



# Department of Vermont Health Access

## Therapeutic Class Review β<sub>2</sub>-Agonist Combination Products

### Overview/Summary

The combination respiratory β<sub>2</sub>-agonists are medications which contain a combination of the bronchodilators albuterol and ipratropium. These combination products are Food and Drug Administration (FDA)-approved for the treatment of bronchoconstriction associated with chronic obstructive pulmonary disease (COPD).<sup>1-3</sup> Although the use of albuterol/ipratropium for the treatment of asthma has not been approved by the FDA, this combination product has been utilized off label for the treatment of severe-persistent asthma in patients who fail recommended asthma therapy.<sup>4</sup> Albuterol acts preferentially on the β<sub>2</sub>-adrenergic receptors. Activation of these receptors on airway smooth muscle leads to the activation of adenylyl cyclase and an increase in intracellular cyclic-3',5'-adenosine monophosphate (cyclic AMP). The increase in cyclic AMP leads to activation of protein kinase A and the inhibition of myosin phosphorylation resulting in lower intracellular ionic calcium and smooth muscle relaxation. Increased cyclic AMP levels also inhibits the release of mediators from mast cells in the airways.<sup>1-3</sup> Ipratropium antagonizes the action of acetylcholine, preventing increases in intracellular calcium and results in bronchodilation.<sup>1-3</sup> The combination of albuterol/ipratropium is available as a metered dose inhaler (Combivent<sup>®</sup>) and a solution for nebulization (Duoneb<sup>®</sup>). The solution for nebulization is currently available generically.

As a result of the Clean Air Act and the Montreal Protocol on Substances that Deplete the Ozone Layer, the FDA made the decision to end production, marketing, and sale of all albuterol metered dose inhalers containing chlorofluorocarbons as their propellant by December 31, 2008. These agents are to be replaced by metered dose inhalers which utilize hydrofluoroalkanes. Combivent<sup>®</sup> has been designated as an essential-use product by the United States Department of Health and Human Services and the FDA, which allowed it to remain on the market past the 2008 deadline. The essential-use designation for Combivent<sup>®</sup> will be effective through December 31, 2013 as the FDA is removing such designations on remaining chlorofluorocarbon products. A replacement product is currently in late stages of development by Boehringer Ingelheim and is expected to be available prior to December 31, 2013.<sup>5</sup>

According to the Global Initiative for Chronic Obstructive Lung Disease and the National Institute for Health and Clinical Excellence guidelines, inhaled bronchodilators are preferred for the management of COPD.<sup>6-7</sup> The guidelines state that regular use of long-acting β<sub>2</sub>-agonists or short- or long-acting anticholinergics improves health status and long-acting anticholinergics reduce the rate of COPD exacerbations and improve the effectiveness of pulmonary rehabilitation.<sup>6-7</sup> Long-acting bronchodilators are more effective and convenient than short-acting bronchodilators however short-acting bronchodilators should be considered initial empiric therapy.<sup>7</sup> The choice of agent should be based on availability and individual response in terms of symptom relief and side effects. Combining bronchodilators with different mechanisms of action and duration may increase the degree of bronchodilation with equivalent or lesser side effects.<sup>6-7</sup>

### Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Albuterol/ipratropium (Combivent <sup>®</sup> , DuoNeb <sup>®*</sup> )	Inhaled β <sub>2</sub> -adrenergic agonists/anticholinergic	✓ *

\*Generic available in at least one dosage form or strength.

### Indications

**Table 2. Food and Drug Administration Approved Indication<sup>1-3</sup>**

Indication	Albuterol/Ipratropium
Treatment of bronchospasm associated with chronic obstructive pulmonary disease in patients requiring more than one bronchodilator	✓

Currently both agents are indicated for the treatment of bronchospasm associated with chronic obstructive pulmonary disease in patients requiring more than one bronchodilator. However, albuterol/ipratropium may also be used off-label for the treatment asthma.<sup>1-4</sup>

**Pharmacokinetics**

**Table 3. Pharmacokinetics<sup>1-4,8-9</sup>**

Generic Name	Onset (hours)	Duration (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Albuterol/ ipratropium	0.16 to 2.00 (albuterol); 0.25 (ipratropium)	3 to 4 (albuterol); 2 to 5 (ipratropium)	30.0 (albuterol); 2.8 (ipratropium)	albuterol 4'-o- sulfate (albuterol); none (ipratropium)	3.8 (albuterol); 2.0 (ipratropium)

**Clinical Trials**

Clinical trials have demonstrated the safety and efficacy of albuterol and ipratropium as monotherapy and combination therapy in patients with chronic obstructive pulmonary disease.<sup>10-14</sup>

**Table 4. Clinical Trials**

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ikeda et al <sup>10</sup>  Ipratropium 40 µg via MDI  vs  ipratropium 80 µg via MDI  vs  albuterol 200 µg via MDI and ipratropium 40 µg via MDI  vs  albuterol 400 µg via MDI and ipratropium 80 µg via MDI  vs  placebo	DB, PC, RCT, XO  Adult male patients with stable COPD with a history of >20 pack-years of cigarette smoking, and FEV <sub>1</sub> <60% and a FEV <sub>1</sub> /FVC <0.7, and chest radiographic findings compatible with pulmonary emphysema	N=26  5 separate visits over a period of 1 month	Primary: Change from baseline in FEV <sub>1</sub> , FVC and the difference in adverse reactions reported  Secondary: Not reported	Primary: All treatment groups resulted in a significant improvement in FEV <sub>1</sub> and FVC when compared with placebo at all time points evaluated ( <i>P</i> <0.01).  Compared to all other regimens at every time point evaluated, 80 µg of ipratropium and 400 µg of albuterol showed significantly greater improvements in FEV <sub>1</sub> ( <i>P</i> <0.05, <i>P</i> <0.01).  The lower dose combination was significantly different in FVC response from the low-dose monotherapy ( <i>P</i> <0.01), but not high-dose monotherapy.  No significant differences were found in terms of the safety of the medications, including pulse rate, blood pressure, and adverse effects (no <i>P</i> value reported).  Secondary: Not reported
Bone et al <sup>11</sup>  Albuterol 100 µg QID via MDI  vs  ipratropium 21 µg QID via MDI	DB, MC, PG, PRO, RCT  Patient's 40 years of age and older diagnosed with COPD with stable disease, relative stable, moderately severe airway	N=534  85 days	Primary: Peak change from baseline in FEV <sub>1</sub> , response AUC, symptom score, and safety  Secondary: Not reported	Primary: Compared to the individual components, the mean peak response in FEV <sub>1</sub> was significantly greater in the combination treatment group ( <i>P</i> <0.001 to <i>P</i> =0.015).  There was no difference in symptom score between the groups ( <i>P</i> value not reported).  Compared with either agent alone, the overall FVC response was significantly greater in the combination group ( <i>P</i> <0.01 to <i>P</i> =0.04).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs albuterol/ipratropium 100/21 $\mu\text{g}$ QID via MDI	obstruction with an $\text{FEV}_1 \leq 65\%$ and $\text{FEV}_1/\text{FVC}$ ratio $\leq 0.70$ , and a smoking history $>10$ pack-years, using at least two prescribed therapeutic agents for COPD control			There were no significant differences between any of the treatment groups in terms of adverse effects or safety ( $P$ value not reported).  Secondary: Not reported
Dorinsky et al <sup>12</sup> Albuterol 180 $\mu\text{g}$ QID via MDI vs ipratropium 36 $\mu\text{g}$ QID via MDI vs equivalent dose of albuterol/ipratropium via MDI	DB, MC, PG, RETRO, RCT  Patients 40 years of age and older diagnosed with COPD, $>10$ pack year smoking history, regularly using at least two bronchodilators for symptom control during 3 months prior to the trials, $\text{FEV}_1 \leq 65\%$ predicted, $\text{FEV}_1/\text{FVC}$ ratio $\leq 0.70$	N=1,067  85 days	Primary: $\text{FEV}_1$ and FVC values before and after administration of the study medications (bronchodilator response defined as an increase in $\text{FEV}_1$ of 12 and 15% from baseline)  Secondary: Not reported	Primary: The percentage of patients demonstrating a 15% increase in $\text{FEV}_1$ at 15 and 30 minutes after medication administration was significantly higher in the albuterol/ipratropium group compared to the individual treatment groups on all test days, and significantly higher than the individual treatment groups after 60 and 120 minutes on test day 1 and 2 (of 4) ( $P < 0.05$ ).  The overall decline in percentage of patients demonstrating a 15% increase in $\text{FEV}_1$ in all groups was small and ranged from 2 to 8% ( $P$ value not reported).  A significantly greater percentage of patients demonstrated a 12 or 15% increase in $\text{FEV}_1$ on three or more test days in the albuterol/ipratropium group compared to the individual treatment groups ( $P < 0.05$ ).  Secondary: Not reported
Friedman et al <sup>13</sup> Albuterol 180 $\mu\text{g}$ QID via MDI vs ipratropium 36 $\mu\text{g}$ QID via MDI	DB, MC, PG, RETRO, RCT  Patients 40 years of age and older diagnosed with COPD, $>10$ pack year smoking history, regularly using at least two	N=1,067  85 days	Primary: Peak change in $\text{FEV}_1$ and the $\text{FEV}_1$ AUC from time 0-4 hours, total health care expenditures, and cost effectiveness ratios	Primary: A statistically significant improvement in $\text{FEV}_1$ in the albuterol/ipratropium group was observed compared to other treatment groups on all test days ( $P < 0.01$ ).  A significantly higher $\text{FEV}_1$ AUC <sub>0-4</sub> in the albuterol/ipratropium group compared to the other treatment groups was observed on all test days ( $P \leq 0.008$ ).  The total cost of treating patients in the ipratropium group and the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs  equivalent dose of albuterol/ipratropium via MDI	bronchodilators for symptom control during 3 months prior to the trials, FEV <sub>1</sub> ≤65% predicted, FEV <sub>1</sub> /FVC ratio ≤0.70		Secondary: Not reported	albuterol/ipratropium group was significantly less than the albuterol group (no <i>P</i> value reported).  No statistical difference was observed between total costs in the ipratropium group and the albuterol/ipratropium group ( <i>P</i> value not reported).  A significantly greater cost effectiveness was observed in the ipratropium and albuterol/ipratropium groups compared to albuterol group ( <i>P</i> <0.05).  Secondary: Not reported
Tashkin et al <sup>14</sup>  Albuterol/ipratropium solution for nebulization QID  vs  albuterol/ipratropium 2 inhalations QID via MDI  vs  albuterol/ipratropium solution for nebulization administered in the morning and albuterol/ipratropium MDI administered in the afternoon and evening	MC, PG, RCT  Men and women 50 years of age and older who met the American Thoracic Society/European Respiratory Society definition of COPD, had a history of >10 pack-years of cigarette smoking, an FEV <sub>1</sub> 30 to 65% of the predicted value, and a post bronchodilator FEV <sub>1</sub> /FVC ratio ≤0.70	N=140  12-weeks	Primary: Quality of life (St. George's Respiratory Questionnaire, completed at baseline, six weeks, and 12 weeks)  Secondary: Patient symptom score, home morning and nighttime daily peak flow before dosing with the study medication and pre- and post-dose FEV <sub>1</sub> in the clinic, safety measures (vital signs, changes in physical findings,	Primary: After six weeks of treatment, the change from baseline in the total quality of life score was clinically (exceeding the 4-unit threshold) and statistically significant for the concomitant treatment group ( <i>P</i> <0.0196).  Patients in the nebulizer-only treatment group approached clinically significant improvements ( <i>P</i> value not reported). Differences between the treatment groups at week six were not statistically significant.  A statistically significant improvement was seen in symptom sub-score at week six for patients using a nebulizer-only or concomitant treatment ( <i>P</i> =0.019 and <i>P</i> <0.004, respectively).  Only the concomitant therapy group achieved a clinically significant improvement from baseline at week six in the Impacts sub-score (-5.1±3.0), however results were not statistically significant ( <i>P</i> value not reported).  At week 12 only the concomitant therapy group approached a clinically significant improvement in total score (-3.5±2.64).  Both the concomitant and nebulizer-only treatment groups demonstrated an improvement in the symptom sub-score ( <i>P</i> =0.0186, <i>P</i> value not reported, respectively).  None of the treatment groups reached a clinically significant improvement in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			and investigator reported disease exacerbations)	<p>the impact sub-score.</p> <p>Changes between the treatment groups in the endpoints measured were not statistically significant.</p> <p>Secondary: Changes in pre- and post-bronchodilator FEV<sub>1</sub> with the treatment groups were not statistically significant at week six or at week 12; only the MDI inhaler treatment group demonstrated a statistically significant change from baseline at week six (<math>P=0.0060</math>).</p> <p>Mean patients symptom scores were similar among the treatment groups at baseline. All three-treatment groups demonstrated an improvement in patient symptom scores from baseline to week six and week 12.</p> <ul style="list-style-type: none"> <li>• Concomitant group               <ul style="list-style-type: none"> <li>○ Baseline: 5.60±0.52</li> <li>○ Week six: 3.90±0.51; <math>P=0.0312</math></li> <li>○ Week 12: 4.30±0.57; <math>P=0.0490</math></li> </ul> </li> <li>• Nebulizer-only group               <ul style="list-style-type: none"> <li>○ Baseline: 5.80±0.60</li> <li>○ Week six: 4.60±0.57; <math>P=0.0539</math></li> <li>○ Week 12: 4.80±0.64; <math>P=0.0461</math></li> </ul> </li> <li>• MDI-only group               <ul style="list-style-type: none"> <li>○ Baseline: 5.80±0.53</li> <li>○ Week six: 4.50±0.50; <math>P</math> value not reported</li> <li>○ Week 12: 4.30±0.56; <math>P</math> value not reported</li> </ul> </li> </ul> <p>The differences in adverse events were not discussed.</p>

Drug regimen abbreviations: QID=four times daily

Study abbreviations: DB=double-blind, MC=multicenter, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, XO=crossover

Miscellaneous abbreviations: AUC=area under the curve, COPD=chronic obstructive pulmonary disease, FEV<sub>1</sub>=forced expiratory volume in 1 second, FVC=forced vital capacity, MDI=metered dose inhaler

**Special Populations****Table 5. Special Populations**<sup>1-3,8-9</sup>

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Albuterol/ ipratropium	No dosage adjustment required in the elderly population.  Safety and efficacy in children have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown

**Adverse Drug Events****Table 6. Adverse Drug Events (%)**<sup>1-3</sup>

Adverse Events	Albuterol/Ipratropium (Solution for Inhalation)	Albuterol/Ipratropium (Metered Dose Inhaler)
<b>Cardiovascular</b>		
Angina	-	<2
Arrhythmia	-	<2
Chest pain	2.6	0.3
Diastolic blood pressure decreased	-	✓
Elevated heart rate	✓	-
Hypertension	-	<2
Hypotension	-	✓
Myocardial ischemia	-	✓
Palpitations	✓	<2
Systolic blood pressure increased	-	✓
Tachycardia	-	<2
<b>Central Nervous System</b>		
Asthenia	-	✓
Central nervous system stimulation	-	✓
Coordination difficulty	-	✓
Dizziness	-	<2
Drowsiness	✓	✓
Fatigue	-	<2
Flushing	✓	✓
Headache	-	5.6
Insomnia	-	<2
Mental disorder	-	✓
Nervousness	-	<2
Paresthesia	-	<2
Tremor	-	<2
Weakness	-	✓
<b>Dermatological</b>		
Angioedema	-	✓
Pruritus	0.3	✓
Skin rash	0.3	✓
Urticaria	0.3	✓
<b>Gastrointestinal</b>		
Constipation	>1	✓
Diarrhea	1.8	<2

Adverse Events	Albuterol/Ipratropium (Solution for Inhalation)	Albuterol/Ipratropium (Metered Dose Inhaler)
Dry mouth	-	<2
Dry throat	-	✓
Dyspepsia	1.3	<2
Gastrointestinal distress	-	✓
Heartburn	-	✓
Motility disorder	-	✓
Nausea	1.4	2
Sore throat	✓	✓
Taste perversion	✓	<2
Vomiting	-	<2
<b>Genitourinary</b>		
Urinary difficulty	-	✓
Urinary tract infection	1.6	<2
<b>Musculoskeletal</b>		
Arthralgia	-	<2
Back pain	✓	-
Leg cramps	1.4	-
Muscle spasms	-	✓
Myalgia	-	✓
Pain	1.3	2.5
<b>Respiratory</b>		
Bronchitis	1.7	12.3
Bronchospasm	✓	0.3
Chronic obstructive pulmonary disease exacerbation	✓	✓
Coughing	-	4.2
Drying of secretions	-	✓
Dysphonia	-	<2
Dyspnea	-	4.5
Hoarseness	-	✓
Increased sputum	-	<2
Influenza	-	1.4
Irritation from aerosol	-	✓
Laryngospasm	-	✓
Lung disease	6.4	-
Nasal congestion	-	✓
Pharyngitis	4.4	2.2
Pneumonia	1.3	1.4
Respiratory disorder	-	2.5
Rhinitis	-	1.1
Sinusitis	✓	2.3
Upper respiratory tract infection	✓	10.9
Voice alterations	>1	-
Wheezing	✓	✓
<b>Other</b>		
Acute eye pain	✓	✓
Alopecia	-	✓
Anaphylactic reaction	-	✓
Blurred vision	✓	✓
Conjunctival hyperaemia	-	✓
Corneal edema	-	✓

Adverse Events	Albuterol/Ipratropium (Solution for Inhalation)	Albuterol/Ipratropium (Metered Dose Inhaler)
Edema	-	<2
Halo vision	-	✓
Hyperhidrosis	-	✓
Hypokalemia	-	✓
Mouth edema	-	✓
Mucosal ulcers	-	✓
Mydriasis	-	✓
Ocular irritation	-	✓
Stomatitis	-	✓
Worsening glaucoma	✓	✓

- Event not reported.

✓ Percent not specified.

### **Contraindications/Precautions**

Albuterol/ipratropium is contraindicated in patients with a history of hypersensitivity to any components of the product or atropine or its derivatives.<sup>1-3</sup> Albuterol/ipratropium inhalation aerosol (Combivent<sup>®</sup>) is contraindicated in patients with a history of hypersensitivity to soya lecithin or related food products such as soybean and peanuts.<sup>1</sup>

Paradoxical bronchospasm has been reported with both inhaled ipratropium and albuterol products and can be life-threatening. The preparation should be discontinued and alternative therapy instituted.<sup>1-3</sup>

The albuterol component of the combination products can produce clinically significant cardiovascular effects including effects on blood pressure and pulse. Discontinuation of the drug may be indicated. Post-marketing reports and published literature have also reported rare occurrences of myocardial ischemia associated with albuterol.  $\beta$ -adrenergic agonists have been reported to produce electrocardiogram changes including flattening of the T wave, QTc interval prolongation, and ST segment depression. Albuterol/ipratropium should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, arrhythmias and hypertension.<sup>1-3</sup>

Fatalities have been reported with excessive use of inhaled sympathomimetic drugs in patients with asthma. The recommended dose should not be exceeded.<sup>1-3</sup>

### **Drug Interactions**

**Table 7. Drug Interactions<sup>1-3</sup>**

Generic Name	Interacting Medication or Disease	Potential Result
$\beta_2$ -adrenergic agonists (all)	$\beta$ -adrenergic agents	Concomitant use may increase the risk for cardiovascular adverse events. Caution is advised when these agents are used together.
$\beta_2$ -adrenergic agonists (all)	Diuretics (i.e., loop diuretics, thiazide diuretics)	Electrocardiogram changes or hypokalemia may potentially be worsened with the addition of a $\beta_2$ -agonist, particularly when the recommended dose is exceeded.
$\beta_2$ -adrenergic agonists (all)	Monoamine oxidase inhibitors	Monoamine oxidase is an enzyme that metabolizes catecholamines. When given with an indirect acting sympathomimetic, hypertensive crisis may occur.
$\beta_2$ -adrenergic agonists (all)	Nonselective $\beta$ -blocking agents	$\beta$ -blockers inhibit the therapeutic effects of $\beta_2$ agonists and may produce bronchospasm in patients with asthma and chronic obstructive pulmonary disease.
$\beta_2$ -adrenergic agonists (all)	Tricyclic antidepressants	Tricyclic antidepressant may potentiate the cardiovascular effects of $\beta$ -adrenergic agonists.

Generic Name	Interacting Medication or Disease	Potential Result
Ipratropium	Anticholinergic agents	Due to a potential for an additive interaction/effect, caution is advised when using ipratropium concomitantly with other anticholinergic-containing medications.

### Dosage and Administration

Table 8. Dosing and Administration<sup>1-3</sup>

Generic Name	Adult Dose	Pediatric Dose	Availability
Albuterol/ ipratropium	Aerosol for oral inhalation: 2 inhalations (albuterol/ ipratropium 120/21 $\mu\text{g}$ ) QID; maximum, 12 inhalations daily  Solution for nebulization: 1 vial (albuterol/ ipratropium 2.5/0.5 mg) QID; maximum, 6 vials daily	Safety and efficacy in children have not been established.	Aerosol for oral inhalation: 120/21 $\mu\text{g}$ * (200 metered inhalations)  Solution for nebulization: 3.0/0.5 mg <sup>†</sup> (3 mL vials)

\* Delivering 103  $\mu\text{g}$  of albuterol (90  $\mu\text{g}$  albuterol base) and 18  $\mu\text{g}$  of ipratropium.

<sup>†</sup>Delivering 2.5 mg albuterol base.

### Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guidelines	Recommendations
Global Initiative for Chronic Obstructive Lung Disease: <b>Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (Updated 2010)</b> <sup>6</sup>	<p><u>Diagnosis</u></p> <ul style="list-style-type: none"> <li>• A clinical diagnosis of chronic obstructive pulmonary disease (COPD) should be considered in any patient who has dyspnea, chronic cough or sputum production and/or a history of exposure to risk factors for the disease.</li> <li>• A diagnosis of COPD should be confirmed by spirometry.</li> <li>• The presence of a post-bronchodilator forced expiratory volume in one second (FEV<sub>1</sub>)/forced vital capacity (FVC) &lt;0.70 confirms the presence of airflow limitation that is not fully reversible.</li> <li>• Assessment of COPD severity is based on the patient's level of symptoms, the severity of the spirometric abnormality and the presence of complications.</li> <li>• A detailed medical history should be obtained for all patients suspected of developing COPD.</li> <li>• Severity of COPD is based on the patient's level of symptoms, the severity of the spirometric abnormality and the presence of complications such as respiratory failure, right heart failure, weight loss and arterial hypoxemia.</li> <li>• Chest radiograph may be useful to rule out other diagnoses and to establish the presence of significant comorbidities such as cardiac failure.</li> <li>• Arterial blood gas tension measurements should be considered for all patients with FEV<sub>1</sub> &lt;50% predicted or clinical signs suggestive of respiratory failure or right heart failure.</li> <li>• COPD is typically a progressive disease; therefore, lung function can be expected to worsen over time, even with the best available care.</li> <li>• Symptoms and objective measures of airflow limitation should be monitored to determine when to modify therapy. In addition, symptom monitoring is used to determine when to modify therapy and to identify any complications that may develop.</li> </ul>

Clinical Guidelines	Recommendations
	<ul style="list-style-type: none"> <li>• Comorbidities are common in COPD and should be actively identified. Comorbidities often complicate the management of COPD, and vice versa.</li> <li>• Screening for <math>\alpha_1</math>-antitrypsin deficiency may be valuable in patients of Caucasian descent who develop COPD at a young age (&lt;45 years of age) or who have a strong family history of the disease.</li> <li>• In some patients with chronic asthma, a clear distinction from COPD is not possible using current imaging and physiological testing techniques and it is assumed that asthma and COPD coexist in these patients. In these instances, current management is similar to that of asthma. Other potential diagnoses (e.g., congestive heart failure, bronchiectasis, tuberculosis, obliterative bronchiolitis, and diffuse panbronchiolitis) are usually easier to distinguish from COPD.</li> </ul> <p><u>Treatment</u></p> <ul style="list-style-type: none"> <li>• The management of COPD should be individualized to address symptoms and improve the patient's quality of life.</li> <li>• None of the medications for COPD have been shown to modify the long term decline in lung function that is hallmark of this disease. Treatment should be focused on reducing symptoms and complications.</li> <li>• Choice of agent within each medication class depends on the availability of medication and the patient's response.</li> <li>• Bronchodilator medications are central to the symptomatic management of COPD. They are given on an as needed basis for relief of persistent or worsening symptoms or on a regular basis to prevent or reduce symptoms.</li> <li>• Inhaled therapy is preferred.</li> <li>• When treatment is given by the inhaled route, attention to effective drug delivery and training in inhaler technique is essential. COPD patients may have more problems in effective coordination with a metered dose inhaler compared to healthy patients; alternative breath-activated or spacer devices are available for most formulations. Dry powder inhalers may be more convenient and possibly provide improved drug deposition, although this has not been established in COPD.</li> <li>• Principle bronchodilators include <math>\beta_2</math>-agonists, anticholinergics and methylxanthines used as monotherapy or in combination.</li> <li>• Regular treatment with long-acting bronchodilators is more effective and convenient than short-acting bronchodilators.</li> <li>• The choice between <math>\beta_2</math>-agonists, anticholinergics, theophylline or combination therapy depends on availability and individual response in terms of symptom relief and side effects.</li> <li>• The order in which the bronchodilator medications are normally introduced into patient care (based on the level of disease severity and clinical symptoms) is: <math>\beta</math>-agonists, anticholinergics and methylxanthines.</li> <li>• Regular use of LABAs or short- or long-acting anticholinergics improves health status.</li> <li>• Long-acting anticholinergics reduce the rate of COPD exacerbations and improve the effectiveness of pulmonary rehabilitation.</li> <li>• Theophylline is effective in COPD, but due to its potential toxicity inhaled bronchodilators are preferred when available. All theophylline studies were performed with slow-release preparations.</li> <li>• Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects compared to</li> </ul>

Clinical Guidelines	Recommendations
	<p>increasing the dose of a single bronchodilator.</p> <ul style="list-style-type: none"> <li>• For single-dose, as needed use, there is no advantage in using levalbuterol over conventional nebulized bronchodilators.</li> <li>• The addition of regular treatment with ICSs to bronchodilator treatment is appropriate for symptomatic COPD patients with an FEV<sub>1</sub> &lt;50% predicted and repeated exacerbations.</li> <li>• Regular treatment with ICSs has been shown to reduce the frequency of exacerbations and thus improve health status for symptomatic patients with an FEV<sub>1</sub> &lt;50% of the predicted value and repeated exacerbations.</li> <li>• Treatment with ICSs increases the likelihood of pneumonia and does not reduce overall mortality.</li> <li>• An ICS combined with a LABA is more effective than the individual components in reducing exacerbations and improving lung function and health status.</li> <li>• Combination ICS/LABA therapy increases the likelihood of pneumonia.</li> <li>• Addition of an ICS/LABA to an anticholinergic appears to provide additional benefits.</li> <li>• There is insufficient evidence to recommend a therapeutic trial with systemic corticosteroids in patients with Stage II, Stage III or Stage IV COPD and poor response to an inhaled bronchodilator.</li> <li>• Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio.</li> <li>• In COPD patients influenza vaccines can reduce serious illness.</li> <li>• The pneumococcal polysaccharide vaccine is recommended for COPD patients ≥65 years old or for patients &lt;65 years old with an FEV<sub>1</sub> &lt;40% of the predicted value.</li> <li>• Long-term administration of oxygen (&gt;15 hours/day) increases survival in patients with chronic respiratory failure.</li> </ul> <p><u>Management of exacerbations</u></p> <ul style="list-style-type: none"> <li>• The most common causes of an exacerbation are tracheobronchial tree infections and air pollution.</li> <li>• Inhaled <math>\beta_2</math>-agonists (particularly inhaled <math>\beta_2</math>-agonists with or without anticholinergics) and systemic corticosteroids are effective treatments for exacerbations of COPD.</li> <li>• Patients experiencing COPD exacerbations with clinical signs of airway infection may benefit from antibiotic treatment.</li> </ul>
<p>National Institute for Health and Clinical Excellence:  <b>Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care (partial update) (2010)</b><sup>7</sup></p>	<p><u>Diagnosis</u></p> <ul style="list-style-type: none"> <li>• Diagnosis should be considered in patients &gt;35 years of age who have a risk factor for the development of COPD and who present with exertional breathlessness, chronic cough, regular sputum production, frequent winter bronchitis or wheeze.</li> <li>• The primary risk factor is smoking.</li> <li>• Spirometry is diagnostic of airflow obstruction. Airflow obstruction is defined as FEV<sub>1</sub> &lt;80% predicted and FEV<sub>1</sub>/FVC &lt;70%.</li> </ul> <p><u>Treatment</u></p> <ul style="list-style-type: none"> <li>• Smoking cessation should be encouraged for all patients with COPD.</li> <li>• Short-acting bronchodilators, as necessary, should be the initial empiric treatment for the relief of breathlessness and exercise limitation.</li> <li>• Long-acting bronchodilators (beta<sub>2</sub> agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators.</li> </ul>

Clinical Guidelines	Recommendations
	<ul style="list-style-type: none"> <li>• Once-daily long-acting muscarinic antagonists are preferred compared to four-times-daily short-acting muscarinic antagonists in patients with stable COPD who remain breathless or who have exacerbations despite the use of short-acting bronchodilators as required and in whom a decision has been made to begin regular maintenance bronchodilator therapy with a muscarinic antagonist.               <ul style="list-style-type: none"> <li>○ FEV<sub>1</sub> <math>\geq</math>50% predicted: long-acting <math>\beta_2</math>-agonist or long-acting muscarinic antagonist.</li> <li>○ FEV<sub>1</sub> &lt; 50% predicted: either long-acting <math>\beta_2</math>-agonist with an inhaled corticosteroid in a combination inhaler or a long-acting muscarinic antagonist.</li> </ul> </li> <li>• In patients with stable COPD and FEV<sub>1</sub> <math>\geq</math>50% who remain breathless or have exacerbations despite maintenance therapy with a long-acting <math>\beta_2</math>-agonist, consider adding an inhaled corticosteroid in a combination inhaler or a long-acting muscarinic antagonist when inhaled corticosteroids are not tolerated or declined.</li> <li>• Consider a long-acting muscarinic antagonist in patients remaining breathless or having exacerbations despite therapy with long-acting <math>\beta_2</math>-agonist and inhaled corticosteroids and vice versa.</li> <li>• Choice of drug should take in to consideration the patient's symptomatic response, preference, potential to reduce exacerbations, and side effects and costs.</li> <li>• In most cases, inhaled bronchodilator therapy is preferred.</li> <li>• Oral corticosteroids are not normally recommended and should be reserved for those patients with advanced COPD in whom therapy cannot be withdrawn following an exacerbation.</li> <li>• Theophylline should only be used after a trial of long-acting and short-acting bronchodilators or if the patient is unable to take inhaled therapy. Combination therapy with <math>\beta_2</math>-agonists and theophylline or anticholinergics and theophylline may be considered in patients remaining symptomatic on monotherapy.</li> <li>• Pulmonary rehabilitation should be made available to patients.</li> <li>• Noninvasive ventilation should be used for patients with persistent hypercapnic respiratory failure.</li> </ul> <p><u>Management of exacerbations</u></p> <ul style="list-style-type: none"> <li>• Patients with exacerbations should be evaluated for hospital admission.</li> <li>• Patients should receive a chest radiograph, have arterial blood gases monitored, have sputum cultured if it is purulent, and have blood cultures taken if pyrexial.</li> <li>• Oral corticosteroids should be used in all patients admitted to the hospital who do not have contraindications to therapy. The course of therapy should be no longer than 14 days.</li> <li>• Oxygen should be given to maintain oxygen saturation above 90%.</li> <li>• Patients should receive invasive and noninvasive ventilation as necessary.</li> <li>• Respiratory physiotherapy may be used to help remove sputum.</li> <li>• Before discharge, patients should be evaluated by spirometry.</li> <li>• Patients should be properly educated on their inhaler technique and the necessity of usage and should schedule a follow up appointment with a health care professional.</li> </ul>

### Conclusions

The combination respiratory  $\beta_2$ -agonists in this review are Food and Drug Administration (FDA) approved for the treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD).<sup>1-3</sup> The agent in this class is a combination of albuterol, a short-acting respiratory  $\beta_2$ -agonist, and ipratropium, a short-acting respiratory anticholinergic. The combination of albuterol/ipratropium is available as a metered dose inhaler (Combivent<sup>®</sup>) and a solution for nebulization (Duoneb<sup>®</sup>). The solution for nebulization is currently available generically.

According to the Global Initiative for Chronic Obstructive Lung Disease and the National Institute for Health and Clinical Excellence guidelines, inhaled bronchodilators are preferred for the management of COPD.<sup>6-7</sup> Guidelines state that regular use of long-acting  $\beta_2$ -agonists or short- or long-acting anticholinergics improves health status and long-acting anticholinergics reduce the rate of COPD exacerbations and improve the effectiveness of pulmonary rehabilitation.<sup>6-7</sup> Long-acting bronchodilators are more effective and convenient than short-acting bronchodilators however short-acting bronchodilators should be considered initial empiric therapy.<sup>7</sup> The choice of agent should be based on availability and individual response in terms of symptom relief and side effects. Combining bronchodilators with different mechanisms of action and duration may increase the degree of bronchodilation with equivalent or lesser side effects.<sup>6-7</sup>

Clinical trials have demonstrated the safety and efficacy of albuterol and ipratropium as monotherapy and combination therapy in patients with COPD.<sup>10-14</sup>

### Appendix I: Utilization Within This Drug Class for DVHA: July 1, 2010 to December 31, 2010

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
Combivent <sup>®</sup>	519	890	58.13%	\$266,981.83	\$299.98
Ipratropium/albuterol	315	637	41.61%	\$37,545.18	\$58.94
Duoneb <sup>®</sup>	1	4	0.26%	\$1,027.28	\$256.95
<b>Class Total:</b>	<b>NA</b>	<b>1,531</b>	<b>100%</b>	<b>\$305,554.29</b>	<b>\$199.58</b>

### Recommendations

In view of the well-established role of the combination  $\beta_2$ -adrenergic agonists (albuterol/ipratropium) in the treatment of chronic obstructive pulmonary disease and the availability of a generic nebulized product, it is recommended that no changes be made to the current Department of Vermont Health Access (DVHA) approval criteria (see below).

#### Duoneb<sup>®</sup> Nebulizer

- The patient has a documented intolerance to generic ipratropium/albuterol nebulizer.

Combivent<sup>®</sup> and the generic ipratropium/albuterol solution for inhalation are preferred products and are available without a prior authorization. A quantity limit of 2 inhalers per 30 days is in place for Combivent<sup>®</sup>.

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