

Texas Vendor Drug Program

Drug Use Criteria: Aerosolized Agents - Metered-Dose Inhalers: Beta₂ Agonists (short-acting)

Publication History

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Notes: 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.

Prepared by:

- Drug Information Service, UT Health San Antonio.
- The College of Pharmacy, The University of Texas at Austin



TEXAS
Health and Human
Services

*Medical and
Social Services*

1 Dosage

1.1 Adults

Beta₂-adrenergic drugs, used routinely in asthma management, can be identified as long-acting or short-acting agents. Both short- and long-acting compounds can be used to prevent bronchospasm. However, short-acting compounds are the drugs of choice for acute bronchospasm as these agents act within minutes to cause bronchodilation. Drugs in this category include albuterol and levalbuterol. For acute bronchospasm, treatment is initiated with a short-acting beta₂-adrenergic agent either as a metered-dose inhaler or a nebulizer solution. Treatment of acute attacks is usually for a finite time based on the intensity of the attack and/or the need for medical attention either through emergency department management or hospitalization. Usage is individualized based on patient characteristics.

Although not FDA-approved, beta₂-selective adrenergic agents such as albuterol are effective in chronic obstructive pulmonary disease (COPD) maintenance therapy to improve lung function and mucociliary clearance. Albuterol has become one of the mainstays of therapy for acute exacerbations of chronic obstructive pulmonary disease COPD due to rapid onset of action as well as efficacy in producing bronchodilation.

For preventive/ maintenance therapy, albuterol is FDA-approved as preventive therapy for exercise-induced asthma. To manage exercise-induced bronchospasm (EIB) in adults, two 90 mcg albuterol inhalations are administered at least 15 to 30 minutes before exercise on an as-needed basis.

Ipratropium/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.

Maximum recommended daily doses for available inhalational beta₂-adrenergic agents as monotherapy and combination therapy are summarized in Table 1 and 2. Prescribed dosages exceeding these criteria will be reviewed.

Table 1: Maximum Adult Daily Dose for Inhalational Beta2-Adrenergic Agents (short-acting) - Monotherapy

Treatment Indication	Drug Name	Dosage Form/ Strength	Maximum Recommended Dosage
Asthma	albuterol aerosol solution (Proventil® HFA, Ventolin HFA®, ProAir® HFA, generic)	aerosol (90 mcg albuterol base/actuation)	12 actuations/day (total dose = 1080 mcg albuterol base)
Asthma	albuterol inhalation powder (ProAir® RespiClick)	(90 mcg albuterol base/actuation)	12 actuations/day (total dose = 1080 mcg albuterol base)
Asthma	levalbuterol (Xopenex HFA®, generic)	aerosol (45 mcg levalbuterol free base/actuation)	12 actuations/day (total dose = 540 mcg levalbuterol free base)

Table 2: Maximum Adult Daily Dose for Inhalational Beta₂-Adrenergic Agents (short-acting) – Combination Therapy

Treatment Indication	Drug Name	Dosage Form/ Strength	Maximum Recommended Dosage
chronic obstructive pulmonary disease	ipratropium/ albuterol (Combivent® Respimat®)	inhalation spray (20 mcg ipratropium/ 100 mcg albuterol/ actuation)	6 actuations/ day (total dose = 120 mcg ipratropium/ 600 mcg albuterol)

1.2 Pediatrics

Proventil® HFA, Ventolin® HFA and ProAir® HFA are FDA-approved for use in children 4 years of age and older for prevention/treatment of bronchospasm and prevention of exercise-induced bronchospasm. Recently, ProAir® RespiClick was also FDA-approved for use in pediatric patients 4 years of age and older to treat or prevent bronchospasm as well as prevent exercise-induced bronchospasm. Levalbuterol is FDA-approved for use in children 4 years of age and older for prevention/treatment of bronchospasm.

To prevent EIB in pediatric patients 4 years of age and older, two albuterol 90 mcg inhalations are administered at least 15 to 30 minutes before exercise on an as-needed basis.

Combination therapy with ipratropium and albuterol is not FDA-approved for use in pediatric patients as safety and efficacy in this patient population have not been established.

Pediatric dosages for short-acting beta₂-agonists used to manage acute asthma exacerbations are summarized in Table 3. Dosages exceeding these recommendations will be reviewed.

Table 3: Maximum Recommended Pediatric Daily Dose for Inhalational Beta₂-Adrenergic Agents (short-acting) - Monotherapy

Treatment Indication	Drug Name	Dosage Form/ Strength	Maximum Recommended Dosage
Asthma	albuterol (Proventil® HFA, Ventolin HFA®, ProAir® HFA)	aerosol solution (90 mcg albuterol base/actuation)	Greater than and equal to 4 years of age: 12 actuations/day (total dose = 1080 mcg albuterol base)
Asthma	Albuterol (ProAir® RespiClick)	inhalation powder (90 mcg albuterol base/actuation)	Greater than and equal to 4 years of age: 12 actuations/day (total dose = 1080 mcg albuterol base)
Asthma	levalbuterol (Xopenex HFA®)	aerosol (45 mcg levalbuterol free base/actuation)	Greater than and equal to 4 years of age: 12 actuations/day (total dose = 540 mcg levalbuterol free base)

2 Duration of Therapy

Metered-dose inhalers are designed to deliver a set number of inhalations based on the canister size as well as the medication prescribed. Days supply for inhalational beta₂-adrenergic agents is summarized in Table 4 and 5, based on the maximum recommended doses listed in Tables 1-3, and the number of actuations per canister or number of capsules per blister card listed in Tables 4 and 5. Excessive use may be identified based on refill frequency. Inappropriate supply of short-acting beta₂-adrenergic agents will be monitored by reviewing excessive refills.

Table 4. Days Supply for Available Short-Acting Beta₂-Adrenergic Agent Metered-Dose Inhalers (Adult and Pediatric Patients) - Monotherapy

Drug	# of Actuations Per Canister	Days Supply (based on maximum dose per day)+
Albuterol (ProAir® HFA) 8.5 g canister	200	~ 16 days
Albuterol (ProAir® RespiClick) 0.65 g inhaler	200	~16 days
Albuterol (Proventil® HFA) 6.7 g canister	200	~ 16 days
Albuterol (Ventolin HFA®) 8 g canister 18 g canister	60 200	5 days ~ 16 days
Levalbuterol (Xopenex HFA®) 8.4 g canister 15 g canister	80 200	~ 6 days ~ 16 days

- + calculated based on canister size and maximum dose allowed per day (summarized in Tables 1 and 2)

Table 5. Days Supply for Available Short-Acting Beta₂-Adrenergic Agent Metered-Dose Inhalers (Adult Patients) – Combination Therapy

Drug	# of Actuations Per Canister	Days Supply (based on maximum dose per day)+
Ipratropium/albuterol (Combivent® Respimat®) (4 g cartridge)	120	20 days

3 Duplicative Therapy

The use of two or more metered-dose inhaler short-acting beta₂-adrenergic compounds concurrently for prevention and control of asthma symptoms is not justified and will be reviewed. Nebulized short-acting beta₂-adrenergic therapy is available for pediatric patients who are too ill or too young to obtain medication from an aerosolized metered-dose device. However, adjunctive administration of a short-acting beta₂-adrenergic agonist metered-dose inhaler with a short-acting beta₂-agonist nebulized bronchodilator is also not recommended and will be reviewed.

Acute asthma exacerbations require treatment with short-acting beta₂-adrenergic agents even though maintenance therapy with a long-acting beta₂-agonist like salmeterol may be prescribed concomitantly. Patients may receive a long- and short-acting beta₂-adrenergic drug concurrently for short time periods to manage acute attacks. Patient profiles containing excessive prescriptions for a short-acting beta₂-adrenergic drug (i.e., frequent refill of short-acting beta₂-adrenergic agonist within a 30-day period) in conjunction with long-acting beta₂-agonists will be reviewed.

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 short-acting beta₂-adrenergic bronchodilators 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. Inhaled Short-Acting Beta₂-Adrenergic Agents Drug-Drug Interactions

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) 2-major (CP)
beta ₂ -agonists	TCA	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) 3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level+
beta2-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)
beta2-agonists	diuretics	potential for worsening of diuretic-associated hypokalemia and/or ECG changes with beta2-agonist concurrent administration, especially with high beta2-agonist doses	administer combination cautiously; monitor potassium levels as necessary	moderate (DrugReax) 3-moderate (CP)
beta2-agonists	atomoxetine	concurrent administration may increase risk of cardiovascular adverse effects (e.g., tachycardia, hypertension); interaction may be less likely with inhaled beta2-agonists	monitor patients for increased cardiovascular adverse effects	major (DrugReax) 3-moderate (CP)
beta2-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	2-major, 3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level+
ipratropium/ albuterol	antimuscarinics	co-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
- COPD = chronic obstructive pulmonary disease
- ECG = electrocardiogram
- MAOIs = monoamine oxidase inhibitors
- TCAs = tricyclic antidepressants

5 References

1. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at micromedexsolutions-com.libproxy.uthscsa.edu/ (cited: March 17, 2019).
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. Available at clinicalpharmacology-ip.com.ezproxy.lib.utexas.edu/. Accessed March 17, 2019.
3. Facts and Comparisons eAnswers [database online]. Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2019; March 17, 2019.
4. AHFS Drug Information 2019. Jackson, WY: Teton Data Systems, Version 8.10.1, 2019. Stat!Ref Electronic Medical Library. Available at: <http://online-statref-com.libproxy.uthscsa.edu/>. Accessed March 17, 2019.
5. National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Full Report 2007. (NIH Publication No. 07-4051). Available at www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed March 17, 2019.
6. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease. 2017 report. Available at goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/. Accessed March 17, 2019.

7. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2018. Available from ginasthma.org. Accessed March 17, 2019.
8. Diaz PT, Knoell DL. Chapter 24. Chronic obstructive pulmonary disease. In: Alldredge BK, Corelli RL, Ernst ME, et al, eds. Koda-Kimble and Young's applied therapeutics: the clinical use of drugs. 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2013:601-18.
9. Self TH, Chrisman CR, Finch CK. Chapter 23. Asthma. In: Alldredge BK, Corelli RL, Ernst ME, et al, eds. Koda-Kimble and Young's applied therapeutics: the clinical use of drugs. 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2013:565-600.
10. Bourdet SV, Williams DM. Chapter 27. Chronic obstructive pulmonary disease (Chapter) In: DiPiro JT, Talbert RL, Yee GC, et al. (eds): Pharmacotherapy: a pathophysiologic approach. 10th edition. New York, McGraw-Hill, 2017. Access Pharmacy Web site. Available at accesspharmacy-mhmedical-com.ezproxy.lib.utexas.edu/index.aspx. Accessed March 17, 2019.
11. Albuterol inhalation aerosol (ProAir® HFA) package insert. Teva Respiratory, February 2019.
12. Albuterol inhalation aerosol (Proventil® HFA) package insert. Merck & Co., Inc., July 2018.
13. Albuterol inhalation aerosol (Ventolin® HFA) package insert. GlaxoSmithKline, March 2018.
14. Levalbuterol inhalation aerosol (Xopenex HFA®) package insert. Sunovion Pharmaceuticals Inc., March 2015.
15. Albuterol inhalation powder (ProAir RespiClick®) package insert. Teva Respiratory, April 2018.
16. Ipratropium/albuterol (Combivent® Respimat® Inhalation Spray) package insert. Boehringer Ingelheim Pharmaceuticals, Inc., June 2016.
17. Ferguson GT, Make B. Management of stable chronic obstructive pulmonary disease. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA. (Accessed March 17, 2019.)
18. Stoller JK. Management of exacerbations of chronic obstructive pulmonary disease. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, (Accessed March 17, 2019.)
19. Blake K. Review of guidelines and the literature in the treatment of acute bronchospasm in asthma. Pharmacotherapy. 2006;26(9 Pt 2):148S-55S.
20. Schreck DM. Asthma pathophysiology and evidence-based treatment of severe exacerbations. Am J Health-Syst Pharm. 2006;63(10 Suppl 3): S5-13.

21. Kelly WH. Risk versus benefit considerations for the β 2-agonists. *Pharmacotherapy*. 2006;26(9Pt2):164S-74S.
22. Bel EH. Clinical practice. Mild asthma. *N Engl J Med*. 2013;369(6):549-57.
23. McCracken JL, Veeranki SP, Ameredes BT, Calhoun WJ. Diagnosis and management of asthma in adults: a review. *JAMA*. 2017;318(3):279-90.