Texas Vendor Drug Program

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

Publication History

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Notes: All criteria may be applied retrospectively. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

Medications listed in the tables and non-FDA approved indications included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

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1 Dosage

1.1 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). Additionally, ipratropium may be administered in conjunction with short-acting beta agonists, corticosteroids, or oxygen in patients with acute, life-threatening asthma exacerbations awaiting transfer to an acute care center. 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, as well as maintenance therapy for asthma. GINA guidelines state that tiotropium is now recommended as Step 4 and 5 add-on therapy in adult asthma patients with a history of exacerbations. Tiotropium is available as a dry inhalation powder in capsule form or aerosol solution for oral inhalation. Due to the compound's extended duration of action, tiotropium is approved for only once daily administration.

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

Glycopyrrolate inhalation powder (Seebri™ Neohaler®) has recently been FDA-approved as maintenance therapy for airflow obstruction in adult patients with COPD.

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.

Combination therapy including umeclidinium (inhaled anticholinergic) plus the long-acting beta-2 agonist (LABA), vilanterol, marketed as Anoro™ Ellipta™, has 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. Three additional anticholinergic/LABA combination products, tiotropium/olodaterol (Stiolto® Respimat®), indacaterol/glycopyrrolate (Utibron™ Neohaler®), and glycopyrrolate/formoterol (Bevespi Aerosphere™) have also gained recent FDA approval for COPD maintenance therapy.

Triple therapy with fluticasone (inhaled corticosteroid), umeclidinium (inhaled anticholinergic), and vilanterol (inhaled LABA), marketed as Trelegy® Ellipta®, is the most recent inhaled anticholinergic combination therapy FDA-approved for use to manage COPD in adults who continue to have bronchospasm while treated with a bronchodilator and require a second bronchodilator.

Recommended doses for anticholinergic MDI monotherapy and combination products are summarized in Tables 1 and 2, respectively. Dosages exceeding the approved recommendations will be reviewed.

Table 1. Maximum Recommended Adult Anticholinergic Metered-Dose Inhaler Daily Dose - Monotherapy

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
chronic obstructive pulmonary disease (COPD)	aclidinium (Tudorza® Pressair®)	dry powder inhaler (400 mcg/actuation)	2 actuations/day (total dose = 800 mcg)
COPD	glycopyrrolate (Seebri™ Neohaler®)	inhalation capsule (15.6 mcg/capsule)	2 actuations/day in divided doses (total dose = 31.2 mcg/day)
COPD	ipratropium bromide HFA (Atrovent® HFA)	aerosol (17 mcg/actuation)	12 actuations/day in divided doses (total dose = 204 mcg)
COPD	tiotropium (Spiriva® HandiHaler®)	inhalation capsule (18 mcg/capsule)	2 inhalations of one capsule powder contents once daily (total dose = 18 mcg)
asthma	tiotropium (Spiriva® Respimat®)	inhalation cartridge (1.25 mcg or 2.5 mcg/ actuation)	2 inhalations of 1.25 mcg/actuation once daily (total dose = 2.5 mcg)
COPD	tiotropium		2 inhalations of 2.5 mcg/actuation once daily (total dose = 5 mcg)
COPD	umeclidinium (Incruse® Ellipta®)	dry powder inhaler (62.5 mcg/actuation)	1 actuation/day (total dose = 62.5 mcg)

Table 2. Maximum Recommended Adult Anticholinergic Metered-Dose Inhaler Daily Dose – Combination Therapy

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
COPD	fluticasone/ umeclidinium/ vilanterol (Trelegy® Ellipta®)	dry powder breath activated (100 mcg/ 62.5 mcg/ 25 mcg/ actuation)	1 inhalation/day (total dose = 100 mcg/62.5 mcg/ 25 mcg)
COPD	glycopyrrolate/ formoterol (Bevespi Aerosphere™)	aerosol (9 mcg/4.8 mcg/actuation)	4 actuations/day in two divided doses (total dose = 36 mcg/19.2 mcg)

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
COPD	Indacaterol/ glycopyrrolate (Utibron™ Neohaler®)	inhalation capsule (27.5 mcg indacaterol/15.6 mcg glycopyrrolate/ capsule)	2 capsules/day in divided doses (1 capsule inhaled twice daily); total dose = 55 mcg/31.2 mcg/day
COPD	ipratropium/ albuterol (Combivent® Respimat®)	aerosol solution (20 mcg ipratropium/100 mcg albuterol base/actuation)	6 actuations/day in divided doses (no more than 6 inhalations/day) (total dose = 120 mcg ipratropium/600 mcg albuterol base)
COPD	tiotropium/ olodaterol (Stiolto® Respimat®)	aerosol solution (2.5 mcg/2.5 mcg/ actuation)	2 inhalations once daily (total dose = 5 mcg/5 mcg)
COPD	umeclidinium/ vilanterol (Anoro® Ellipta®)	inhalation powder (62.5 mcg/25 mcg/actuation)	1 actuation/day (total dose = 62.5 mcg/25 mcg)

1.2 Pediatrics

Tiotropium is FDA-approved for asthma maintenance therapy in pediatric patients 6-17 years of age. Safety and efficacy of inhaled aclidinium, ipratropium, umeclidinium, and glycopyrrolate in children have not been established, as COPD does not usually develop in the pediatric population. Maximum recommended inhaled anticholinergic pediatric dosages are summarized in Table 3. Dosages exceeding these recommendations will be reviewed.

Table 3. Maximum Recommended Anticholinergic Metered-Dose Inhaler Pediatric Daily Dose

Treatment Indication	Drug Name	Dosage Form / Strength	Patient Age / Maximum Recommended Dosage
asthma	tiotropium (Spiriva® Respimat®)	inhalation cartridge (1.25 mcg/ actuation)	6-17 years of age: 2 inhalations of 1.25 mcg/ actuation once daily (total dose = 2.5 mcg)

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 Tables 4 and 5, based on the maximum recommended dose and the number of actuations per canister or number of capsules per blister card listed in Tables 1-3. Excessive use may be identified based on refill frequency. Inappropriate supply of inhaled anticholinergic agents will be monitored by reviewing excessive refills.

Table 4. Days Supply for Anticholinergic Metered-Dose Inhaler Products - Monotherapy

Drug	# of Actuations Per Canister	Days Supply (based on maximum dose per day)
aclidinium	60	30
glycopyrrolate inhalation capsule	60 capsules per box	30
ipratropium bromide HFA (12.9 g inhaler)	200	~16-17
tiotropium inhalation capsules (5 capsules, 30 capsules, 90 capsules)	5 to 90 (based on capsule number prescribed)	5 to 90 (based on number of capsules prescribed)
tiotropium inhalation spray 1.25 mg/actuation	28 60	14 30
tiotropium inhalation spray 2.5 mcg/actuation	28 60	14 30
umeclidinium inhalation powder box of 7 foil blister powder strips box of 30 foil blister powder strips	 7 30	 7 30

Table 5. Days Supply for Anticholinergic Metered-Dose Inhaler Products – Combination Therapy

Drug	# of Actuations Per Canister	Days Supply (based on maximum dose per day)
fluticasone/ umeclidinium/ vilanterol inhalation powder 14 inhalations (*2 strips: one contains fluticasone, the other contains combination of umeclidinium and vilanterol; combination of ingredients from both strips = one dose)	14	14
30 inhalations*	30	30
glycopyrrolate/formoterol aerosol inhalation (10.7 g inhaler)	120	30
ipratropium/albuterol spray (4 g cartridge)	120	20

Drug	# of Actuations Per Canister	Days Supply (based on maximum dose per day)
tiotropium/olodaterol spray (4 g cartridge)	60	30
umeclidinium/ vilanterol powder 7 blisters per ingredient (14 blisters total) or 30 blisters per ingredient (60 blisters total)	 7 30	 7 30

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 6. 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 6. Drug-Drug Interactions with Inhaled Combination Anticholinergics

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level
fluticasone/ umeclidinium/ vilanterol	strong CYP3A4 inhibitors (e.g., azole antifungals, erythromycin, clarithromycin, protease inhibitors)	potential for increased steroid concentrations with risk for excessive adrenal suppression and Cushing syndrome development	concurrent administration not advised; if combined administration necessary, give cautiously; monitor patients for signs/ symptoms of corticosteroid excess	fluticasone: major (DrugReax) 2-major (CP)
ipratropium/ albuterol glycopyrrolate/ formoterol, tiotropium/ olodaterol, umeclidinium/ vilanterol	QT interval-prolonging medications (e.g., dofetilide, ziprasidone)	combined administration of beta2-agonists with drugs known to prolong the QT interval may increase arrhythmia risk	administer combination cautiously or avoid combination; monitor closely	contraindicated (DrugReax) 1-severe (CP)
ipratropium/ albuterol, umeclidinium/ vilanterol, glycopyrrolate/ formoterol, tiotropium/ olodaterol	MAOIs* (including linezolid)	concurrent administration of MAOIs with beta2-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, umeclidinium / vilanterol, glycopyrrolate / formoterol, tiotropium / olodaterol	beta blockers	concurrent administration may decrease effectiveness of beta-adrenergic blocker or beta2- 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, umeclidinium / vilanterol, glycopyrrolate / formoterol, tiotropium / olodaterol	diuretics	potential for worsening of diuretic associated hypokalemia and/or ECG changes with beta-agonis concurrent administration especially with high beta-agonist doses	administer combination cautiously; monitoring potassium levels may be necessary	3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level
steroids	quinolones	increased potential for serious tendonitis, tendon rupture with concurrent therapy	closely monitor patients requiring combination therapy; discontinue quinolone if tendon pain develops	3-moderate (CP)
systemic steroids	bupropion	potential increased seizure risk due to systemic steroid-induced lowering of seizure threshold	utilize only recommended bupropion dosages; initiate bupropion therapy with low doses and titrate slowly when combination therapy warranted; closely monitor patients for seizure development	major (DrugReax)
umeclidinium / vilanterol	strong CYP3A4 inhibitors (e.g., fluconazole, ketoconazole, ritonavir, nefazodone)	adjunctive administration may result in elevated vilanterol serum levels and enhanced pharmacologic and adverse effects, including QT interval prolongation, as vilanterol is a CYP3A4 substrate	administer combination cautiously, and closely monitor patients for adverse cardiovascular/QT interval outcomes	contraindicated (DrugReax) 2-major (CP)

- +CP = Clinical Pharmacology
- *MAOIs = monoamine oxidase inhibitors
- ^TCAs = tricyclic antidepressant

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