Therapeutic Class Overview
Beta Agonist and Anticholinergic Combinations

INTRODUCTION

- Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities. The abnormalities are usually caused by exposure to noxious particles or gases. Airflow limitation is caused by a combination of small airway disease (eg, obstructive bronchiolitis) and parenchymal destruction (emphysema); the relative contributions of each component vary between patients. The most common symptoms of COPD include dyspnea, cough, and sputum production (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2017).
- COPD affects more than 5% of the adult population and is the major contributor to mortality from chronic lower respiratory diseases, the third leading cause of death in the United States (Centers for Disease Control and Prevention, 2012). Globally, COPD is the fourth leading cause of death and is expected to be the third leading cause of death by 2020; the burden of COPD continues to increase due to continued exposure to risk factors and aging of the population (GOLD, 2017).
- Cigarette smoking is the main risk factor for COPD; other risk factors include biomass fuel exposure (such as from cooking and heating in poorly ventilated dwellings) and air pollution. Host factors such as genetic abnormalities, abnormal lung development, and accelerated aging can predispose individuals to COPD development (GOLD, 2017).
- Patients with COPD may experience exacerbations, which are periods of acute worsening of respiratory symptoms (GOLD, 2017).
- Pharmacologic therapy for COPD can reduce symptoms, reduce the frequency and severity of exacerbations, and improve patients' health status and exercise tolerance. There is no conclusive evidence that COPD medications modify the long-term decline in lung function characteristic of COPD (GOLD, 2017).
- Pharmacologic options for COPD treatment comprise several classes, including β_2-agonists, anticholinergics, methylxanthines, various combination products (including bronchodilators with inhaled corticosteroids [ICSs]), and the phosphodiesterase (PDE)-4 inhibitor roflumilast. Pharmacologic treatments should be individualized based on symptom severity, risk of exacerbations, side effects, comorbidities, drug availability, and cost, as well as the patient's response, preference, and ability to use various drug delivery devices (GOLD, 2017).
- Inhaled bronchodilators are central to COPD symptom management, and are usually given on a regular basis to prevent or reduce symptoms. Several long-acting inhaled bronchodilators are available, and use of short-acting bronchodilators on a regular basis is not generally recommended (GOLD, 2017).
- Available β_2-agonist/anticholinergic combinations include COMBIVENT® RESPIMAT® and DUONEB®, which are combinations of the short-acting agents, albuterol and ipratropium, and the combination long-acting β_2-agonists (LABAs)/long-acting anticholinergics (also called long-acting muscarinic antagonists [LAMAs]) ANORO™ ELLIPTA™ (umeclidinium/vilanterol), STIOLTO™ RESPIMAT® (tiotropium/olodaterol, UTIBRON™ NEOHALER® (glycopyrrolate/indacaterol), and BEVESPI AEROSPHERE™ (glycopyrrolate/formoterol fumarate) (see Table 1).
- Updated 2017 GOLD guidelines place the use of combination LAMA/LABAs more prominently than in previous versions, recommending dual bronchodilator therapy as a first- or second-line treatment for most patients with COPD (with the exception of low-risk patients with milder symptoms) (GOLD, 2017).
- For many years, an inhalation aerosol combining ipratropium and albuterol was available as the COMBIVENT® inhaler. Original COMBIVENT contained chlorofluorocarbons (CFCs) and has been discontinued due to regulations limiting the use of CFCs. It has been replaced by a newer formulation, COMBIVENT RESPIMAT inhalation spray (Food and Drug Administration, 2015). Because original COMBIVENT is unavailable, information on this product is no longer included in this review. However, data from some clinical studies using original COMBIVENT is still included as it may be relevant to evaluation of COMBIVENT RESPIMAT.
- Medispan class/subclass: sympathomimetics; adrenergic combinations.

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ANORO ELLIPTA (umeclidinium/vilanterol)	GlaxoSmithKline	12/18/2013	-
BEVESPI AEROSPHERE (glycopyrrolate/formoterol fumarate)	AstraZeneca	04/25/2016	-
COMBIVENT RESPIMAT (ipratropium/albuterol)	Boehringer Ingelheim	10/07/2011	-
DUONEB (ipratropium/albuterol)	various	03/21/2001	✔
STIOLTO RESPIMAT (tiotropium/olodaterol)	Boehringer Ingelheim	05/21/2015	-
UTIBRON NEOHALER* (glycopyrrolate/indacaterol)	Novartis	10/29/2015	-

*UTIBRON NEOHALER has not yet been made available by its manufacturer. Launch plans are currently pending.

(Drugs@FDA, 2016; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2016)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	ANORO ELLIPTA	BEVESPI AEROSPHERE	COMBIVENT RESPIMAT	DUONEB	STIOLTO RESPIMAT	UTIBRON NEOHALER
Long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema	✔				✔	
Long-term, twice-daily, maintenance treatment of airflow obstruction in patients with COPD		✔				✔
For use in patients with COPD on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator			✔			
For the treatment of bronchospasm associated with COPD in patients requiring more than one bronchodilator				✔		

(Prescribing information: ANORO ELLIPTA, 2016; BEVESPI AEROSPHERE, 2016; COMBIVENT RESPIMAT, 2016; DUONEB, 2012; STIOLTO RESPIMAT, 2016; UTIBRON NEOHALER, 2016)

Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Ipratropium/albuterol

- The combination of ipratropium and albuterol is a well-established treatment that has been used for many years in the management of COPD.
- Several double-blind, randomized, controlled studies have demonstrated greater effectiveness of the combination of ipratropium and albuterol in a metered dose inhaler (MDI) compared to monotherapy with either of the individual components (Bone et al, 1994; Dorinsky et al, 1999; Friedman et al, 1999). Demonstrated improvements relative to monotherapies include the following:
    - Mean peak response in forced expiratory volume in one second (FEV_1) (Bone et al, 1994)
    - Overall forced vital capacity (FVC) response (Bone et al, 1994)
    - The percentage of patients demonstrating a 15% increase in FEV_1 after medication administration (Dorinsky et al, 1999)
    - FEV_1 area under the curve (AUC) (0 to 4 hours) (Friedman et al, 1999)
- A multicenter, randomized controlled trial evaluating ipratropium/albuterol given via MDI four times daily, via nebulizer four times daily, and via nebulizer twice daily (morning and night) and MDI twice daily (afternoon and evening) demonstrated no significant differences among groups in quality-of-life scores, peak flow measurements, or patient symptom scores (Tashkin et al, 2007).
- A double-blind, double-dummy trial comparing ipratropium/albuterol 20 mcg/100 mcg via RESPIMAT inhaler four times daily to ipratropium/albuterol 36 mcg/206 mcg via MDI four times daily demonstrated non-inferiority of the RESPIMAT inhaler to the MDI based on FEV_1 and FVC endpoints (ZuWallack et al, 2010).

Umeclidinium/vilanterol

- A multicenter, double-blind, placebo-controlled, randomized controlled trial (N=1,532) compared once-daily doses of umeclidinium/vilanterol 62.5 mcg/25 mcg (ANORO ELLIPTA) to umeclidinium 62.5 mcg alone, vilanterol 25 mcg alone, or placebo. The primary endpoint, least squares mean (LSM) change in FEV_1 from baseline, was significantly greater in the umeclidinium/vilanterol group (171 mL) compared to the placebo group (4 mL; P<0.001), as well as compared to the umeclidinium monotherapy group (119 mL; P=0.004) and the vilanterol monotherapy group (76 mL; P<0.001). Improvements were also noted for ANORO ELLIPTA in the weighted mean FEV_1 over 0 to 6 hours post-dose, rescue albuterol use, COPD exacerbations, and St. George's Respiratory Questionnaire (SGRQ) (Donohue et al, 2013).
- Two multicenter, double-blind, double-dummy, active-controlled, randomized controlled trials (N=843 and 869), reported together, evaluated umeclidinium/vilanterol 62.5 mcg/25 mcg (ANORO ELLIPTA), umeclidinium/vilanterol 125 mcg/25 mcg, and tiotropium 18 mcg (SPIRIVA HANDIHALER). One trial had an additional arm evaluating vilanterol 25 mcg monotherapy, and the other had an additional arm evaluating umeclidinium 125 mcg monotherapy (Decramer et al, 2014).
    - In the first trial, the LSM difference in trough FEV_1 was greater for umeclidinium/vilanterol 62.5 mcg/25 mcg (211 mL) compared to vilanterol 25 mcg (121 mL) and tiotropium 18 mcg (121 mL) (P=0.0006 vs either monotherapy). The weighted mean (wm) FEV_1 over 0 to 6 hours also favored combination therapy over tiotropium alone or vilanterol alone. Most patient-reported endpoints appeared comparable with combination therapy and monotherapy (Decramer et al, 2014).
    - In the second trial, the LSM difference in trough FEV_1 was greater for umeclidinium/vilanterol 62.5 mcg/25 mcg (208 mL) compared to tiotropium 18 mcg (149 mL) (P=0.0182), but was not significantly different from monotherapy with umeclidinium 125 mcg (186 mL) (P=0.38). The wm FEV_1 over 0 to 6 hours favored combination therapy over tiotropium alone or umeclidinium alone. Most patient-reported endpoints appeared comparable with combination therapy and monotherapy (Decramer et al, 2014).
- Two identical multicenter, double-blind, placebo-controlled, crossover studies (N=308 and N=349), reported together, evaluated the use of umeclidinium/vilanterol 62.5 mcg/25 mcg, umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 125 mcg, umeclidinium 62.5 mcg, vilanterol 25 mcg, and placebo. Co-primary endpoints were exercise endurance time (EET) and FEV_1. These studies led to inconsistent results, with one study demonstrating small but statistically significant improvement in EET compared to placebo, and the other showing no significant improvement. The differences in trial results seemed to be explained by unexpected improvements observed in the placebo group in one

of the trials, and a *post-hoc* integrated analysis demonstrated significant improvement for umeclidinium/vilanterol vs placebo. Both studies demonstrated improved lung function based on FEV_1 compared to placebo. Comparisons were not presented between the combination therapies and monotherapy with umeclidinium or vilanterol (Maltais et al, 2014).

- A 12-week, non-inferiority, randomized, double-blind, triple-dummy, parallel group study (N=967) compared umeclidinium/vilanterol (62.5/25 mcg once daily) to tiotropium (18 mcg once daily) plus indacaterol (150 mcg once daily). When comparing trough FEV_1 on day 85, umeclidinium/vilanterol demonstrated non-inferiority to combination treatment with tiotropium and indacaterol. Other measures, including rescue medication use, TDI focal scores, and SGRQ scores, were also similar among both treatment groups on day 85 (P values not provided) (Kalberg et al, 2016).

Tiotropium/Olodaterol

- A multicenter, double-blind, placebo-controlled, crossover trial (N=219) evaluated tiotropium/olodaterol 5 mcg/5 mcg (STIOLTO RESPIMAT) compared to placebo, olodaterol 5 mcg monotherapy, tiotropium 2.5 mcg monotherapy, tiotropium 5 mcg monotherapy, and combination tiotropium/olodaterol 2.5 mcg/5 mcg daily. Tiotropium/olodaterol 5 mcg/5 mcg demonstrated a greater change from baseline in the FEV_1 AUC (0 to 24 hours) (244 mL) compared to placebo (-37 mL) and compared to each monotherapy (117 to 133 mL) (P<0.0001). Additional lung function endpoints were also favorable for tiotropium/olodaterol compared to placebo and monotherapies (Beeh et al, 2015).
- Two multicenter, double-blind, parallel group, active controlled, randomized trials (N=2,624 and 2,539), reported together, evaluated tiotropium/olodaterol 5 mcg/5 mcg compared to olodaterol 5 mcg monotherapy, tiotropium 2.5 mcg monotherapy, tiotropium 5 mcg monotherapy, and combination tiotropium/olodaterol 2.5 mcg/5 mcg daily. In both trials, the tiotropium/olodaterol 5 mcg/5 mcg group demonstrated improvement over monotherapy with either tiotropium or olodaterol in each co-primary endpoint, including the FEV_1 AUC (0 to 3 hours), trough FEV_1, and SGRQ. Dyspnea, assessed by the change from baseline in transition dyspnea index (TDI) focal score, was also improved with combination therapy (Buhl et al, 2015).

Glycopyrrolate/Indacaterol

- Two 12-week, multicenter, randomized, double-blind, parallel group, placebo- and active-controlled studies (N=2,038) evaluated the efficacy and safety of indacaterol/glycopyrrolate. Patients were randomized (1:1:1:1) to indacaterol/glycopyrrolate (27.5/15.6 mcg twice daily), indacaterol (27.5 mcg twice daily), glycopyrrolate (15.6 mcg twice daily), or placebo. Pooled data demonstrated that the group that received combination indacaterol/glycopyrrolate had statistically superior measurements in terms of FEV_1 AUC (0 to 12 hours) compared with its monocomponents (P<0.001). When compared to placebo, the group that received combination treatment with indacaterol/glycopyrrolate also had statistically significant improvements in SGRQ, TDI scores, and use of rescue medications (P<0.001) (Mahler et al, 2015).
- A comparative trial in 1,680 patients with COPD and at least 1 exacerbation during the previous year showed a significant reduction in COPD exacerbation rate with indacaterol/glycopyrrolate compared to salmeterol/fluticasone (rate ratio, 0.89; 95% CI, 0.83 to 0.96; P=0.003) (Wedzicha et al, 2016).

Glycopyrrolate/Formoterol fumarate

- Efficacy and safety of glycopyrrolate/formoterol fumarate (18/9.6 mcg twice daily) were demonstrated in two 24-week, phase 3, multi-center, double-blind, placebo-controlled trials, PINNACLE-1 and PINNACLE-2 (total N=3,718) (Martinez et al, 2017).
    - In both trials, glycopyrrolate/formoterol fumarate demonstrated a larger increase in mean change from baseline in trough FEV_1 at week 24 relative to placebo and to either monotherapy. In PINNACLE-1, the differences for glycopyrrolate/formoterol fumarate were 150 mL vs. placebo, 59 mL vs. glycopyrrolate, and 64 mL vs. formoterol fumarate (P<0.0001 for all comparisons), and in PINNACLE-2, these differences were 103 mL, 54 mL, and 56 mL, respectively (P<0.001 for all comparisons).
    - Improvements compared to placebo were also noted in secondary endpoints including peak FEV_1 and daily rescue albuterol use. There was also a trend toward improvement in the SGRQ responder rate (improvement in score of 4 or more), with an odds ratio vs placebo of 1.49 (95% confidence interval [CI], 1.05 to 2.11) in PINNACLE-1 and 1.31 (95% CI, 0.94 to 1.84) in PINNACLE-2.

Meta-Analyses

- A meta-analysis of 26 randomized controlled trials comparing the efficacy of umeclidinium/vilanterol, indacaterol/glycopyrrolate, formoterol plus tiotropium, salmeterol plus tiotropium, or indacaterol plus tiotropium to tiotropium alone found that umeclidinium/vilanterol is comparable to other LAMA/LABA fixed dose combination agents with respect to trough FEV_1, SGRQ scores, TDI focal scores, and need for rescue medication use (Huisman et al, 2015).
- A meta-analysis of 27 trials (N=30,361) including 4 LAMA/LABA fixed-dose combination agents (aclidinium/formoterol 400/12 mcg [not FDA approved for use in the US], glycopyrrolate/indacaterol 110/50 mcg, tiotropium/olodaterol 5/5 mcg, and umeclidinium/vilanterol 62.5/25 mcg) showed non-significant differences in efficacy, exacerbations, and discontinuation rates. Safety profiles were also similar among the products (Schlueter et al, 2016).

Treatment Guidelines

- The 2017 GOLD guidelines underwent a significant update from prior guideline versions. The guidelines state that the management strategy for stable COPD should be predominantly based on an assessment of the patient's symptoms and future risk of exacerbations. The risk of exacerbations is now based solely on the exacerbation history, whereas in previous versions of the guideline, risk assessment also included consideration of airflow limitation assessed by spirometry. Key recommendations from the GOLD guidelines are as follows (GOLD, 2017):
  - Inhaled bronchodilators are recommended over oral bronchodilators.
  - LAMAs and LABAs are preferred over short-acting agents except for patients with only occasional dyspnea.
  - Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on one bronchodilator, treatment should be escalated to two.
  - Long-term monotherapy with ICSs is not recommended. Long-term treatment with ICSs may be considered in association with LABAs for patients with a history of exacerbations despite treatment with long-acting bronchodilators.
  - Treatment recommendations are given for patients with COPD based on their GOLD patient group (see Table 3 below).
    - Group A: Patients should be offered bronchodilator treatment (short- or long-acting). This should be continued if symptomatic benefit is documented.
    - Group B: Initial therapy should consist of a long-acting bronchodilator (LAMA or LABA). For patients with persistent breathlessness on monotherapy, use of two bronchodilators is recommended (LAMA + LABA). For patients with severe breathlessness, initial therapy with two bronchodilators may be considered. If the addition of a second bronchodilator does not improve symptoms, it is suggested that treatment could be stepped down to a single bronchodilator.
    - Group C: Initial therapy should be a LAMA. Patients with persistent exacerbations may benefit from adding a second long-acting bronchodilator (LAMA + LABA, preferred) or using an ICS + LABA.
    - Group D: It is recommended to start therapy with a LAMA + LABA combination. In some patients, initial therapy with an ICS + LABA may be the first choice; these patients may have a history and/or findings suggestive of asthma-COPD overlap. In patients who develop further exacerbations on LAMA + LABA therapy, alternative pathways include escalation to a LAMA + LABA + ICS (preferred) or a switch to an ICS + LABA. If patients treated with a LAMA + LABA + ICS still have exacerbations, options for selected patients may include addition of roflumilast, addition of a macrolide, or stopping the ICS.

Table 3. Assessment of symptoms and risk of exacerbations to determine GOLD patient group

Exacerbation history	Symptoms	
	mMRC 0 to 1 CAT <10	mMRC ≥2 CAT ≥10
≥2 (or ≥1 leading to hospital admission)	C	D
0 or 1 (not leading to hospital admission)	A	B

CAT = COPD assessment test; mMRC = modified British Medical Research Council questionnaire

- Guidelines from the American College of Chest Physicians and the Canadian Thoracic Society for prevention of acute exacerbations of COPD state that LAMA/LABA combinations are effective in reducing acute COPD exacerbations, but do not state that this combination is superior to LAMA monotherapy (Criner et al, 2015).

SAFETY SUMMARY

- Both albuterol/ipratropium combination products are contraindicated in patients with hypersensitivity to any component of the product, or hypersensitivity to atropine or its derivatives. ANORO ELLIPTA is contraindicated in patients with hypersensitivity to any component of the product, as well as in patients with severe hypersensitivity to milk proteins. BEVESPI AEROSPHERE and UTIBRON NEOHALER are contraindicated in patients with hypersensitivity to any component of the product. BEVESPI AEROSPHERE, STIOLTO RESPIMAT, and UTIBRON NEOHALER are all contraindicated in patients with asthma without use of a long-term asthma control medication (and are not indicated for the treatment of asthma).
- There are no boxed warnings for the albuterol/ipratropium combination products. ANORO ELLIPTA, BEVESPI AEROSPHERE, STIOLOTO RESPIMAT and UTIBRON NEOHALER have boxed warnings that are standard for the LABAs, which state that LABAs increase the risk of asthma-related death. Data from a large placebo-controlled U.S. trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including formoterol, one of the active ingredients in BEVESPI AEROSPHERE, indacaterol, one of the active ingredients in UTIBRON NEOHALER, vilanterol, one of the active ingredients in ANORO ELLIPTA, and olodaterol, one of the active ingredients in STIOLOTO RESPIMAT. The safety and efficacy of ANORO ELLIPTA, BEVESPI AEROSPHERE, STIOLOTO RESPIMAT, and UTIBRON NEOHALER in patients with asthma have not been established, and these products are not indicated for the treatment of asthma.
- Warnings and precautions are very similar among products, and include the following:
    - Paradoxical bronchospasm: May produce paradoxical bronchospasm, which can be life-threatening. If it occurs, discontinue the product and institute alternative therapy.
    - Cardiovascular effect: β_2-agonists can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, and/or symptoms. If these symptoms occur, the product may need to be discontinued. In addition, electrocardiogram (ECG) changes may occur. Use with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
    - Ocular effects: Ipratropium and other anticholinergic agents may increase intraocular pressure, which may precipitate or worsen narrow-angle glaucoma. Use with caution in patients with narrow-angle glaucoma. In addition, avoid spraying product into eyes, as this can cause eye pain and visual symptoms.
    - Urinary retention: Ipratropium and other anticholinergic agents may cause urinary retention. Use caution when administering this medication to patients with prostatic hyperplasia or bladder-neck obstruction.
    - Do not exceed recommended dose: Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma.
    - Hypersensitivity reactions: Urticaria, angioedema, rash, pruritus, bronchospasm, laryngospasm, oropharyngeal edema, and anaphylaxis may occur. If such a reaction occurs, discontinue therapy and consider alternative treatment.
    - Coexisting conditions: Due to the β_2-agonist component, use with caution in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines.
    - Hypokalemia: β-agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.
    - Drug interactions with strong cytochrome P4503A4 inhibitors; increased cardiovascular effects may occur (ANORO ELLIPTA only).
    - Reports of anaphylactic reactions in patients with severe milk protein allergy (ANORO ELLIPTA only).

- Deterioration of disease and acute episodes; drug has not been studied in this setting and is not to relieve acute symptoms (ANORO ELLIPTA and STIOLTO RESPIMAT only).

- Adverse reactions are similar among products and include back pain, bronchitis, upper respiratory infection, lung disease, headache, dyspnea, nasopharyngitis/pharyngitis, and cough.
- In a 12-week trial comparing COMBIVENT RESPIMAT to COMBIVENT inhalation aerosol, rates of adverse reactions were very similar between groups. In a 48-week safety trial, most adverse reactions were similar in type and rate between treatment groups; however, cough occurred more frequently in patients enrolled in the COMBIVENT RESPIMAT group (7%) than the COMBIVENT inhalation aerosol group (2.6%).
- The choice of a specific LAMA/LABA fixed dose combination product is not based on any difference in the safety profile (Matera et al, 2016).

DOSING AND ADMINISTRATION

Table 3. Dosage and Administration

Drug	Dosage Form and Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
ANORO ELLIPTA	Disposable inhaler containing two double-foil blister strips: 62.5 mcg/25 mcg	One inhalation once daily	Do not exceed recommended dose	Opening the cover of the inhaler prepares a dose for inhalation. If the inhaler is opened and closed without inhalation, the dose is lost. The inhaler contains a dose counter.
BEVESPI AEROSPHERE	Inhalation spray; each actuation delivers 9 mcg of glycopyrrolate and 4.8 mcg of formoterol fumarate	Two inhalations twice daily	Use in the morning and in the evening	Each canister delivers 120 inhalations. The canister has an attached dose indicator, which indicates how many inhalations remain; dose indicator display will move after every tenth actuation.
COMBIVENT RESPIMAT	Inhalation spray; each actuation delivers 20 mcg ipratropium bromide and 100 mcg albuterol (equivalent to 120 mcg albuterol sulfate) from the mouthpiece.	One inhalation four times daily	Patients may take additional inhalations as needed; maximum six inhalations per 24 hours	Each cartridge delivers 120 metered actuations after preparation for use (60 actuations in the institutional pack). The inhaler has an indicator that shows approximately how much medicine is left. Once the actuations have been used, the inhaler locks so it can no longer be used.
DUONEB	3 mL sterile solution for nebulization in sterile low-density polyethylene unit-dose vials	One 3 mL vial by nebulization four times daily	Patients may take additional doses as needed; maximum six doses per 24 hours	DUONEB should be administered via a jet nebulizer connected to an air compressor with an adequate air flow, equipped with a mouthpiece or suitable face mask.
STIOLTO RESPIMAT	Inhalation spray; each actuation delivers 3.124 mcg tiotropium bromide monohydrate, equivalent to 2.5 mcg tiotropium, and 2.736	Two inhalations once daily	Take at the same time each day; do not exceed the recommended dose	Each cartridge delivers 60 metered actuations after preparation for use (28 in the institutional pack). Once the actuations have been used,

Drug	Dosage Form and Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	mcg olodaterol hydrochloride, equivalent to 2.5 mcg olodaterol			the inhaler locks so it can no longer be used.
UTIBRON NEOHALER	Inhalation powder; each capsule contains 27.5 mcg of indacaterol and 15.6 mcg of glycopyrrolate	One inhalation of capsule contents twice daily	Take at the same time each day (1 capsule in the morning, and 1 capsule in the evening); do not exceed the recommended dose	Administer via Neohaler device only.

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
ANORO ELLIPTA (umeclidinium/ vilanterol)	No dose adjustment is required.	Safety and efficacy have not been established.	No dose adjustment is required.	No dose adjustment is required for moderate impairment. Not studied in patients with severe impairment.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.
BEVESPI AEROSPHERE (glycopyrrolate/ formoterol fumarate)	No dose adjustment is required.	Safety and efficacy have not been established.	Pharmaco-kinetics have not been studied; use with caution.	Pharmacokinetics have not been studied; use with caution as formoterol is cleared hepatically.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.
COMBIVENT RESPIMAT & DUONEB (ipratropium/ albuterol)	No marked differences in adverse reactions have been observed; no dosage adjustment is necessary.	Safety and efficacy have not been established.	Pharmaco-kinetics have not been studied; use with caution.	Pharmacokinetics have not been studied; use with caution.	Pregnancy Category C* Unknown whether excreted in breast milk; a decision should be made whether to discontinue nursing or discontinue the drug.
STIOLTO RESPIMAT (tiotropium/ olodaterol)	No dose adjustment is required.	Safety and efficacy have not been established.	No dose adjustment is required. Patients with creatinine clearance ≤60 mL/min should be monitored for anticholinergic effects.	No dose adjustment is required with mild and moderate impairment. Not studied with severe impairment.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
UTIBRON NEOHALER (glycopyrrolate/ indacaterol)	No dose adjustment is required.	Safety and efficacy have not been established.	No dose adjustment is required. Patients with creatinine clearance ≤30 mL/min should be monitored for anticholinergic effects.	No dose adjustment is required.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.

*Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- Pharmacologic therapy for COPD can reduce symptoms, reduce the frequency and severity of exacerbations, and improve patients' health status and exercise tolerance. The combination of ipratropium and albuterol is a well-established treatment that has been used for many years in the management of COPD; however, it requires dosing four times per day for maintenance therapy. Newer combination products are now available, which are administered either once daily (ANORO ELLIPTA and STIOLTO RESPIMAT) or twice daily (BEVESPI AEROSPHERE and UTIBRON NEOHALER).
- Ipratropium and albuterol combination products include inhalers and vials for nebulization. Based on available information, efficacy appears to be comparable between these two products.
- With respect to lung function, each LAMA/LABA combination has been demonstrated to be more effective than use of its individual components. Data is limited on the effects of combination therapy compared to monotherapy on the rate of exacerbations and on patient-reported endpoints such as dyspnea.
- A meta-analysis of 27 trials including four LAMA/LABA fixed dose combination agents (aclidinium/formoterol [not FDA approved for use in the US], glycopyrrolate/indacaterol, tiotropium/olodaterol, and umeclidinium/vilanterol) did not show significant differences in efficacy, exacerbations, or discontinuation rates. Safety profiles were also similar among the products (Schlueter et al, 2016).
- The original COMBIVENT inhalation aerosol has been discontinued because it contained CFCs. A replacement inhaler, COMBIVENT RESPIMAT, has been introduced and has been demonstrated to be non-inferior to the inhalation aerosol. COMBIVENT RESPIMAT is dosed at one inhalation four times daily, in contrast to original COMBIVENT, which was dosed at two inhalations four times daily.
- Clinical guidelines generally favor long-acting bronchodilators over short-acting bronchodilators for maintenance therapy of COPD.
- Updated 2017 GOLD guidelines recommend the use of LAMA/LABA combination therapy as a first- or second-line treatment in most patients with COPD, with the exception of low-risk patients with milder symptoms (GOLD, 2017).

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Publication Date: December 29, 2016