Texas Vendor Drug Program

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

Publication History

1. Developed January 1995.
2. Revised **April 2023;** April 2021; March 2019; March 2017; November 2015; March 2014; August 2012; June 2012; October 2010; January 2008; January 2003; January 2002; January 2001; March 2000; January 2000; February 1999; February 1998; February 1997; August 1995.

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).[1-3] 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., **nausea,** tachycardia, arrhythmia, tremor).[4,5] 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. The "2020 Focused Updates to the Asthma Management Guidelines" do not address the use of short acting muscarinic antagonist agents.[6] 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.[1,2,7]

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.[1,2,8,9] GINA guidelines state that tiotropium is recommended as Step 4 and 5 add-on therapy in adults, adolescents, and children 6 years of age or older with asthma and a history of exacerbations.[5] 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®), is 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.[10] Umeclidinium (Incruse Ellipta®), another breath-actuated inhalation powder, is also approved for long-term COPD maintenance treatment.[11]

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.[12] 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®, is FDA-approved for use in adults with COPD as maintenance therapy.[13] This product is the first dual therapy bronchodilator available for once daily use. Three additional anticholinergic/LABA combination products, tiotropium/olodaterol (Stiolto Respimat®), glycopyrrolate/formoterol (Bevespi Aerosphere®), and aclidinium bromide/ formoterol (Duaklir Pressair®) are also FDA approved for COPD maintenance therapy.[1,2,14-16]

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. In September of 2020 it was approved for the maintenance treatment of asthma in patients 18 years of age and older.[1,2,17]

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[1-3,8-11]

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

Table 2. Maximum Recommended Adult Anticholinergic Metered-Dose Inhaler Daily Dose – Combination Therapy[1,2,12-18]

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
aclidinium bromide/ formoterol fumarate (Duaklir Pressair®)	inhalation powder: 400 mcg/ 12 mcg/ inhalation	COPD	2 actuations/day (1 actuation twice daily); total dose = 800 mcg/24 mcg/day
budesonide, glycopyrrolate, formoterol fumarate (Breztri Aerosphere®)	**aerosol: 160 mcg/ 9 mcg/ 4.8 mcg/ actuation**	**COPD**	**2 inhalations twice daily; total dose = 640 mcg/ 36 mcg/ 19.2 mcg/ day**
fluticasone/ umeclidinium/ vilanterol (Trelegy Ellipta®)	inhalation powder: 100 mcg/ 62.5 mcg/ 25 mcg/ inhalation	asthma	1 inhalation/day (total dose = 100 mcg/62.5 mcg/ 25 mcg)
		COPD	1 inhalation/day (total dose = 100 mcg/62.5 mcg/ 25 mcg)

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
	inhalation powder: 200 mcg/ 62.5 mcg/ 25 mcg/ inhalation	asthma	1 actuation/day; total dose = 200 mcg/62.5 mcg/ 25 mcg/day
glycopyrrolate/ formoterol (Bevespi Aerosphere®)	aerosol: 9 mcg/4.8 mcg/actuation	COPD	4 actuations/day in two divided doses (total dose = 36 mcg/19.2 mcg)
ipratropium/ albuterol (Combivent Respimat®)	aerosol solution: 20 mcg ipratropium/100 mcg albuterol base/actuation	COPD	6 actuations/day in divided doses (no more than 6 inhalations/day) (total dose = 120 mcg ipratropium/600 mcg albuterol base)
tiotropium/ olodaterol (Stiolto Respimat®)	aerosol solution: 2.5 mcg/2.5 mcg/ actuation	COPD	2 inhalations once daily (total dose = 5 mcg/5 mcg)
umeclidinium/ vilanterol (Anoro Ellipta®)	inhalation powder: 62.5 mcg/25 mcg/actuation	COPD	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. 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 [1,2,9]

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)

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[1-3,8-11]

Drug	# of Actuations Per Canister	Days' Supply (based on maximum dose per day)[+]
aclidinium 400 mcg/ actuation	30 60	15 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	60	30
tiotropium inhalation spray 2.5 mcg/actuation	60	30
umeclidinium inhalation powder box of 30 foil blister powder strips	30	30

[+]*calculated based on canister size/blister package size and maximum dose allowed per day*

Table 5. Days' Supply for Anticholinergic Metered-Dose Inhaler Products – Combination Therapy[1,2,12-18]

Drug	# of Actuations Per Canister	Days' Supply (based on maximum dose per day)[+]
aclidinium bromide/ formoterol fumarate inhalation *400 mcg/12 mcg/inhalation*	60	30
budesonide/ glycopyrrolate/ formoterol fumarate ***160 mcg/ 9 mcg/ 4.8 mcg/ actuation***	**120**	**30**
fluticasone furoate/ umeclidinium/ vilanterol inhalation powder *100 mcg/62.5 mcg/25 mcg/actuation* 60 blisters *(one strip contains fluticasone, one strip contains umeclidinium and vilanterol)*	30	30
fluticasone furoate/ umeclidinium/ vilanterol inhalation powder *200 mcg/62.5 mcg/25 mcg/actuation* 60 blisters *(one strip contains fluticasone, one strip contains umeclidinium and vilanterol)*	30	30
glycopyrrolate/formoterol aerosol inhalation 10.7 g inhaler	120	30
ipratropium/albuterol spray (4 g cartridge)	120	20
tiotropium/olodaterol spray (4 g cartridge)	60	30
umeclidinium/vilanterol inhalation powder 60 blisters *(one strip contains umeclidinium, one strip contains vilanterol)*	30	30

[+]*calculated based on canister size/blister package size and maximum dose allowed per day*

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.

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[2]

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	major (CP)
ipratropium/ albuterol, umeclidinium/ vilanterol, glycopyrrolate/ formoterol, tiotropium/ olodaterol	MAOIs* (including linezolid)	concurrent administration of MAOIs with beta$_2$-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	**moderate (CP)**
ipratropium/ albuterol, umeclidinium/ vilanterol,	beta blockers	concurrent administration may	combination not recommended in	**moderate (CP)**

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level
glycopyrrolate/ formoterol, tiotropium/ olodaterol		decrease effectiveness of beta-adrenergic blocker or $beta_2$-agonists like albuterol	asthma/COPD patients; if adjunctive therapy necessary, utilize cardioselective beta blocker (e.g., atenolol, bisoprolol)	
ipratropium/ albuterol, umeclidinium/ vilanterol, glycopyrrolate/ formoterol, tiotropium/ olodaterol	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	moderate (CP)
steroids	quinolones	increased potential for serious tendonitis, tendon rupture with concurrent therapy	closely monitor patients requiring combination therapy; discontinue quinolone if tendon pain develops	
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	**moderate (CP)**
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	**moderate (CP)**

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

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