Aerosolized Agents - Metered-Dose Inhalers (MDIs): Anticholinergic Drugs

Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with [*].

1.* Dosage

Adults

Ipratropium (Atrovent®), a short-acting, inhalational anticholinergic agent, is FDA-approved to manage bronchospasm associated with chronic bronchitis and emphysema, collectively known as chronic obstructive pulmonary disease (COPD). Ipratropium is considered a second-line agent in the treatment of asthma as the bronchodilatory effects seen with ipratropium are less than those seen with beta-adrenergic drugs. While not FDA approved, the Expert Panel 3 guidelines from the National Heart Lung and Blood Institute document benefit when multiple ipratropium doses are administered adjunctively with beta2-agonists in the emergency department to manage more severe acute asthma exacerbations, and the Global Initiative for Asthma (GINA) guidelines state that ipratropium may be considered an alternative bronchodilator in patients who experience adverse effects to short-acting beta2-agonists (e.g., tachycardia, arrhythmia, tremor). Ipratropium is available as a metered-dose, inhalation aerosol solution and is FDA-approved for use in adult COPD patients receiving an aerosol bronchodilator who continue to have bronchospasm and require a second bronchodilator.

Tiotropium (Spiriva®) is a long-acting, inhalational anticholinergic agent FDA-approved for long-term use in managing bronchospasm associated with COPD, and reducing COPD exacerbations. Tiotropium is available as a dry inhalation powder in capsule form for oral inhalation through an inhalation device. Due to the compound’s extended duration of action, tiotropium is approved for only once daily administration.

Aclidinium (Tudorza®) has recently been FDA-approved as long-term maintenance therapy for bronchospasm associated with COPD. Aclidinium is available as a breath-actuated dry powder inhaler, and is dosed twice daily.

Ipratropium is also available in combination with albuterol as Combivent® Respimat®, which is FDA-approved for use in adult COPD patients receiving an aerosol bronchodilator who continue to have bronchospasm and require a second bronchodilator. This propellant-free product provides a slow-moving mist to supply the active ingredients and has replaced the metered-dose inhaler which used chlorofluorocarbons to deliver medication (i.e., Combivent®). Combivent® Respimat® requires only one actuation per dose compared to the older Combivent® product, which required two actuations per dose.

A new combination therapy, umeclidinium (inhaled anticholinergic) plus vilanterol (long-acting beta-2 agonist, marketed as Anoro™ Ellipta™, has recently been FDA-approved for use in adults with COPD as maintenance therapy. This product is the first dual therapy bronchodilator available for once daily use.

Recommended doses for anticholinergic MDI monotherapy and combination products are summarized in Table 1. Dosages exceeding the approved recommendations will be reviewed.
<table>
<thead>
<tr>
<th>DRUG</th>
<th>MAXIMUM DAILY DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>aclidinium (Tudorza™ Pressair™) dry powder inhaler (400 mcg/actuation)</td>
<td>2 inhalations/day (total dose = 800 mcg)</td>
</tr>
<tr>
<td>ipratropium bromide HFA (Atrovent® HFA) aerosol (17 mcg/actuation)</td>
<td>12 actuations/day (total dose = 204 mcg)</td>
</tr>
<tr>
<td>tiotropium (Spiriva® HandiHaler®) aerosol (18 mcg/actuation)</td>
<td>2 inhalations of powder contents of one capsule daily (total dose = 18 mcg)</td>
</tr>
</tbody>
</table>

**Combination Therapy**

| ipratropium/albuterol aerosol solution (Combivent® Respimat®) [20 mcg ipratropium/100 mcg albuterol base per actuation] | 6 actuations/day (total dose = 120 mcg ipratropium/600 mcg albuterol base) |
| umclidinium/vilanterol inhalation powder (Anoro™ Ellipta™) [62.5 mcg/25 mcg per actuation] | 1 actuation/day [total dose = 62.5 mcg/25 mcg] |

**Pediatrics**

Safety and efficacy of inhaled aclidinium, ipratropium and tiotropium in children have not been established, as COPD does not usually develop in the pediatric population.

2. **Duration of Therapy**

Inhalational anticholinergic agents are suitable for chronic administration as side effects are minimal and drug effectiveness is maintained over years of regular, continuous use. Since inhalation anticholinergics are indicated in the management of chronic, lifelong diseases, there is no basis for limiting the duration of therapy. However, days supply for each MDI anticholinergic canister is limited based on the number of inhalations per canister as well as the maximum recommended dose per day. Days supply for inhalational anticholinergic therapy is summarized in Table 2, based on the maximum recommended dose listed in Table 1 and the number of actuations per canister or number of capsules per blister card listed in Table 2. Excessive use may be identified based on refill frequency. Inappropriate supply of inhaled anticholinergic agents will be monitored by reviewing excessive refills.
### TABLE 2
Days Supply for Anticholinergic MDI Products

<table>
<thead>
<tr>
<th>DRUG</th>
<th># OF ACTUATIONS PER CANISTER</th>
<th>DAYS SUPPLY (based on maximum dose per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aclidinium</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td>ipratropium bromide HFA (12.9 g inhaler)</td>
<td>200</td>
<td>~16-17</td>
</tr>
<tr>
<td>tiotropium (5 capsules, 30 capsules, 90 capsules)</td>
<td>5 to 90 (based on capsule number prescribed)</td>
<td>5 to 90 (based on number of capsules prescribed)</td>
</tr>
<tr>
<td><strong>Combination Therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ipratropium/albuterol spray (4 g cartridge)</td>
<td>120</td>
<td>20</td>
</tr>
<tr>
<td>umeclidinium/ vilanterol powder 30 blisters per ingredient – 60 blisters total</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

3.* **Duplicative Therapy**

Concurrent administration of inhaled anticholinergics has not been evaluated in controlled studies and may not offer additional clinical benefit, but may increase anticholinergic adverse effects. Combined administration of multiple inhaled anticholinergics is not recommended and will be reviewed.

Although inhaled anticholinergic systemic absorption is minimal, adjunctive administration with other anticholinergic medications has the potential to amplify anticholinergic pharmacologic and adverse effects. Combined therapy with inhaled anticholinergics and other anticholinergic dosage forms should be considered cautiously.

4.* **Drug-Drug Interactions**

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions.

Drug interactions considered clinically relevant for inhaled anticholinergics with beta agonists are summarized in Table 3. Only those drug-drug interactions classified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed:
Table 3
Drug-Drug Interactions with Inhaled Combination Anticholinergics

<table>
<thead>
<tr>
<th>TARGET DRUG</th>
<th>INTERACTING DRUG</th>
<th>INTERACTION</th>
<th>RECOMMENDATIONS</th>
<th>CLINICAL SIGNIFICANCE*</th>
</tr>
</thead>
</table>
| ipratropium/albuterol | MAOIs (including linezolid) | concurrent administration of MAOIs with beta agonists may increase risk of development of tachycardia, hypomania, or agitation due to potentiation of effects on vascular system | administer combination cautiously or within 2 weeks of MAOI discontinuation; observe patients for adverse effects | major (DrugReax)  
1-severe (CP) |
| ipratropium/albuterol | TCAs^              | concurrent administration of TCAs with beta agonists may potentiate effects on cardiovascular system and increase risk of adverse events | cautiously administer TCAs and beta agonists together, including within 2 weeks of TCA discontinuation; monitor patients and observe for changes in blood pressure, heart rate and ECG | moderate (DrugReax)  
moderate (CP) |
| ipratropium/albuterol | beta blockers      | concurrent administration may decrease effectiveness of beta-adrenergic blocker or beta-2 agonists like albuterol | combination not recommended in asthma/COPD patients; if adjunctive therapy necessary, utilize cardioselective beta blocker (e.g., atenolol, bisoprolol) | major (DrugReax)  
2-major (CP) |
| ipratropium/albuterol | diuretics          | potential for worsening of diuretic associated hypokalemia and/or ECG changes with beta-agonist concurrent administration, especially with high beta-agonist doses | administer combination cautiously; monitoring potassium levels may be necessary | 3-moderate (CP) |

*MAOIs = monoamine oxidase inhibitors  
^CP = Clinical Pharmacology  
^TCAs = tricyclic antidepressants
REFERENCES


Prepared by: Drug Information Service, the University of Texas Health Science Center at San Antonio, and the College of Pharmacy, The University of Texas at Austin.

File: vdp_crt_aamdia