

## **Indiana Medicaid Therapeutics Committee** **Therapeutic Class Review Summary**

### **Therapeutic Class:**

Agents to Treat COPD

### **Overview:**

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow obstruction, secondary airway inflammation, and emphysematous changes of the lung. The primary physiological abnormality in COPD is a decline in the forced expiratory volume in one second (FEV1) and the FEV1 to forced vital capacity ratio (FEV1/FVC). Based on the guideline of Global Initiative for Chronic Obstructive Lung Disease for patients with moderate to severe COPD (FEV1 < 80% of predicated normal and FEV1/FVC < 70%), regular maintenance treatment is required. Current pharmacological therapies include inhaled  $\beta_2$ -agonists, anticholinergics, and corticosteroids. The focus of this review is on the anticholinergics, which includes ipratropium, tiotropium, and ipratropium and albuterol combination.

Anticholinergics improve airflow and alleviate symptoms of COPD by inducing bronchodilation through the blockade of acetylcholine to muscarinic receptors in the airway. When administered by oral inhalation, systemic effects are minimal. The available agents are ipratropium and tiotropium. Ipratropium is a short-acting agent and should be administered every 4-6 hours. Tiotropium is similar to ipratropium structurally. However, tiotropium has a long duration of action over 24 hours and is administered once-daily, which is a major advantage over ipratropium. Tiotropium is not indicated for the initial treatment of acute episodes of bronchospasm, but has recently received approval to reduce exacerbations in COPD patients. In clinical studies, tiotropium achieved a greater improvement in FEV1, quality of life, and reduction in rate of exacerbation than ipratropium or placebo. However, data do not indicate that anticholinergics reduce the mortality and morbidity (number of hospitalizations) of COPD.

$\beta_2$ -agonists produce bronchodilation by stimulating  $\beta_2$  receptors. Because of different mechanisms, the combination of  $\beta_2$ -agonists and anticholinergics might increase the degree of bronchodilation achieved. In clinical studies, the combination of albuterol and ipratropium demonstrated greater and more sustained improvements on FEV1 than the individual components. However, there were no differences in symptom scores and other indicators. FDA recently approved a new therapy for the treatment of COPD. Arformoterol (Brovana™), an enantiomer of formoterol, is a selective, long-acting beta-2 adrenergic receptor agonist indicated for the long-term, twice-daily maintenance treatment of bronchoconstriction in patients with COPD (see Long-Acting Beta-Agonist TCR and Executive Summary). Advair® Diskus 250/50mcg is also approved for the maintenance treatment of airflow obstruction and reducing exacerbations in patients with



COPD including chronic bronchitis and emphysema (see Long Acting Beta-Agonist/Glucocorticoid TCR and Executive Summary).

The side effects of anticholinergics are generally mild. Dry mouth is the most commonly reported side effect. Of note, the labeling for Spiriva® HandiHaler® has recently been updated to include the following post-marketing adverse events: dysphagia, intestinal obstruction, intraocular pressure increase, oral candidiasis, immediate hypersensitivity reactions including angioedema (swelling of the lips, tongue, or throat), itching, and rash. Ipratropium solution for nebulization is available generically. Other products, ipratropium inhaler, tiotropium, and ipratropium and albuterol combination products are available as brand name products only. Boehringer Ingelheim has recently discontinued Atrovent® and will continue to manufacture Atrovent® HFA.

| Generic Name          | Trade Name                     | Manufacturer                     | Generic                               |
|-----------------------|--------------------------------|----------------------------------|---------------------------------------|
| Ipratropium           | Atrovent®,<br>Atrovent®<br>HFA | Boehringer<br>Ingelheim, Various | Y (nebulizer solution)<br>N (inhaler) |
| Ipratropium/Albuterol | Combivent®,<br>Duoneb®         | Boehringer<br>Ingelheim, Dey LP  | N<br>Y (nebulizer solution)           |
| Tiotropium            | Spiriva®,<br>HandiHaler®       | Boehringer<br>Ingelheim/Pfizer   | N                                     |

**Summary:**

For patients with persistent COPD symptoms, maintenance treatments are necessary. In general, long-acting anticholinergics seem to be more effective than short-acting anticholinergics, and combination products seem to be more effective than single agents in the improvement of short-term indicators (eg, FEV1). However, data do not demonstrate the advantage of these agents on long-term outcomes (e.g., death, hospitalization).