Therapeutic Class Overview
Inhaled Anticholinergics

Therapeutic Class Overview/Summary:
The inhaled anticholinergics are a class of bronchodilators primarily used in the management of chronic obstructive pulmonary disease (COPD), a condition characterized by progressive airflow restrictions that are not fully reversible.[1-3] Symptoms associated with COPD typically include dyspnea, cough, sputum production, wheezing and chest tightness. Specifically, inhaled anticholinergics work via the inhibition of acetylcholine at parasympathetic sites in bronchial smooth muscle causing bronchodilation. Meaningful increases in lung function can be achieved with the use of inhaled anticholinergics in patients with COPD.[1-3] The available single-entity inhaled anticholinergics include aclidinium (Tudorza® Pressair), glycopyrrolate (Seebri Neohaler®), ipratropium (Atrovent®, Atrovent® HFA), tiotropium (Spiriva®, Spiriva Respimat®) and umeclidinium (Incruse Ellipta®) with the combination products including glycopyrrolate/indacaterol (Utibron Neohaler®), umeclidinium/vilanterol (Anoro Ellipta®), tiotropium/olodaterol (Stiolto Respimat®) and ipratropium/albuterol, formulated as either an inhaler (Combivent Respimat®) or nebulizer solution (DuoNeb).[4-15] Ipratropium, a short-acting bronchodilator, has a duration of action of six to eight hours and requires administration four times daily. Aclidinium, glycopyrrolate, tiotropium and umeclidinium are considered long-acting bronchodilators. Aclidinium is dosed twice daily, while glycopyrrolate, tiotropium and umeclidinium are administered once daily. Ipratropium is available as a metered dose aerosol inhaler for oral inhalation as well as a solution for nebulization. Aclidinium, glycopyrrolate, tiotropium and umeclidinium are available as dry powder inhalers for oral inhalation, with tiotropium also formulated as an inhalation aerosol.[4-15]

Aclidinium, glycopyrrolate, ipratropium and tiotropium, are Food and Drug Administration (FDA)-approved for the maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. Tiotropium is the only inhaled anticholinergic that is FDA-approved for reducing exacerbations associated with COPD. Additionally, tiotropium soft mist inhaler (Spiriva Respimat®) has been approved for the chronic management of asthma and updated guidelines recommend its use as add-on thereapy.[9,16] Ipratropium/albuterol is indicated for the treatment of bronchospasms associated with COPD in patients who require more than one bronchodilator. Glycopyrrolate/indacaterol, umeclidinium, umeclidinium/vilanterol and tiotropium/olodaterol are FDA-approved for the maintenance treatment of airflow obstruction in patients with COPD.[4-15]

Table 1. Current Medications Available in the Therapeutic Class[4-15,17]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Aclidinium (Tudorza® Pressair)	Bronchospasm associated with COPD, maintenance treatment†	Powder for inhalation: 400 µg	-
Glycopyrrolate (Seebri Neohaler®)	Airflow obstruction in patients with COPD, maintenance treatment†	Powder for inhalation: 15.6 µg	-
Ipratropium* (Atrovent HFA®)	Bronchospasm associated with COPD, maintenance treatment	Aerosol for oral inhalation (Atrovent HFA®): 17 µg Solution for nebulization: 500 µg (0.02%)	✔
Tiotropium (Spiriva®, Spiriva	Asthma, maintenance	Aerosol for inhalation	-

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Respimat®)	treatment (aerosol for inhalation); Bronchospasm associated with COPD, maintenance treatment†, reduce exacerbations in patients with COPD	(Spiriva Respimat®): 1.25 µg/actuation 2.5 µg/actuation Powder for inhalation (Spiriva HandiHaler®): 18 µg	
Umeclidinium (Incruse Ellipta®)	Airflow obstruction in patients with COPD, maintenance treatment*	Powder for inhalation: 62.5 µg	-
Combination Products			
Glycopyrrolate/indacaterol (Utibron Neohaler®)	Airflow obstruction in patients with COPD, maintenance treatment†	Powder for inhalation: 15.6 µg/27.5 µg	-
Ipratropium/albuterol* (Combivent Respimat®)	Bronchospasm associated with COPD in patients requiring more than one bronchodilator	Inhalation spray (Combivent Respimat®): 20/100 µg‡ Solution for nebulization (DuoNeb®): 0.5/3.0 mg	✔
Tiotropium/olodaterol (Stiolto Respimat®)	Airflow obstruction in patients with COPD, maintenance treatment†	Inhalation Spray 5/5 µg	-
Umeclidinium/vilanterol (Anoro Ellipta®)	Airflow obstruction in patients with COPD, maintenance treatment†	Powder for inhalation: 62.5/25 µg	-

*Generic available in at least one dosage form or strength.
†Long-term maintenance treatment.
‡Delivering 18 µg of ipratropium and 103 µg of albuterol (90 µg albuterol base).

Evidence-based Medicine

- In general, the inhaled anticholinergics have demonstrated to improve lung function and/or exercise tolerance in patients with chronic obstructive pulmonary disease (COPD).[18-80] Few head-to-head trials have noted significant differences in improvements in lung function favoring tiotropium over ipratropium.[20,43,44] A meta-analysis evaluating tiotropium added to combination inhaled corticosteroid (ICS)/long acting β-agonist (LABA) therapy compared to ICS/LABA alone for the treatment of asthma did not demonstrate a significant difference between the groups in the primary endpoints of exacerbations requiring oral corticosteroids, quality of life or serious adverse events.[81]
- The efficacy of glycopyrrolate is based primarily on the dose-ranging trials in 471 subjects with COPD and two placebo-controlled confirmatory trials in 867 subjects with COPD. The primary efficacy endpoint from the two placebo-controlled confirmatory trials, GEM1 and GEM2, was the change from baseline in FEV_1 $AUC_{0 \text{ to } 12 \text{ h}}$ following the morning dose at day 85 compared with placebo. In both trials, the glycopyrrolate group demonstrated a larger increase in mean change from baseline in FEV_1 $AUC_{0 \text{ to } 12 \text{ h}}$ compared to placebo.
    - In GEM1, the change from baseline least squares (LS) mean was 0.125 L in the glycopyrrolate group compared to -0.014 L in the placebo group (Treatment difference LS Mean, 0.139 L; 95% CI, 0.095 to 0.184; P values not reported).

    - For GEM2, the change from baseline LS mean was 0.115 L in the glycopyrrolate group compared to -0.008 L in the placebo group (Treatment difference LS Mean, 0.123 L; 95% CI, 0.081 to 0.165; P values not reported).[5,77,78]
- The efficacy of indacaterol/glycopyrrolate was based primarily on the results of two 12-week efficacy studies (FLIGHT1 & 2).[12,79] Both were identical, multicenter, randomized, double-blinded, placebo- and active-controlled, and parallel-group trials in subjects with COPD. A total of 2,038 individuals were randomized to indacaterol/glycopyrrolate 27.5 µg/15.6 µg twice-daily (BID), indacaterol 27.5 µg BID, glycopyrrolate 15.6 mcg BID, or placebo BID. The primary endpoint was the change from baseline in FEV_1 AUC_{0-12h} following the morning dose at Day 85 compared with placebo, glycopyrrolate 15.6 µg BID, and indacaterol 27.5 µg BID.
    - In both trials, Utibron Neohaler® (indacaterol/glycopyrrolate) demonstrated a larger increase in mean change from baseline in FEV_1 AUC_{0-12h} compared to placebo, indacaterol 27.5 µg BID, and glycopyrrolate 15.6 µg BID (treatment difference: 103 mL and 88 mL vs indacaterol and glycopyrrolate, respectively, P<0.001). In addition, both indacaterol and glycopyrrolate monotherapies had a statistically greater response than placebo at week 12 in terms of FEV_1 AUC_{0-12h} (treatment difference: 143 mL and 158 mL, respectively, P<0.001).[79]

Key Points within the Medication Class

- According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines:[1]
    - Inhaled bronchodilators are preferred for the management of COPD. Regular use of long-acting β2-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.
    - The GOLD guidelines emphasize that the use of long-acting bronchodilators is more effective and convenient than the use of short-acting bronchodilators.
- According to the National Institute for Clinical Excellence (NICE):[2]
    - Short-acting bronchodilators should be the initial empiric treatment for the relief of breathlessness and exercise limitation while long-acting bronchodilators should be used in patients who remain symptomatic with use of short-acting agents.
    - Once-daily, long-acting anticholinergic agents are preferred compared to four-times-daily short-acting anticholinergics in patients with stable COPD who remain symptomatic despite use of short-acting agents and in whom the decision has been made to begin regular maintenance therapy with an anticholinergic agent.
- According to the Global Initiative for Asthma (GINA), tiotropium (Spiriva Respimat®) is an option for add-on therapy in patients 12 years and older in uncontrolled asthma at both steps 4 and 5 in the treatment algorithm.[16] Other Asthma guidelines have not been updated since tiotropium has received this expanded indication.[82]
- Other Key Facts:
    - Ipratropium and ipratropium/albuterol solutions for nebulization are the only inhaled anticholinergic products that are currently available generically.

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