Texas Vendor Drug Program

Drug Use Criteria: Aerosolized Agents - Metered-Dose Inhalers (MDIs): Beta$_2$ Adrenergic Drugs (Short-Acting)

Publication History

1. Developed January 1995.
2. Revised April 2021; March 2019; March 2017; May 2016; February 2016; July 2014; October 2012; October 2010; January 2008; March 2003; March 2002; March 2001; March 2000; May 1999; February 1999; February 1998; March 1997; August 1995.

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 that may be 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

1 Dosage

1.1 Adults

Beta$_2$-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 beta$_2$-adrenergic agent either as a metered-dose inhaler or a nebulizer solution. Treatment of acute attacks is usually for a finite time period 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, beta$_2$-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 beta$_2$-adrenergic agents as monotherapy and combination therapy are summarized in Tables 1 and 2. Prescribed dosages exceeding these criteria will be reviewed.

Table 1. Maximum Adult Daily Dose for Inhalational Beta$_2$-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®, ProAir Digihaler®)	(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 Beta$_2$-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, ProAir® HFA, and ProAir RespiClick® 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

Digihaler® 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 beta$_2$-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 Beta$_2$-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)	*≥ 4 years of age:* 12 actuations/day (total dose = 1080 mcg albuterol base)
asthma	albuterol (ProAir RespiClick®, ProAir Digihaler®)	inhalation powder (90 mcg albuterol base/actuation)	*≥ 4 years of age:* 12 actuations/day (total dose = 1080 mcg albuterol base)
asthma	levalbuterol (Xopenex HFA®)	aerosol (45 mcg levalbuterol free base/actuation)	*≥ 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 beta$_2$-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 beta$_2$-adrenergic agents will be monitored by reviewing excessive refills.

Table 4. Days' Supply for Available Short-Acting Beta$_2$-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 (ProAir Digihaler®) 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 Beta$_2$-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 beta$_2$-adrenergic compounds concurrently for prevention and control of asthma symptoms is not justified and will be reviewed. Nebulized short-acting beta$_2$-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 beta$_2$-adrenergic agonist metered-dose inhaler with a short-acting beta$_2$-agonist nebulized bronchodilator is also 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$_2$-agonist like salmeterol 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. Patient profiles containing excessive prescriptions for a short-acting beta$_2$-adrenergic drug (i.e., frequent refill of short-acting beta$_2$-adrenergic agonist within a 30-day time period) in conjunction with long-acting beta$_2$-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 beta$_2$-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 Beta$_2$-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	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) 3-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	moderate (DrugReax) 3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[+]
$beta_2$-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)
$beta_2$-agonists	QTc interval-prolonging medications (e.g., class I, III anti-arrhythmic, 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)
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: https://www-micromedexsolutions-com.libproxy.uthscsa.edu/ (cited: February 25, 2021).
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2021. Available at: http://clinicalpharmacology-ip.com.ezproxy.lib.utexas.edu/. Accessed February 25, 2021.
3. Facts and Comparisons eAnswers [database online]. Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2021; February 25, 2021.

4. American Society of Health-System Pharmacists. 2021. AHFS Drug Information® - 2021st Ed. Bethesda, MD. American Society of Health-System Pharmacists®. ISBN-10: 1-58528-654-0, ISBN-13: 978-1-58528-654-6. ISSN: 8756-6028. STAT!Ref Online Electronic Medical Library. https://online.statref.com/document/cQfe8yqMRNqgSGqm4Qo8Qj. Accessed *February 25, 2021*.
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: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed February 26, 2021.
6. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease. 2021 report. Available at: https://goldcopd.org/2021-gold-reports/. Accessed February 26, 2021.
7. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2020. Available from: https://ginasthma.org/reports/. Accessed February 26, 2021.
8. Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC). 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. J Allergy Clin Immunol. 2020 Dec;146(6):1217-1270.
9. 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.
10. 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.
11. Bourdet SV, Williams DM. Chapter 44. Chronic obstructive pulmonary disease (Chapter) In: DiPiro JT, Talbert RL, Yee GC, et al. (eds): Pharmacotherapy: a pathophysiologic approach. 11th edition. New York, McGraw-Hill, 2020. Access Pharmacy Website. Available at: https://accesspharmacy-mhmedical-com.ezproxy.lib.utexas.edu/index.aspx. Accessed February 26, 2021.
12. Albuterol inhalation aerosol (ProAir® HFA) package insert. Teva Respiratory, August 2020.
13. Albuterol inhalation aerosol (Proventil® HFA) package insert. Merck & Co., Inc., October 2019.
14. Albuterol inhalation aerosol (Ventolin® HFA) package insert. GlaxoSmithKline, February 2021.
15. Levalbuterol inhalation aerosol (Xopenex HFA®) package insert. Sunovion Pharmaceuticals Inc., June 2020.
16. Albuterol inhalation powder (ProAir RespiClick®) package insert. Teva Respiratory, October 2020.
17. Albuterol inhalation powder (ProAir Digihaler®) package insert. Teva Respiratory, October 2020.
18. Ipratropium/albuterol (Combivent® Respimat® Inhalation Spray) package insert. Boehringer Ingelheim Pharmaceuticals, Inc., October 2020.
19. Ferguson GT, Make B. Management of stable chronic obstructive pulmonary disease. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA. February 2021. (Accessed March 3, 2021.)

20. Stoller JK. Management of exacerbations of chronic obstructive pulmonary disease. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA. February 2021. (Accessed March 3, 2021.)
21. Blake K. Review of guidelines and the literature in the treatment of acute bronchospasm in asthma. Pharmacotherapy. 2006;26(9 Pt 2):148S-55S.
22. Schreck DM. Asthma pathophysiology and evidence-based treatment of severe exacerbations. Am J Health-Syst Pharm. 2006;63(10 Suppl 3):S5-13.
23. Kelly WH. Risk versus benefit considerations for the β2-agonists. Pharmacotherapy. 2006;26(9Pt2):164S-74S.
24. Bel EH. Clinical practice. Mild asthma. N Engl J Med. 2013;369(6):549-57.
25. McCracken JL, Veeranki SP, Ameredes BT, Calhoun WJ. Diagnosis and management of asthma in adults: a review. JAMA. 2017;318(3):279-90.