TEXAS Health and Human Services

Medicaid Drug Use Criteria

Nebulized Bronchodilators

- Developed February 2008.
- Revised March 2020; March 2018; February 2016; June 2014; November 2012; September 2012; October 2010.

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

Short-acting, nebulized beta2-adrenergic bronchodilators are FDA-approved for use in the relief of acute, potentially recurrent bronchospasm in patients with reversible obstructive airway disease. Long-acting, nebulized beta2-adrenergic agents are FDA-approved for use as maintenance therapy in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.[1-15]

Revefenacin (Yupelri®), a new long-acting anticholinergic, is FDA-approved as maintenance therapy for COPD.[12] The anticholinergic, ipratropium, is FDA-approved to manage bronchospasm associated with exacerbations of COPD either as monotherapy or in combination with beta adrenergic agents.[1-5, 9] 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,[16] and the Global Initiative for Asthma (GINA) guidelines state that ipratropium may be considered an alternative bronchodilator for emergency treatment in patients who experience adverse effects to short-acting beta2-agonists (e.g., tachycardia, arrhythmia, tremor).[17] Ipratropium/racemic albuterol combination therapy is FDA-approved for use as second-line therapy in adult COPD patients who continue to experience bronchospasm with an aerosol bronchodilator and require a second bronchodilator.[18] Recommended adult dosages are summarized in Tables 1-5. Patient profiles with dosages exceeding these recommendations will be reviewed.

Table 1. Maximum Recommended Nebulized Bronchodilator Dosages in Adults: Monotherapy: Short-Acting Sympathomimetics[1-8]

Treatment Indication	Drug Name	Dosage Strength	Maximum Recommended Dosage
Bronchospasm in reversible obstructive airway disease (e.g., asthma)	Racemic albuterol (various generics)	2.5 mg/3 mL; (0.083%); 2.5 mg/0.5 mL (0.5%)	2.5 mg four times daily by nebulization* (maximum dose per day: 10 mg)
Bronchospasm in reversible obstructive airway disease (e.g., asthma)	Levalbuterol (Xopenex®, generics)	0.31 mg/3 ml; 0.63 mg/3 ml; 1.25 mg/3 ml; 1.25 mg/0.5 ml	1.25 mg three times daily by nebulization^

- *Manufacturers of racemic albuterol state that more frequent administration or higher doses not recommended; however, in severe asthma exacerbations, the National Asthma Education and Prevention Program Expert Panel (NAEPPEP) recommends racemic albuterol doses of 2.5-5 mg every 20 minutes for 3 doses, then 2.5-10 mg every 1-4 hours as needed, or 10-15 mg/hour by continuous nebulization
- ^For acute asthma exacerbations, NAEPPEP recommends levalbuterol doses of 1.25-2.5 mg every 20 minutes for 3 doses, then 1.25-5 mg every 1-4 hours as needed

Table 2. Maximum Recommended Nebulized Bronchodilator Dosages in Adults: Monotherapy: Short-Acting Anticholinergics[1-5, 9]

Treatment Indication	Drug Name	Dosage Strength	Maximum Recommended Dosage
Chronic obstructive pulmonary disease (COPD)	Ipratropium (various generics)	500 mcg/2.5 ml (0.02%)	500 mcg four times daily, with doses 6 hours apart

Table 3. Maximum Recommended Nebulized Bronchodilator Dosages in Adults: Monotherapy: Long-Acting Sympathomimetics[1-5, 10, 11]

Treatment Indication	Drug Name	Dosage Strength	Maximum Recommended Dosage
Chronic obstructive pulmonary disease (COPD)	Arformoterol (Brovana®)	15 mcg/2 ml	15 mcg twice daily by nebulization
COPD	Formoterol (Perforomist®)	20 mcg/2 ml	20 mcg twice daily by nebulization

Table 4. Maximum Recommended Nebulized Bronchodilator Dosages in Adults: Monotherapy: Long-Acting Anticholinergics[1-5, 12]

Treatment Indication	Drug Name	Dosage Strength	Maximum Recommended Dosage
Chronic obstructive pulmonary disease (COPD) – maintenance therapy	Revefenacin (Yupelri®)	175 mcg/3 ml	175 mcg once daily

Table 5. Maximum Recommended Nebulized Bronchodilator Dosages in Adults: Combination Therapy[1-5, 18]

Treatment Indication	Drug Name	Dosage Strength	Maximum Recommended Dosage
Bronchospasm associated with chronic obstructive pulmonary disease (COPD)	Ipratropium/ racemic albuterol (generic)	0.5 mg/3 mg# per 3 ml	3 ml 6 times per day

- #2.5 mg racemic albuterol base

1.2 Pediatrics

Short-acting beta$_2$-adrenergic bronchodilators are FDA-approved to manage bronchospasm episodes in pediatric patients with reversible obstructive airway disease. Racemic albuterol nebulized solution is FDA-approved to provide bronchospasm relief in children 2 years of age and older with reversible obstructive airway disease. Levalbuterol nebulized solutions are FDA-approved for use in the

management and prevention of acute asthma exacerbations in children 6 years of age and older. Ipratropium is FDA-approved for use in children 12 years of age and older for management of bronchospasm associated with COPD.[1-19] Recommended dosages are summarized in Tables 6 and 7. Patient profiles with dosages exceeding these recommendations will be reviewed.

Table 6. Maximum Recommended Nebulized Bronchodilator Pediatric Dosages: Short-Acting Sympathomimetics[1-8]

Drug Name	Dosage Strength	Maximum Recommended Dosage
Racemic albuterol (generics)	0.63 mg/3 ml (0.021%) or 1.25 mg/3 ml (0.042%)	2-12 years of age: 1.25 mg 4 times daily (5 mg/day)
Racemic albuterol (generics)	2.5 mg/3 ml (0.083%); 2.5 mg/ 0.5 ml (0.5%)	2-17 years of age: 2.5 mg 4 times daily (10 mg/day)
Levalbuterol (Xopenex®, generics)	0.31 mg/3 ml; 0.63 mg/3 ml; 1.25 mg/3 ml; 1.25 mg/0.5 ml	6 years to 11 years of age:# 0.63 mg three times daily (every 6-8 hours) 12 years of age and older:^ 1.25 mg three times daily (every 6-8 hours)

- + Manufacturers state that more frequent administration or higher doses not recommended; however, in severe asthma exacerbations, the National Asthma Education and Prevention Program Expert Panel (NAEPPEP) recommends racemic albuterol doses of 2.5-5 mg every 20 minutes for 3 doses, then 2.5-10 mg every 1-4 hours as needed, or 10-15 mg/hour by continuous nebulization
- # For acute asthma exacerbations in children 6-11 years of age, NAEPPEP recommends levalbuterol doses of 0.075 mg/kg (1.25 mg minimum) every 20 minutes x 3 doses, then 0.075—0.15 mg/kg (5mg max) every 1—4 hours as needed
- ^ For acute asthma exacerbations in children 12 years and older, NAEPPEP recommends levalbuterol doses of 1.25-2.5 mg every 20 minutes for 3 doses, then 1.25-5 mg every 1-4 hours as needed

Table 7. Maximum Recommended Nebulized Bronchodilator Pediatric Dosages: Short-Acting Anticholinergics[1-5, 9]

Drug Name	Dosage Strength	Maximum Recommended Dosage
Ipratropium (various generics)	500 mcg/2.5 ml (0.02%)	Greater than or equal to 12 years of age: 500 mcg 4 times daily, every 6 hours apart

Nebulized long-acting beta2-adrenergic bronchodilators and long-acting anticholinergics as well as combination therapy with ipratropium and racemic albuterol are not indicated for use in pediatric patients as safety and efficacy of these agents in this patient population have not been established.Duration of Therapy [1-26]

Administration of short-acting, nebulized beta$_2$-adrenergic bronchodilators may be repeated indefinitely for acute asthma exacerbations, as asthma is a chronic, lifelong disease. However, administering short-acting, nebulized beta$_2$-adrenergic agents for longer than 48 hours with each exacerbation is indicative of worsening asthma control and is not recommended. Utilization of large quantities of short-acting beta$_2$-adrenergic nebulizer solutions within a 90-day time period is not recommended and will be reviewed.

Ipratropium, long-acting, nebulized beta$_2$-adrenergic bronchodilators, and combination therapy with ipratropium/racemic albuterol are indicated for the management of COPD, a chronic, lifelong disease, and may be continued indefinitely under accepted guidelines.

2 Duplicative Therapy[1-26]

Adjunctive administration of multiple short-acting or long-acting, nebulized beta$_2$-adrenergic bronchodilators does not provide additional clinical benefit and may result in additive adverse effects. Combined administration of multiple nebulized short-acting or long-acting beta$_2$-adrenergic bronchodilators is not recommended and will be reviewed.

Acute asthma exacerbations require treatment with short-acting, beta$_2$-adrenergic agents even though maintenance therapy with a long-acting, beta$_2$-adrenergic agent may be prescribed concomitantly. Patients may receive a long- and short-acting beta$_2$-adrenergic drug concurrently for short time periods to manage acute attacks. Nebulized formoterol or arformoterol used in conjunction with excessive

administration of a short-acting beta$_2$-adrenergic drug (i.e., frequent refill of short-acting beta$_2$-adrenergic agonist within a 30-day time period) is not recommended and will be reviewed.

Concurrent administration of ipratropium nebulized solution monotherapy with ipratropium/racemic albuterol combination therapy does not provide additional clinical benefit and may result in additive adverse effects. Combined administration of ipratropium and ipratropium combination therapy is not recommended and will be reviewed.

3 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. Drug-drug interactions considered clinically relevant for nebulized bronchodilators 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. Nebulized Bronchodilator Drug-Drug Interactions[1-12, 18, 19]

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level
beta$_2$-agonists	MAOIs$^+$ (including linezolid)	concurrent administration of MAOIs with beta$_2$-agonists may increase risk 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)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level
beta$_2$-agonists	TCAs^	concurrent administration of TCAs with beta$_2$-agonists may potentiate effects on cardiovascular system and increase risk of adverse events	cautiously administer TCAs and beta$_2$-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)
beta$_2$-agonists	beta blockers	concurrent administration may decrease effectiveness of beta-adrenergic blocker or beta-2 agonists	combination not recommended in asthma/COPD patients; if adjunctive therapy necessary, utilize cardioselective beta blocker (e.g., atenolol, bisoprolol)	major (DrugReax) 2-major (CP)
beta$_2$-agonists	diuretics	potential for worsening of diuretic-associated hypokalemia and/or ECG changes with beta$_2$-agonist concurrent administration, especially with high beta$_2$-agonist doses	administer combination cautiously; monitor potassium levels as necessary	3-moderate (CP)
beta$_2$-agonists	atomoxetine	concurrent administration may increase risk of cardiovascular adverse effects (e.g., tachycardia, hypertension); interaction may be less likely with inhaled beta$_2$-agonists	monitor patients for increased cardiovascular adverse effects	major (DrugReax) 3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level
beta$_2$-agonists	QTc interval-prolonging medications (e.g., class I, III anti-arrhythmics, tricyclic antidepressants, dolasetron)	concurrent administration may increase risk of cardiotoxicity (e.g., life-threatening arrhythmias, cardiac arrest) as arformoterol and formoterol may cause QTc interval prolongation and, rarely, torsades de pointes	administer combination cautiously	1-severe, 2-major, 3-moderate (CP)
ipratropium, ipratropium/ racemic albuterol	antimuscarinics	concurrent administration may produce additive anticholinergic effects and potential for increased adverse effects	cautiously administer ipratropium with other antimuscarinics; monitor for increased adverse effects	minor (DrugReax) 3-moderate (CP)

- * CP = Clinical Pharmacology
- + MAOIs = monoamine oxidase inhibitors
- ^ TCA = tricyclic antidepressants
- #ECG = electrocardiogram

4 References

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