or LAMA to ICS Therapy Versus Increasing ICS Doses For Asthma Exacerbations

A 2023 Cochrane review assessed the safety and efficacy of adding a LABA to ICS therapy or LAMA to ICS therapy, compared with increasing the ICS dose in adolescents 12 years and older and adults with asthma not well controlled on medium-dose ICS.[3] The literature search was conducted through December 2022.[3] Studies comparing 2 of the following treatments, medium- or high-dose ICS monotherapy, LABA-ICS or LAMA-ICS met inclusion criteria. Thirty-five RCTs (n=38,276) with a median duration of 24 weeks met inclusion criteria.[3] The mean age of participants was 44.1 years, 38% were white, and 69% were male.[3] A pair-wise meta-analysis and NMA were conducted to synthesize data from the 35 RCTs. All studies were industry-funded and conducted in multiple centers.[3] All except 6 studies excluded current smokers.[3] Most studies were double-blinded, reducing the risk of performance and detection bias.[3] Two open-label studies had increased risk of bias, which decreased confidence in the ACQ score outcomes.[3] Missing outcome data in several outcomes due to high or uneven attrition rates led to a high risk of bias in those RCTs.[3] There was more data identified for LABAs than for LAMAs.[3]

The primary outcome of interest was frequency of moderate to severe asthma exacerbations, using similar definitions as the previous 2022 Cochrane review.[3] For moderate to severe exacerbations, specific conclusions from the pairwise meta-analysis include:

- In the meta-analysis of 16 RCTs (n=11,141), ICS-LABA reduces moderate to severe exacerbations compared with ICS monotherapy (RR 0.69; 95% CI 0.60 to 0.79; moderate-certainty evidence).[3]
- The pairwise evidence is very uncertain for the effect of high-dose ICS monotherapy on moderate to severe exacerbations compared to medium-dose ICS monotherapy due to imprecision, a lack of robustness, and missing data.[3]

Evidence from 25 RCTs (n=25,583) which compared 6 treatment groups in the NMA regarding asthma exacerbations suggested:

- Medium-dose ICS-LAMA, medium-dose ICS-LABA, and high-dose ICS-LABA reduce moderate to severe asthma exacerbations compared to medium-dose ICS monotherapy (HR 0.56; 95% CrI 0.38 to 0.82; low-certainty evidence; HR 0.70; 95% CrI 0.59 to 0.82; moderate-certainty evidence; and HR 0.59; 95% CrI 0.46 to 0.76; moderate-certainty evidence, respectively).[3]
- High-dose ICS-LABA reduces the hazard of moderate to severe exacerbations compared to high-dose ICS monotherapy (HR 0.63, 95% CrI 0.47 to 0.84; moderate-certainty evidence). [3]
- Compared with medium-dose ICS monotherapy, high-dose ICS monotherapy does not reduce asthma exacerbations (HR 0.94; 95% CrI 0.70 to 1.24; moderate-certainty evidence).[3]

Most comparisons between the meta-analysis and NMA aligned except for the NMA evidence which suggests high-dose ICS-LABA reduces moderate to severe exacerbations compared to medium-dose ICS monotherapy (HR 0.59; 95% CrI 0.46 to 0.76; moderate-certainty).[3] The pairwise analysis suggested no difference between these 2 therapies in reducing asthma moderate to severe exacerbations (RR 0.71, 95% CI 0.33 to 1.56; 2 studies, n=1759; low-certainty evidence).[3]
A secondary outcome measure was asthma control as assessed by the change from baseline in ACQ and AQLQ scores at 6 and 12 months. Evidence from the fixed-effect meta-analysis suggests:

- Medium-dose ICS-LABA reduces the ACQ score at 12 months compared to medium-dose ICS and high-dose ICS (mean difference -0.18, 95% CrI -0.26 to -0.09; moderate-certainty evidence and mean difference -0.13, 95% CrI -0.23 to -0.03; moderate certainty, respectively).[3]
- High-dose ICS-LABA reduces the ACQ score at 12 months compared to medium-dose ICS and high-dose ICS (mean difference -0.20, 95% CrI -0.26 to -0.14; high-certainty evidence and mean difference -0.15, 95% CrI -0.24 to -0.06; high-certainty evidence, respectively).[3]
- However, these differences do not reach the MCID of 0.5 units.[3] There is insufficient evidence to suggest that there is a clinically meaningful difference in the ACQ scores at 6 or 12 months for any of the treatment comparisons based upon low- to high-certainty evidence.[3] The NMA produced similar results.[3] For AQLQ scores, both the pairwise meta-analysis and NMA failed to identify clinically important differences between groups (MCID of 0.5 units).

An ACQ responder was defined as someone who experiences a clinically meaningful improvement int their ACQ score as defined as a reduction in the ACQ score by 0.5 or more points on the 7-point ACQ scale.[3]For the outcome of ACQ responder at 6 and 12 months the pairwise meta-analysis showed:

- Medium-dose and high-dose ICS-LABA and medium-dose ICS-LAMA increase ACQ responders at 6 months compared to medium-dose ICS monotherapy (RR 1.15, 95% CI 1.07 to 1.22; 2 studies, n=1853 participants, high-certainty evidence; RR 1.14, 95% CI 1.05 to 1.23; 1 study, n=1210, high-certainty evidence and RR 1.10, 95% CI 1.03 to 1.18; 3 studies, n=2219; moderate-certainty evidence, respectively).[3]
- Little or no difference in ACQ responders at 6 and 12 months was observed in other comparisons.[3]
- High-dose ICS-LABA increases ACQ responders at 12 months compared to medium-dose ICS monotherapy (RR 1.12, 95% CI 1.04 to 1.21; 1 study, n=1167; high- certainty evidence).[3]
- Medium-dose ICS/LABA likely increases ACQ responders at 12 months compared to medium-dose and high-dose ICS monotherapy (RR 1.19, 95% CI 1.09 to 1.29; 1 study, n=774 participants and RR 1.12, 95% CI 1.03 to 1.20; 1 study, n=784 participants; moderate-certainty evidence, respectively).[3]

- The above results are in accordance with those of the NMA except for high-dose ICS-LABA versus high-dose ICS monotherapy for which the NMA evidence suggests that high-dose ICS-LABA increases the odds of ACQ responders at 12 months compared to high-dose ICS (OR 1.42, 95% CrI 1.10 to 1.84; moderate-certainty evidence), while the pairwise evidence does not (OR 1.23, 95% CI 0.93 to 1.63; 1 study, n=1177 participants; moderate-certainty).[3]

For outcomes related to AEs, the pairwise meta-analysis showed:

- Medium-dose ICS-LAMA likely reduces all-cause AEs and results in a slight reduction in treatment discontinuation due to AEs compared to medium-dose ICS monotherapy (RR 0.86; 95% CI 0.77 to 0.96; 4 RCTs, n=2,238; moderate-certainty evidence; and RR 0.51, 95% CI 0.26 to 0.99; 4 RCTs, n=2,239; moderate-certainty evidence, respectively).[3]
- ICS-LABA or ICS-LAMA does not reduce asthma-related or all-cause SAEs compared to medium-dose-ICS monotherapy (very low-to high-certainty evidence) based on data from the NMA.[3]
- High-dose ICS and medium dose ICS monotherapy likely have little or no difference for the included safety outcomes as well as high-dose ICS/LABA compared to medium-dose ICS/LABA.[3] Evidence from the NMA is in agreement with the pairwise evidence on treatment discontinuation due to AEs, but very uncertain on all-cause AEs, due to imprecision and heterogeneity.[3]

The findings from this review suggest medium- or high-dose ICS-LABA and medium-dose ICS-LAMA reduce moderate to severe asthma exacerbations and increase the odds of ACQ responders compared to medium-dose ICS whereas high-dose ICS probably does not.[3] The evidence is generally stronger for medium-dose and high-dose ICS-LABA than for medium-dose ICS-LAMA primarily due to a larger evidence base.[3] Medium-dose ICS-LAMA likely reduces all-cause AEs and results in a slight reduction in treatment discontinuation due to AEs compared to medium-dose ICS.[3]

After review, 22 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria),[28-40] wrong study design of included trials (e.g., observational),[41-47] comparator (e.g., no control or placebo-controlled),[48,49] or outcome studied (e.g., non-clinical).[50]

New Guidelines:

<u>Global Initiative for Asthma - 2023 Update</u>

The updated GINA guidance was published in July 2023.[4] Key changes in this report include: clarification of terminology for asthma medications, addition of as-needed ICS/SABA reliever therapy to GINA track 2, and additional tables describing low, medium, and high daily ICS dosing were added based on provider requests.[4]

Asthma Medication Terminology

In the past, “controller medication” was used to described ICS-containing medications prescribed for regular daily treatment.[4] This became confusing after combination ICS-LABAs were introduced as relievers for as-needed use. To avoid confusion, the term “controller medication” has been replaced with maintenance treatment or ICS-containing treatment.[4] The term ”maintenance” describes the prescribed frequency of administration, not the particular class of medication.[4] The term anti-inflammatory reliever (AIR) has been introduced and includes as-needed ICS-formoterol or ICS-SABA in steps 1 and 2 for adults and adolescents.[4] Use of as-needed ICS-formoterol is considered off-label in the US, as these products are not FDA-approved for relief of bronchospasm. Non-formoterol LABAs in combination with ICS should not be used as relievers, due to insufficient evidence for their safety and efficacy.[4] In steps 3 through 5 for

adults and adolescents, ICS-formoterol is used as maintenance and reliever therapy (MART).[4] MART is also called SMART (single-inhaler maintenance and reliever therapy). Evidence for MART therapy is only published for combination ICS-formoterol inhalers.[4]

Treatment Recommendations

Adult and adolescent treatment options are separated into 2 tracks, based on the choice of reliever inhaler (see **Table 1**). In Track 1, the preferred reliever is low-dose ICS-formoterol because it reduces the risk of severe exacerbations compared with using a SABA reliever, and because of the simplicity of the regimen.[4] In Track 2, the reliever is as-needed SABA or as-needed ICS-SABA. Track 2 is an option if Track 1 is not possible or if a patient stable, with good adherence and no exacerbations in the past year on their current therapy.[4] Starting treatment with SABA alone trains the patient to regard SABA as their primary asthma treatment.[4] Due to safety concerns, GINA does not recommend treatment of asthma in adults or adolescents with SABA alone due to the increased risk of exacerbations and asthma-related death.[4] However, as needed SABA or ICS-SABA may be an option if as needed ICS-formoterol is not available or affordable.[4] Patients should be assessed for adherence to ICS-containing therapy before starting SABA monotherapy as a part of the reliever regimen.[4]

For Step 1 therapy, the preferred maintenance treatment is low-dose ICS-formoterol taken as-needed for symptom relief.[4] This strategy is supported by evidence from 2 studies comparing as-needed low-dose budesonide-formoterol with SABA-only treatment in patients taking SABA alone, low-dose ICS, or leukotriene receptor antagonists (LTRAs).[4] Compared with as-needed SABA alone, as-needed low dose ICS-formoterol reduced severe exacerbations and ED/ hospital visits by about two-thirds.[4] Compared with daily low-dose ICS plus as-needed SABA, as-needed low-dose ICS-formoterol reduces severe exacerbations to a similar extent and reduces ED/hospital visits by approximately one-third, with a very small difference in symptom control favoring ICS-formoterol.[4]

The preferred Step 3 option is low-dose ICS-formoterol as both maintenance and reliever treatment.[4] Compared with maintenance ICS-LABA or higher dose ICS with an as-needed SABA, low-dose ICS-formoterol reduces the risk of severe asthma exacerbations with a similar level of symptom control.[4] A new step 4 option in the 2023 GINA report is higher maintenance dose ICS-LABA plus as-needed ICS-SABA in adults over 18 years of age.[4] This is based on evidence that showed use of an ICS-SABA reliever reduced severe exacerbations compared with using SABA monotherapy (albuterol) as a reliever.[4] **Table 5** provides a summary of 2023 GINA approaches for asthma treatment in adolescents and adults. For patients whose asthma is not well controlled on a particular treatment, the provider should assess adherence, inhaler technique, risk factors and comorbidities before considering a different medication in the same step or increasing the ICS dose.[4]

Table 5. GINA 2023 Recommendations for Asthma Therapy In Adolescents And Adults.[4]

GINA Step	Track 1 (Preferred) Reliever: As-needed low dose ICS-formoterol	Track 2 (Alternative) Reliever: As needed SABA or as needed ICS-SABA)
Steps 1 and 2: Symptoms less than 4-5 days/week	• Maintenance: As-needed-only low dose ICS-formoterol	• Step 1 Maintenance: Take ICS taken whenever SABA is taken • Step 2 Maintenance: Low dose ICS
Step 3: Symptoms most days, or waking with asthma once a week or more	• Maintenance: Low dose ICS-formoterol	• Maintenance: Low dose ICS-LABA

Step 4: Daily symptoms, or waking with asthma once a week or more, and low lung function	• Maintenance: Medium dose ICS-formoterol	• Maintenance: Medium/high-dose ICS-LABA
Step 5: Daily symptoms, or waking with asthma once a week or more, and low lung function	• Maintenance: ○ Add on LAMA ○ Refer for phenotypic assessment with or without biologic therapy ○ Consider high dose ICS-formoterol	• Maintenance: ○ Add-on LAMA ○ Refer for phenotypic assessment with or without biologic therapy ○ Consider high dose ICS-LABA
Abbreviations: GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; ICS-LABA = inhaled corticosteroid-long-acting beta agonist combination; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; SABA = short acting beta agonist		

Approaches for asthma treatment in children aged 6 to 11 years of age are different from adult and adolescent recommendations (see **Table 6**). There is only one recommendation for a reliever medication: as-needed SABA in Steps 1 through 4 or ICS-formoterol in Steps 3 and 4.[4] A preferred maintenance medication is suggested for each step, with other maintenance medications suggested as an alternative. For children aged 6 to 11 years with mild asthma, taking an ICS whenever SABA is taken is safer than using SABA alone and is the preferred maintenance medication.[4] The preferred Step 2 maintenance treatment in children is daily low-dose ICS.[4] There are 3 preferred maintenance options for children in Step 3: low-dose ICS-LABA, medium-dose ICS, or very dose low budesonide-formoterol inhaler as MART.[4] Very low-dose budesonide-formoterol (i.e. 100/6 mcg once daily) showed a large reduction in severe asthma exacerbations for children, compared with the same dose of an ICS-formoterol or higher dose of ICS.[4] For step 4, the preferred maintenance medications are medium-dose ICS/LABA or low-dose ICS-formoterol MART.

Table 6. GINA 2023 Approaches To Initial Asthma Therapy In Children Aged 6 to 11 years.[4]

GINA Step	Preferred Maintenance Medication	Other Maintenance Medication Options
Step 1	• Reliever: As needed SABA • Maintenance: Low-dose ICS taken whenever SABA taken	• Reliever: As needed SABA • Maintenance: Consider daily low dose ICS
Step 2	• Reliever: As needed SABA • Maintenance: Low-dose daily ICS	• Reliever: As needed SABA • Maintenance: Daily LTRA or low dose ICS taken whenever SABA taken
Step 3	• Reliever: As needed SABA or ICS-formoterol • Maintenance: Low dose ICS/LABA or medium dose ICS or very low dose ICS-formoterol MART	• Reliever: As needed SABA or ICS-formoterol • Maintenance: Low dose ICS plus LTRA
Step 4	• Reliever: As needed SABA or ICS-formoterol • Maintenance: Medium dose ICS/LABA, or low dose ICS-formoterol MART	• Reliever: As needed SABA or ICS-formoterol • Maintenance: Add tiotropium or add LTRA
Step 5	• Reliever: As needed SABA or ICS-formoterol • Maintenance: Refer for phenotypic assessment with or without higher dose ICS/LABA or add-on therapy (e.g., anti-IgE, anti-IL4, or anti-IL5)	• Reliever: As needed SABA or ICS-formoterol • Maintenance: As last resort, consider add-on low dose OCS, but consider side effects

Abbreviations: ICS = inhaled corticosteroid; ICS-LABA = inhaled corticosteroid-long-acting beta-agonist combination; IgE = immunoglobulin E; IL = interleukin; LABA = long-acting beta agonist; LTRA = leukotriene receptor antagonist; MART = maintenance and reliever therapy; OCS = oral corticosteroids; SABA = short acting beta-2 agonist

Summary of GINA 2023 Medication Recommendations and Strength of Evidence

- SABAs are highly effective for quick relief of asthma symptoms, but patients treated with SABAs alone are at risk of asthma-related death and urgent asthma-related health care use, even if good symptom control (high-quality evidence).[4]
- Regular or frequent LABA use alone is not recommended without ICS due to risk of asthma exacerbations (high-quality evidence).[4]
- Combination low-dose ICS-formoterol as both reliever and maintenance therapy is effective in improving asthma symptom control, and reduces exacerbations requiring oral corticosteroids and hospitalizations compared to same or higher dose of controller with as-needed SABA reliever (high-quality evidence).[4]
- In step 4, in patients with persistently uncontrolled asthma despite medium- or high-dose ICS-LABA, consider adding on a LAMA as a separate inhaler (age ≥ 6 years) or combination triple therapy inhaler (age ≥ 18 years).[4] Evidence shows this strategy may modestly improve lung function but not symptoms (high-quality evidence).[4]
- In patients having exacerbations with low-dose ICS-LABA, ICS dose should be increased to medium or higher, or treatment switched to maintenance and reliever therapy with ICS-formoterol before adding LAMA (high-quality evidence).[4]

Global Initiative for Chronic Obstructive Lung Disease – 2023 Update

The 2023 GOLD report contains several important revisions and updates including: a new definition of COPD; a revision of the patient classification system; a new definition of COPD exacerbation; and updated evidence on therapeutic interventions to reduce COPD mortality.[5] Based on the different causes that can contribute to COPD, the GOLD 2023 report outlines an updated taxonomic classification of COPD using etiotypes to reflect recent evidence supporting an updated definition of COPD (see **Table 7**).[5,51] The goal is to raise awareness about non–smoking-related COPD and to stimulate research on the mechanisms and corresponding diagnostic, preventive, or therapeutic approaches for other types of COPD which are highly prevalent around the globe.[5]

Table 7. GOLD 2023 COPD Etiotypes[5,51]

Classification	Description
COPD-G: Genetically determined COPD	• Alpha-1 antitrypsin deficiency (AATD) • Other genetic variants with smaller effects acting in combination
COPD-D: COPD due to abnormal lung development	• Early life events, including premature birth and low birthweight, among others
COPD-C: Cigarette smoking	• Exposure tobacco smoke, including *in utero* or via passive smoking • Vaping or e-cigarette use • Cannabis
COPD-P: Pollution exposure	• Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD-I: COPD due to infections	• Childhood infections, tuberculosis-associated COPD, HIV-associated COPD
COPD-A: COPD and Asthma	• Particularly childhood asthma
COPD-U: COPD of unknown cause	• Unknown causes

The GOLD 2023 report includes a modification of the ABCD assessment tool used in previous reports to recognize the clinical impact of exacerbations independently of the level of symptoms of the patient.[5] Exacerbations of COPD (ECOPD) negatively affect health status, disease progression, and prognosis.[52] The previous GOLD definition of ECOPD was highly non-specific and defined exacerbations as "acute worsening of respiratory symptoms that results in additional therapy".[19] To address these limitations, the GOLD 2023 guidance now defines ECOPD as: "an event characterized by dyspnea and/or cough and sputum that worsen over ≤14 days, which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insult to the airways."[5] The thresholds proposed for symptoms and history of exacerbations in the previous year are unchanged from previous GOLD documents, so the A and B groups remain unchanged, while the former C and D groups are now merged into a single group termed "E" (for "Exacerbations").[5] **Table 8** provides details of the new ABE assessment tool.

Table 8. 2023 GOLD Symptom Assessment/Exacerbation Risk for Patients with COPD[5]

Classification	Assessment Test	Exacerbations
GOLD Category A	mMRC 0-1 or CAT <10	History of 0-1 moderate to severe exacerbations (not leading to hospitalization) per year
GOLD Category B	mMRC ≥2 or CAT ≥10	History of 0-1 moderate to severe exacerbations (not leading to hospitalization) per year
GOLD Category E	mMRC ≥2 or CAT ≥10	History of ≥2 moderate/severe exacerbations or ≥1 exacerbation (leading to hospitalization) per year
Abbreviations: CAT = COPD Assessment Test; COPD = Chronic Obstructive Lung Disease; GOLD = Global Initiative for COPD; mMRC = modified Medical Research Council questionnaire		

The ABE assessment tool is the foundation for initiation of COPD inhaler treatment.[5] The treatment of patients in Group A remains the same as previous reports: a bronchodilator (i.e., SABA, SAMA, LABA, or LAMA) with a long-acting bronchodilator preferred unless very occasional dyspnea is present (strong recommendation).[5] For patients in Group B, a LAMA-LABA inhaler is now recommended for initial treatment since dual therapy is more effective than monotherapy, with similar side effects (strong recommendation).[5] For patients in Group E, LAMA-LABA is the recommended initial therapy (strong recommendation).[5] In patients with blood eosinophils ≥300 cells/µL, triple inhaler therapy (LABA/LAMA/ICS) can be considered.[5] This is recommendation is based upon expert opinion as direct evidence is not available to guide therapy in naïve individuals.[52] **Table 9** summarizes the pharmacotherapy guidance for initial treatment of COPD which is simplified from the 2022 guidance.

Table 9. GOLD 2023 Initial Pharmacologic Treatment Recommendations[5]

≥ 2 moderate exacerbations or ≥ 1 leading to a hospitalization per year	**Group E** **LABA + LAMA*** *Consider LABA + LAMA + ICS if blood eosinophils ≥ 300*	
0 or 1 moderate exacerbations per year (not leading to hospital admission)	**Group A** **A bronchodilator**	**Group B** **LABA + LAMA***
	mMRC 0-1; CAT <10	mMRC ≥ 2; CAT ≥ 10
****Single inhaler therapy may be more convenient and effective than multiple inhalers*** Abbreviations: CAT = COPD Assessment Tool; eos = eosinophils; ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; LAMA = long-acting muscarinic antagonist; mMRC = modified Medical Research Council Dyspnea Questionnaire		

Previous studies such as the TORCH clinical trial[53] and the SUMMIT trial[54] failed to show efficacy of a LABA-ICS combination in reducing the mortality of COPD patients compared to placebo.[5] These trials had no requirement for a history of previous exacerbations. The largest LAMA treatment trial, UPLIFT, didn't demonstrate a reduction in mortality compared to placebo.[5] The majority of patients included in this study utilized an ICS.[5] Recently, evidence has emerged from two large randomized clinical trials, IMPACT[55] and ETHOS[27] which show that LABA-LAMA-ICS combinations reduce all-cause mortality compared to ICS-LABA therapy (IMPACT: HR 0.72; 95% CI, 0.53 to 0.99 and ETHOS: HR 0.51; 95% CI, 0.33 to 0.80).[5] These trials were enriched for symptomatic patients (CAT ≥ 10) with a history of frequent (≥ 2 moderate exacerbations) and/or severe exacerbations (≥ 1 exacerbation requiring a hospital admission).[5]

Summary of GOLD 2023 Recommendations:
Bronchodilators in COPD

- Inhaled bronchodilators (i.e., SABA, SAMA, LABA, or LAMA) in COPD are central to symptom management and commonly given on a regular basis to prevent or reduce symptoms (High-Quality Evidence).[5]
- Regular and as-needed use of SABA or SAMA improves FEV_1 and symptoms (High-Quality Evidence).[5]
- Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV_1 and symptoms (High-Quality Evidence).[5]
- LABAs and LAMAs significantly improve lung function, dyspnea, health status, and reduce exacerbation rates (High-Quality Evidence).[5]
- LAMAs have a greater effect on exacerbation reduction compared with LABAs (High-Quality Evidence) and decrease hospitalizations (Moderate-Quality Evidence).[5]
- Combination treatment with a LABA-LAMA increases FEV_1 and reduces symptoms compared to monotherapy (High-Quality Evidence).[5]
- Combination treatment with a LABA-LAMA reduces exacerbations compared to monotherapy (Moderate-Quality Evidence).[5]
- Tiotropium improves the effectiveness of pulmonary rehabilitation in increasing exercise performance (Moderate-Quality Evidence).[5]

Anti-inflammatory Therapy in Stable COPD

- An ICS combined with a LABA is more effective than individual components administered as monotherapy in improving lung function and health status and reducing exacerbations in patients with exacerbations and modest to very severe COPD (High-Quality Evidence).[5]
- Regular treatment with ICS increased the risk of pneumonia especially in those with severe disease (High-Quality Evidence).[5]
- Triple inhaled therapy of LABA-LAMA-ICS improves lung function, symptoms and health status and reduces exacerbations compared to LABA-ICS, LABA-LAMA or LAMA monotherapy (High-Quality Evidence).[5]

After review, one guideline was excluded due to poor quality (extensive conflict of interest).[56]

New Formulations or Indications:

- A new ICS-SABA product, albuterol 90 mcg and budesonide 80 mcg (AIRSUPRA) received FDA approval in January 2023. This is the first ICS-SABA combination inhaler approved in the U.S. The albuterol-budesonide inhaler is indicated for the as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma 18 years of age and older.[7] In the MANDALA trial, albuterol-budesonide showed a statistically significant reduction in time to first severe asthma exacerbation compared with albuterol monotherapy.[6] The recommended dose is 2 puffs as needed for asthma symptoms; not to exceed more than 6 doses in a 24-hour period.[7] The most common adverse effects observed in clinical trials included headache, oral candidiasis, cough, and dysphonia.[7] An insufficient number of pediatric patients (aged 4 to 17 years)

were enrolled in the Phase 3 RCTs (MANDALA and DENALI), so safety and efficacy in children and adolescents has not been established.[7] A summary of the phase 3 trials which led to FDA-approval is provided in **Table 10** below.

- In April 2023, a new formulation of budesonide 160 mcg and formoterol 4.8 mcg (SYMBICORT AEROSPHERE) received FDA approval as maintenance treatment of patients with COPD.[8] The original budesonide-formoterol (SYMBICORT) products contain formoterol 4.5 mcg and 80 to 160 mcg of budesonide. The recommended dose of SYMBICORT AEROSPHERE is 2 puffs twice daily.[8] It is not indicated for relief of acute bronchospasm or for treatment of asthma.[8] The efficacy of SYMBICORT AEROSPHERE was evaluated in two randomized, double-blind, multicenter, parallel group trials (TELOS and SOPHOS) in patients with COPD who remained symptomatic despite maintenance treatment for COPD.[8] Compared with formoterol monotherapy, combination budesonide-formoterol improved time to first and rate of moderate- to severe-COPD exacerbations. A summary of the phase 3 trials is provided in **Table 10** below.

Randomized Controlled Trials:
A total of 370 citations were manually reviewed from the initial literature search. After further review, 366 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trials are summarized in the table below. The full abstracts are included in **Appendix 2**.

Table 10. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary and Secondary Outcome	Results	Notes/Limitations
Papi A, et al.[6] MANDALA DB, PG. MC, Phase 3 RCT N=3132 Duration: 24 weeks 296 Centers in 11 countries	1. High dose albuterol 90 mcg and budesonide 80 mcg, 2 puffs as needed, maximum 6 doses per day (n=1016) vs 2. Low dose albuterol 90 mcg and budesonide 40 mcg, 2 puffs as needed, maximum 6 doses per day (n=1057) vs 3.Albuterol 90 mcg, 2 puffs as needed,	Adults and children aged 4 years and older with uncontrolled (i.e., 1 exacerbation within previous 12 months) moderate-to-severe asthma receiving medium to high dose ICS or low to high dose ICS/LABA maintenance therapy. Children less than 12 years of age were not randomized to high-dose albuterol/budesonide treatment arm. 97% of participants were 12 years of age and older.	Primary: Time to first severe asthma exacerbation. Severe exacerbation defined as: -Use of systemic corticosteroids for at least 3 consecutive days -An emergency department or urgent care visit for asthma requiring corticosteroids -An inpatient hospitalization for asthma Secondary: Annualized rate of severe asthma exacerbation	A. <u>Time to first asthma exacerbation (ITT analysis)</u> 1 vs 3 HR 0.74 95% CI 0.62 to 0.89 P=0.001 2 vs 3 HR 0.84 95% CI 0.71 to 1.00 P=0.052 B. <u>Annualized rate of severe asthma exacerbation (ITT analysis)</u> 1. 0.43 2. 0.48 3. 0.58 1 vs 3	• Most patients were white (90%) and female (64%) with a mean age of 50 years old. • Small proportion of children were enrolled (3%) and they did not receive the high-dose combination product due to risk of adverse effects. • Moderate exacerbations were not assessed. Only severe exacerbations were included as an outcome. • Trial was funded by the manufacturer.

	maximum 6 doses per day (n=1059)			RR 0.75 95% CI 0.61 to 0.91 2 vs 3 RR 0.81 95% CI 0.66 to 0.98	• Only the high dose albuterol-budesonide showed a statistically significant reduction in time to first severe asthma exacerbation in the ITT analysis. ITT results with low-dose formulation were not statistically significant.
Chipps B, et al.[57] DENALI DB, PG, MC Phase 3 RCT N=1,001 126 sites across 3 continents (North America, Europe, and South America) 12 weeks	1. High dose albuterol 90 mcg and budesonide 80 mcg, 2 puffs 4 times a day (n=197) vs 2. Low dose albuterol 90 mcg and budesonide 40 mcg, 2 puffs 4 times a day (n=204) vs 3.Albuterol 90 mcg, 2 puffs 4 times a day (n=201) vs. 4. Budesonide 80 mcg, 2 puffs 4 times a day (n=200) vs 5. Placebo, 2 puffs 4 times a day (n=199)	Patients aged ≥ 12 years with mild-to-moderate asthma receiving as-needed SABA or low-dose maintenance ICS plus as-needed SABA therapy at a stable dose for ≥ 30 days prior to enrollment. 10 children aged 4 to 11 years were enrolled, but not assigned to high-dose albuterol-budesonide treatment arm.	Co-primary endpoints: A. Change from baseline in FEV_1 AUC from 0 to 6 hours over 12 weeks B. Change from baseline in trough FEV_1 at week 12	A. <u>LSM change from baseline in FEV_1 AUC from 0 to 6 hours over 12 weeks (mLs)</u> 1. 258.6 2. 242.2 3. 157.2 4. 178 5. 96.7 High dose combo vs. PBO Difference: 161.9 95% CI 109.4 to 214.5 P<0.001 Low dose combo vs. PBO Difference: 145.5 95% CI 93 to 197.9 P<0.001 High dose combo vs. albuterol Difference: 101.4 95% CI 48.8 to 154.1 P<0.001 Low dose combo vs. albuterol Difference: 84.9 95% CI 32.3 to 137.5 P=0.002 High dose combo vs. ICS	• Most patients were white (90%) and female (61%) with a mean age of 50 years old. • Small proportion of children were enrolled and they did not receive the high-dose combination product due to risk of adverse effects. • Short term study (12 weeks). • Four times a day dosing used in this study exceeds recommended budesonide dosing recommendations. • Manufacturer contributed to trial funding, trial design, data collection, data analysis, data interpretations, and writing of the report. • Investigators reported several conflicts of interest. • Time to onset and duration of bronchodilation with albuterol-budesonide were

				Difference: 80.7 95% CI 28.4 to 132.9 P=0.003 Low dose combo vs. ICS Difference: 64.2 95% CI 12.1 to 116.4 P=0.016 <u>B. LSM change in trough FEV_1 at week 12 (mLs)</u> 1. 135.5 2. 123.5 3. 2.7 4. 73.3 5. 35.6 High dose combo vs. PBO Difference: 99.9 95% CI 30.9 to 168.8 P=0.005 Low dose combo vs. PBO Difference: 87.9 95% CI 18.8 to 156.9 P=0.013 High dose combo vs. albuterol Difference: 99.9 95% CI 30.9 to 168.8 P=0.005 Low dose combo vs. albuterol Difference: 120.8 95% CI 51.5 to 190.1 P<0.001 High dose combo vs. ICS Difference: 26.6 95% CI -41. 6 to 94.7 P=0.444	similar to those with albuterol.

				Low dose combo vs. ICS Difference: 14.6 95% CI -53.6 to 82.8 P=0.675	
Ferguson GT, et al.[58] TELOS DB, PG, MC, Phase 3 RCT Duration: 24 weeks N=2389 Conducted at 253 sites across 7 countries	1. High dose budesonide 320 mcg/formoterol fumarate dihydrate 10 mcg, 2 puffs twice daily (n=664) vs 2. Low dose budesonide 160 mcg/formoterol fumarate dihydrate 10 mcg, 2 puffs twice daily (n=649) vs 3 .Formoterol fumarate dihydrate 10 mcg, 2 puffs twice daily (n=648) vs 4. Budesonide 320 mcg, 2 puffs twice daily (n=209) vs 5. Budesonide 400 mcg/formoterol 12 mcg 2 puffs twice daily (n=219): open-label arm, NI assessment *Formoterol fumarate dihydrate 10 mcg =	Adults 40 to 80 years of age with symptomatic COPD despite treatment with 1 or more bronchodilators (CAT score ≥ 10). Patients did not have to have a history of COPD exacerbation.	Co-primary endpoints: A.Change from baseline in pre-dose trough FEV_1 and B. Change from baseline in pre-dose FEV_1 AUC from 0 to 4 hours at 24 weeks	<u>A.LSM change from baseline in pre-dose trough FEV_1 (mLs) at 24 weeks</u> High dose combo vs. formoterol Difference 39 95% CI 8 to 59 P=0.0018 High dose combo vs. ICS Difference 65 95% CI 29 to 101 P=0.0004 Low dose combo vs. formoterol Difference 20 95% CI -13 to 44 P=0.1132 Low dose combo vs. ICS Difference 45 95% CI 10 to 81 P<0.0131 <u>B. Change from baseline in pre-dose FEV_1 AUC from 0 to 4 hours (mLs) at 24 weeks)</u> High dose combo vs. formoterol Difference 34 95% CI 8 to 59 P=0.0092 High dose combo vs. ICS Difference 173	• Most patients were white (97%) and male (61%) with a mean age of 64 years old with a smoking history of 44 pack-years. • 70% of enrolled subjects did not have a COPD exacerbation in the previous 12 months prior to enrollment. • 2 efficacy and statistical analysis approaches, US and EU, were used in the study based on regional regulatory requirements. • Short term study (24 weeks), was not long enough to investigate exacerbation rates. • Study was funded by manufacturer. Several investigators reported conflict of interest due to grant support from the manufacturer or employment by the manufacturer. • Budesonide/formoterol 320/10 mcg and 160/10 mcg effectively improved lung function relative to budesonide monotherapy

	formoterol fumarate 9.6 mcg			95% CI 136 to 210 Low dose combo vs. formoterol Difference 18 95% CI -7 to 44 P=0.1621 Low dose combo vs. ICS Difference 157 95% CI 120 to 194 P<0.0001	(which is not a recommended COPD therapy).
Hanania NA, et al.[59] SOPHOS DB, PG, MC, Phase 3 RCT Duration: 12 to 52 weeks N=1,843 292 centers in 18 countries	1. High dose budesonide 320 mcg/formoterol fumarate dihydrate 10 mcg, 2 puffs twice daily (n=624) vs 2. Low dose budesonide 160 mcg/formoterol fumarate dihydrate 10 mcg, 2 puffs twice daily (n=627) vs 3. Formoterol fumarate dihydrate 10 mcg, 2 puffs twice daily (n=613)	Adults 40 to 80 years of age with symptomatic COPD despite treatment with 1 or more bronchodilators (CAT score ≥ 10). Documented history of at least 1 moderate-to-severe COPD exacerbation in the previous 12 months.	Primary Outcome: Change from baseline in pre-dose trough FEV_1 at 12 weeks Secondary Outcome: Rate of moderate/severe COPD exacerbation	<u>A.Change from baseline in pre-dose trough FEV_1 at 12 weeks (mLs) – US approach</u> 1. 72 2. 69 3. 37 1 vs 3 Difference 34 95% CI 9 to 60 P=0.0081 2 vs 3 Difference 32 95% CI 7 to 57 P=0.0134 <u>B. Rate of moderate/severe COPD exacerbations over 52 weeks</u> 1.0.93 2.0.98 3.1.39 1 vs 3 RR 0.67 95% CI 0.54 to 0.82 P=0.0001 2 vs 3 RR 0.71	• Most patients were white (83%) and male (57%) with a mean age of 65 years old with a smoking history of 45 pack-years • 2 efficacy and statistical analysis approaches, US and EU, were used in the study based on regional regulatory requirements. • Only 10% of participants completed treatment at 52 weeks. • Study was funded by manufacturer. Several investigators reported conflict of interest due to grant support from the manufacturer or employment by the manufacturer. • Both doses of budesonide/formoterol resulted in statistically significant improvements in lung function compared with formoterol MDI.

				95% CI 0.58 to 0.87 P=0.001	

Abbreviations: AUC = area under the curve; CAT = COPD assessment tool; CI = confidence interval; DB = double-blind; COPD = Chronic Pulmonary Obstructive Disease; EU = European Union; FEV_1 = forced expiratory volume in 1 second; HR = hazard ratio; ICS = inhaled corticosteroid; ITT = intention-to- treat; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; LSM =least squares mean; MC= multi-center; mcg = micrograms; MDI = multi-dose inhaler; mLs = milliliters; NI = noninferiority; PG = parallel group; RCT = randomized clinical trial; RR = rate ratio; US = United States

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Appendix 1: Current Preferred Drug List

Long-Acting Muscarinic Antagonists (LAMA)

Generic	Brand	Route	Form	PDL
umeclidinium bromide	INCRUSE ELLIPTA	INHALATION	BLST W/DEV	Y
tiotropium bromide	SPIRIVA HANDIHALER	INHALATION	CAP W/DEV	Y
tiotropium bromide	TIOTROPIUM BROMIDE	INHALATION	CAP W/DEV	Y
ipratropium bromide	ATROVENT HFA	INHALATION	HFA AER AD	Y
tiotropium bromide	SPIRIVA RESPIMAT	INHALATION	MIST INHAL	Y
ipratropium bromide	IPRATROPIUM BROMIDE	INHALATION	SOLUTION	Y
ipratropium/albuterol sulfate	IPRATROPIUM-ALBUTEROL	INHALATION	AMPUL-NEB	Y
ipratropium/albuterol sulfate	COMBIVENT RESPIMAT	INHALATION	MIST INHAL	Y
aclidinium bromide	TUDORZA PRESSAIR	INHALATION	AER POW BA	N
revefenacin	YUPELRI	INHALATION	VIAL-NEB	N

Beta-Agonists, Inhaled Long Acting (LABA)

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

Beta-Agonists, Inhaled Short-Acting (SABA)

Generic	Brand	Route	Form	PDL
albuterol sulfate	ALBUTEROL SULFATE HFA	INHALATION	HFA AER AD	Y
albuterol sulfate	PROAIR HFA	INHALATION	HFA AER AD	Y
albuterol sulfate	PROVENTIL HFA	INHALATION	HFA AER AD	Y
albuterol sulfate	VENTOLIN HFA	INHALATION	HFA AER AD	Y
albuterol sulfate	ALBUTEROL SULFATE	INHALATION	VIAL-NEB	Y
albuterol sulfate	PROAIR RESPICLICK	INHALATION	AER POW BA	N
albuterol sulfate	PROAIR DIGIHALER	INHALATION	AER PW BAS	N
albuterol	ALBUTEROL	INHALATION	AER REFILL	N
levalbuterol tartrate	LEVALBUTEROL TARTRATE HFA	INHALATION	HFA AER AD	N
levalbuterol tartrate	XOPENEX HFA	INHALATION	HFA AER AD	N
levalbuterol HCl	LEVALBUTEROL CONCENTRATE	INHALATION	VIAL-NEB	N
levalbuterol HCl	LEVALBUTEROL HCL	INHALATION	VIAL-NEB	N

Corticosteroids, Inhaled (ICS)

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

*Anticipate discontinuation of branded product in January 2024 as generic product will be manufactured by Glaxo

Corticosteroids/SABA & LABA Combinations, Inhaled

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

LAMA/LABA Combination, Inhalers

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

Appendix 2: Abstracts of Comparative Clinical Trials

Albuterol-Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma[6]

BACKGROUND: As asthma symptoms worsen, patients typically rely on short-acting beta-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 mug of albuterol and 160 mug of budesonide (with each dose consisting of two actuations of 90 mug and 80 mug, respectively [the higher-dose combination group]), a fixed-dose combination of 180 mug of albuterol and 80 mug of budesonide (with each dose consisting of two actuations of 90 mug and 40 mug, respectively [the lower-dose combination group]), or 180 mug of albuterol (with each dose consisting of two actuations of 90 mug [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 mug of albuterol and 160 mug 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.).

Albuterol-Budesonide Pressurized Metered Dose Inhaler in Patients With Mild-to-Moderate Asthma: Results of the DENALI Double-Blind Randomized Controlled Trial[57]

Background: In the phase 3 MANDALA trial, as-needed albuterol-budesonide pressurized metered-dose inhaler significantly reduced severe exacerbation risk vs as-needed albuterol in patients with moderate-to-severe asthma receiving inhaled corticosteroid-containing maintenance therapy. This study (DENALI) was conducted to address the US Food and Drug Administration combination rule, which requires a combination product to demonstrate that each component contributes to its efficacy.

Research question: Do both albuterol and budesonide contribute to the efficacy of the albuterol-budesonide combination pressurized metered-dose inhaler in patients with asthma?

Study design and methods: This phase 3 double-blind trial randomized patients aged ≥ 12 years with mild-to-moderate asthma 1:1:1:1:1 to four-times-daily albuterol-budesonide 180/160 µg or 180/80 µg, albuterol 180 µg, budesonide 160 µg, or placebo for 12 weeks. Dual-primary efficacy end points included change from baseline in FEV1 area under the curve from 0 to 6 h (FEV1 AUC0-6h) over 12 weeks (assessing albuterol effect) and trough FEV1 at week 12 (assessing budesonide effect).

Results: Of 1,001 patients randomized, 989 were ≥ 12 years old and evaluable for efficacy. Change from baseline in FEV1 AUC0-6h over 12 weeks was greater with albuterol-budesonide 180/160 µg vs budesonide 160 µg (least-squares mean [LSM] difference, 80.7 [95% CI, 28.4-132.9] mL; P = .003). Change in trough FEV1 at week 12 was greater with albuterol-budesonide 180/160 and 180/80 µg vs albuterol 180 µg (LSM difference, 132.8 [95% CI, 63.6-201.9] mL and 120.8

[95% CI, 51.5-190.1] mL, respectively; both P < .001). Day 1 time to onset and duration of bronchodilation with albuterol-budesonide were similar to those with albuterol. The albuterol-budesonide adverse event profile was similar to that of the monocomponents.
Interpretation: Both monocomponents contributed to albuterol-budesonide lung function efficacy. Albuterol-budesonide was well tolerated, even at regular, relatively high daily doses for 12 weeks, with no new safety findings, supporting its use as a novel rescue therapy.
Clinical trial registration: ClinicalTrials.gov; No.: NCT03847896

Budesonide/Formoterol MDI With Co-Suspension Delivery Technology In COPD: The TELOS Study[58]
Background: TELOS compared budesonide (BD)/formoterol fumarate dihydrate (FF) metered dose inhaler (BFF MDI), formulated using innovative co-suspension delivery technology that enables consistent aerosol performance, with its monocomponents and budesonide/formoterol fumarate dihydrate dry powder inhaler (DPI) in patients with moderate to very severe chronic obstructive pulmonary disease (COPD), without a requirement for an exacerbation history.
Study Methods: In this phase III, double-blind, parallel-group, 24-week study (NCT02766608), patients were randomised to BFF MDI 320/10 µg (n=664), BFF MDI 160/10 µg (n=649), FF MDI 10 µg (n=648), BD MDI 320 µg (n=209) or open-label budesonide/formoterol DPI 400/12 µg (n=219). Primary end-points were change from baseline in morning pre-dose trough forced expiratory volume in 1 s (FEV_1) and FEV_1 area under the curve from 0-4 h (AUC_{0-4}). Time to first and rate of moderate/severe exacerbations were assessed.
Results: BFF MDI 320/10 µg improved pre-dose trough FEV_1 *versus* FF MDI (least squares mean (LSM) 39 mL; p=0.0018), and BFF MDI 320/10 µg and 160/10 µg improved FEV_1 AUC_{0-4} *versus* BD MDI (LSM 173 mL and 157 mL, respectively; both p<0.0001) at week 24. BFF MDI 320/10 µg and 160/10 µg improved time to first and rate of moderate/severe exacerbations *versus* FF MDI. Treatments were well tolerated, with pneumonia incidence ranging from 0.5-1.4%.BFF MDI improved lung function *versus* monocomponents and exacerbations *versus* FF MDI in patients with moderate to very severe COPD.

Efficacy And Safety Of Two Doses Of Budesonide/Formoterol Fumarate Metered Dose Inhaler In COPD[59]
Background: Inhaled corticosteroid/long-acting β_2-agonist combination therapy is a recommended treatment option for patients with chronic obstructive pulmonary disease (COPD) and increased exacerbation risk, particularly those with elevated blood eosinophil levels. SOPHOS (NCT02727660) evaluated the efficacy and safety of two doses of budesonide/formoterol fumarate dihydrate metered dose inhaler (BFF MDI) *versus* formoterol fumarate dihydrate (FF) MDI, each delivered using co-suspension delivery technology, in patients with moderate-to-very severe COPD and a history of exacerbations.
Study Methods: In this phase 3, randomised, double-blind, parallel-group, 12–52-week, variable length study, patients received twice-daily BFF MDI 320/10 µg or 160/10 µg, or FF MDI 10 µg. The primary endpoint was change from baseline in morning pre-dose trough forced expiratory volume in 1 s (FEV_1) at week 12. Secondary and other endpoints included assessments of moderate/severe COPD exacerbations and safety.
Results: The primary analysis (modified intent-to-treat) population included 1843 patients (BFF MDI 320/10 µg, n=619; BFF MDI 160/10 µg, n=617; and FF MDI, n=607). BFF MDI 320/10 µg and 160/10 µg improved morning pre-dose trough FEV_1 at week 12 *versus* FF MDI (least squares mean differences 34 mL [p=0.0081] and 32 mL [p=0.0134], respectively), increased time to first exacerbation (hazard ratios 0.827 [p=0.0441] and 0.803 [p=0.0198], respectively) and reduced exacerbation rate (rate ratios 0.67 [p=0.0001] and 0.71 [p=0.0010], respectively). Lung function and exacerbation benefits were driven by patients with blood eosinophil counts ≥150 cells·mm^{-3}. The incidence of adverse events was similar, and pneumonia rates were low (≤2.4%) across treatments.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) 1996 to October Week 3 2023; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to October 25, 2023

1	Cholinergic Antagonists/ or Anti-Asthmatic Agents/ or Bronchodilator Agents/	31447
2	Ipratropium/ or Albuterol, Ipratropium Drug Combination/	912
3	Tiotropium Bromide/	1291
4	Muscarinic Antagonists/ or aclidinium.mp.	8748
5	umeclidinium.mp.	290
6	Glycopyrrolate/	844
7	Salmeterol/	1633
8	formeterol.mp.	6
9	indacterol.mp.	2
10	olodaterol.mp.	228
11	arformoterol.mp.	46
12	Budesonide, Formoterol Fumarate Drug Combination/ or Budesonide/	4464
13	Fluticasone-Salmeterol Drug Combination/ or Fluticasone/	3332
14	Beclomethasone/	1726
15	Mometasone Furoate/	878
16	flunisolide.mp. or Anti-Asthmatic Agents/	13131
17	ciclesonide.mp.	408
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	45667
19	limit 18 to (english language and humans)	33938
20	limit 19 to yr="2022 -Current"	1833
21	limit 20 to (clinical trial, all or controlled clinical trial or guideline or meta-analysis or "systematic review")	370

Appendix 4: Key Inclusion Criteria

Population	Children and Adults with Asthma; Adults with Chronic Obstructive Pulmonary Disease
Intervention	SABA, LABA, SAMA, LAMA, and ICS monotherapy or in combination
Comparator	SABA, LABA, SAMA, LAMA, and ICS monotherapy or in combination
Outcomes	Asthma and COPD exacerbations, Quality of Life, Adverse Effects
Setting	Outpatient

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	
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

Approval Criteria		
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: *2/24 (DM); 10/23 (SF); 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*

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	
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

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 non-preferred 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: *2/24 (DM); 10/23 (SF); 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: *4/1/24; 1/1/21; 3/1/18; 10/13/16; 1/1/16; 1/15; 1/14; 9/12; 1/10*