

Texas Vendor Drug Program

Drug Use Criteria: Aerosolized Agents - Metered-Dose Inhalers (MDIs): Beta₂ Adrenergic Drugs (Long-Acting)

Publication History

1. Developed January 1995.
2. Revised **April 2023**; April 2021; March 2019; March 2017; October 2014; February 2013; October 2012; January 2011; July 2007; March 2003; April 2002; March 2001; March 2000; February 1999; March 1998; March 1997; August 1995.

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.

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1 Dosage

Long-acting, selective beta₂-agonists (LABAs) are FDA-approved for use as adjunctive therapy with long-term asthma control medications, such as inhaled corticosteroids (ICS), in managing reversible obstructive airways disease, including asthma and nocturnal asthma, in patients inadequately controlled with long-term asthma control medications. LABAs are contraindicated for use as monotherapy in asthma management due to an increased risk of asthma-related death as well as increased risks in asthma-related hospitalizations in pediatric and adolescent patients.^{1,2} Serevent Diskus® (salmeterol) is FDA-approved for asthma in adults and children four years of age and older **when used with an ICS**, and it is also FDA-approved for use to acutely prevent exercise-induced bronchospasm (EIB) on an as-needed basis.¹⁻³ LABAs are FDA-approved for use in adults as maintenance therapy for bronchoconstriction associated with chronic obstructive pulmonary disease (COPD), including emphysema and chronic bronchitis. Striverdi Respimat® (olodaterol) is another LABA available without an ICS, and it is FDA-approved for the management of COPD. It does not have an FDA-approval for asthma.^{1,2,4}

LABAs combined with ICS are FDA-approved for use in adults and children as asthma maintenance therapy: Advair® HFA metered aerosol (fluticasone propionate/salmeterol) is FDA-approved for use in patients 12 years of age and older, and Dulera® (mometasone/formoterol) inhalation aerosol is FDA-approved for use in patients 5 years of age and older.^{1,2,5,6} Advair Diskus® (fluticasone propionate/salmeterol) inhalation powder is FDA-approved for use in asthma maintenance in patients 4 years of age and older.^{1,2,7} AirDuo RespiClick® and AirDuo Digihaler® (fluticasone/salmeterol) inhalation powders provide additional dosage strengths, and they have been approved for use in patients with asthma who are 12 years and older.^{1,2,8,9} Symbicort® (budesonide/formoterol) inhalation aerosol and Advair Diskus® (fluticasone propionate/salmeterol) are FDA-approved for use in adults as COPD maintenance therapy.^{1,2,7,10} Symbicort® is also FDA-approved for the management of asthma in adults and children 6 years of age and older. The combination Breo Ellipta® (fluticasone/ vilanterol) is FDA approved for the management of COPD and asthma in patients 18 years of age and older.^{1,2,11}

The Global Initiative for Asthma (GINA) “Global Strategy for Asthma Management and Prevention” guidelines recommend the use of

combination ICS-LABA with budesonide and formoterol as maintenance and rescue therapy for most patients.^{1,2}

Anoro Ellipta® (umeclidinium/vilanterol), Bevespi Aerosphere® (glycopyrrolate/formoterol), and Stiolto Respimat® (tiotropium/olodaterol) are indicated for use in adults as maintenance therapy for COPD but are not FDA-approved for use in asthma.^{1,2,13-15}

Additionally, a triple therapy inhaler containing fluticasone, umeclidinium and vilanterol, Trelegy Ellipta®, is approved for COPD management to treat airway obstruction and reduce exacerbations, and for the maintenance treatment of asthma in patients 18 years of age and older.^{1,2,16}

Duaklir Pressair® (aclidinium bromide/ formoterol) is a long-acting beta agonist and long-acting muscarinic antagonist combination product approved for the management of COPD in adults.^{1,2,17}

1.1 Adults

To manage EIB in adults, one salmeterol 50 mcg inhalation is administered at least 30 minutes before exercise on an as needed basis and should not be repeated for at least 12 hours after administration of the previous dose. Patients receiving twice daily LABA doses chronically should not administer additional LABA doses for EIB management.

Maximum recommended adult daily doses for LABA use as monotherapy in asthma and COPD are summarized in Table 1. Prescribed dosages exceeding these guidelines will be reviewed.

Table 1. LABA Maximum Daily Dosage Recommendations in Adults with Asthma and COPD: Monotherapy¹⁻⁴

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
olodaterol hydrochloride (Striverdi Respimat®)	inhalation aerosol: 2.5 mcg/actuation	COPD	2 actuations once daily; total dose = 5 mcg/day

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
salmeterol (Serevent Diskus®)	inhalation powder: 50 mcg/inhalation	asthma	2 actuations/day in divided doses (1 actuation twice daily); total dose = 100 mcg/day
		COPD	2 actuations/day in divided doses (1 actuation twice daily); total dose = 100 mcg/day

COPD = chronic obstructive pulmonary disease

LABA/ICS combinations are FDA-approved for use in asthma and COPD maintenance therapy. Advair Diskus® 250 mcg/50 mcg is the only fluticasone/salmeterol dose approved for use in adult patients with COPD.^{1,2,7} Symbicort® 80 mcg/4.5 mcg and 160 mcg/4.5 mcg are FDA-approved for use in asthma, while 160 mcg/4.5 mcg is the recommended strength for budesonide/formoterol in COPD.^{1,2,10} Advair HFA®, AirDuo RespiClick®, AirDuo Digihaler®, and Dulera® are FDA-approved for asthma management only.^{1,2,5,6,8,9}

Maximum adult daily dosages for LABA combination therapy are summarized in Table 2. Dosages exceeding these recommendations will be reviewed.

Table 2. LABA Maximum Daily Dosage Recommendations in Adults with Asthma and COPD: Combination Therapy^{1,2,5-11,13-19}

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
aclidinium bromide/ formoterol fumarate (Duaklir Pressair®)	inhalation powder: 400 mcg/12 mcg/ inhalation	chronic obstructive pulmonary disease (COPD)	2 actuations/day (1 actuation twice daily); total dose = 800 mcg/24 mcg/day
budesonide/ formoterol (Symbicort®, generics)	inhalation aerosol: 80 mcg/4.5 mcg/ inhalation	asthma	4 actuations/day (2 actuations twice daily); total dose = 320 mcg/18 mcg/day

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
	inhalation aerosol: 160 mcg/4.5 mcg/ inhalation	asthma	4 actuations/day (2 actuations twice daily); total dose = 640 mcg/18 mcg/day
		COPD	4 actuations/day (2 actuations twice daily); total dose = 640 mcg/18 mcg/day
budesonide/ glycopyrrolate/ formoterol fumarate (Breztri Aerosphere®)	inhalation aerosol: 160 mcg/9 mcg/4.8 mcg/inhalation	COPD	4 actuations/day (2 actuations twice daily); total dose = 640 mcg/ 36 mcg/ 19.2 mcg/ day
fluticasone propionate/ salmeterol xinafoate (Advair HFA®, generics)	inhalation aerosol: 45 mcg fluticasone/21 mcg salmeterol/ inhalation	asthma	4 actuations/day (2 actuations twice daily); total dose = 180 mcg/84 mcg/day
	inhalation aerosol: 115 mcg fluticasone/21 mcg salmeterol/ inhalation		4 actuations/day (2 actuations twice daily); total dose = 460 mcg/84 mcg/day
	inhalation aerosol: 230 mcg fluticasone/21 mcg salmeterol/ inhalation		4 actuations/day (2 actuations twice daily); total dose = 920 mcg/84 mcg/day
fluticasone propionate/ salmeterol (Advair Diskus®, Wixela Inhub®, generics)	inhalation powder: 100 mcg fluticasone/50 mcg salmeterol/ inhalation	asthma	2 actuations/day in divided doses (1 actuation twice daily); total dose = 200 mcg/100 mcg/day
	inhalation powder: 250 mcg fluticasone/50 mcg salmeterol/ inhalation	asthma	2 actuations/day in divided doses (1 actuation twice daily); total dose =500 mcg/100 mcg/day

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
		COPD	2 actuations/day in divided doses (1 actuation twice daily); total dose = 500 mcg/100 mcg/day
	inhalation powder: 500 mcg fluticasone/50 mcg salmeterol/ inhalation	asthma	2 actuations/day in divided doses (1 actuation twice daily); total dose = 1000 mcg/100 mcg/day
fluticasone propionate/ salmeterol (AirDuo RespiClick®)	inhalation powder: 55 mcg fluticasone/14 mcg salmeterol/ inhalation	asthma	2 actuations/day in divided doses (1 actuation twice daily); total dose = 110 mcg/28 mcg/day
	inhalation powder: 113 mcg fluticasone/14 mcg salmeterol/ inhalation		2 actuations/day in divided doses (1 actuation twice daily); total dose = 226 mcg/28 mcg/day
	inhalation powder: 232 mcg fluticasone/14 mcg salmeterol/ inhalation		2 actuations/day in divided doses (1 actuation twice daily); total dose = 464 mcg/28 mcg/day
fluticasone propionate/ salmeterol (AirDuo Digihaler®)	inhalation powder: 55 mcg fluticasone/ 14 mcg salmeterol/ inhalation	asthma	2 actuations/day in divided doses (1 actuation twice daily); total dose = 110 mcg/28 mcg/day
	inhalation powder: 113 mcg fluticasone/ 14 mcg salmeterol/ inhalation		2 actuations/day in divided doses (1 actuation twice daily); total dose = 226 mcg/28 mcg/day
	inhalation powder: 232 mcg fluticasone/ 14 mcg salmeterol/ inhalation		2 actuations/day in divided doses (1 actuation twice daily); total dose = 464 mcg/28 mcg/day

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
fluticasone furoate/ umeclidinium/ vilanterol (Trelegy® Ellipta®)	inhalation powder: 100 mcg/ 62.5 mcg/ 25 mcg/inhalation	asthma	1 actuation/day; total dose = 100 mcg/62.5 mcg/ 25 mcg/day
		COPD	1 actuation/day; total dose = 100 mcg/62.5 mcg/ 25 mcg/day
fluticasone furoate/ vilanterol (Breo® Ellipta®, generics)	inhalation powder: 100 mcg fluticasone/25 mcg vilanterol/ inhalation	asthma	1 actuation/day; total dose = 100 mcg/25 mcg/day
		COPD	
	inhalation powder: 200 mcg fluticasone/25 mcg vilanterol/ inhalation	asthma	1 actuation/day; total dose = 200 mcg/25 mcg/day
glycopyrrolate/ formoterol (Bevespi Aerosphere®)	inhalation aerosol: 9 mcg glycopyrrolate/ 4.8 mcg formoterol/ actuation	COPD	4 actuations/day in two divided doses (2 actuations twice daily); total dose = 36 mcg/19.2 mcg/day
mometasone/ formoterol (Dulera®)	inhalation aerosol: 100 mcg mometasone/5 mcg formoterol/ inhalation	asthma	<i>for patients on medium-dose inhaled corticosteroids:</i> 4 actuations/day in divided doses (2 actuations twice daily); total dose = 400 mcg/20 mcg/day

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
	inhalation aerosol: 200 mcg mometasone/ 5 mcg formoterol/ inhalation		<i>patients on high-dose inhaled corticosteroids:</i> 4 actuations/day in divided doses (2 actuations twice daily); total dose = 800 mcg/20 mcg/day
tiotropium/ olodaterol (Stiolto® Respimat®)	inhalation aerosol: 2.5 mcg tiotropium/2.5 mcg olodaterol/ inhalation	COPD	2 actuations once daily (total dose = 5 mcg/5 mcg/day)
umeclidinium/ vilanterol (Anoro® Ellipta®)	inhalation powder: 62.5 mcg umeclidinium/25 mcg vilanterol/ inhalation	COPD	1 actuation/day; total dose = 62.5 mcg/25 mcg/day

1.2 Pediatrics

The safety and efficacy of **inhaled** salmeterol in children < 4 years of age **has** not been established.¹⁻³ Olodaterol **is** not approved for use in children as safety and efficacy of these agents have not been established in the pediatric population.^{1,2,4} Similarly, the glycopyrrolate/formoterol, acclidinium/formoterol, fluticasone/vilanterol, and the umeclidinium/vilanterol combination products are not FDA-approved for pediatric use as safety and efficacy have not been determined in this patient population for these inhalation combinations.^{1,2,11,13,14,17}

To prevent EIB in pediatric patients 4 years of age and older, one salmeterol 50 mcg inhalation is administered at least 30 minutes before exercise on an as-needed basis; doses should not be repeated for at least 12 hours after administration of the previous dose.¹⁻³ Patients receiving twice daily LABA doses chronically should not administer additional LABA doses for EIB management.

Pediatric dosages for LABAs used as maintenance asthma therapy are summarized in Tables 3 and 4.

Table 3. Pediatric LABA Maximum Daily Dosage Recommendations for Asthma: Monotherapy¹⁻³

Drug Name	Dosage Form/ Strength	Patient Age/Maximum Recommended Dosage
salmeterol (Serevent® Diskus®)	inhalation powder: 50 mcg/inhalation	≥ 4 years of age: 2 actuations/day (1 actuation twice daily); total dose = 100 mcg/day

Table 4. Pediatric LABA Maximum Daily Dosage Recommendations for Asthma: Combination Therapy^{1,2,5-10}

Drug Name	Dosage Form/ Strength	Patient Age/Maximum Recommended Dosage
budesonide/ formoterol (Symbicort®)	inhalation aerosol: 80 mcg/4.5 mcg/ inhalation	6 to 11 years of age: 4 actuations/day in divided doses (2 actuations twice daily); total dose = 320 mcg/18 mcg/day
		≥ 12 years of age: 4 actuations/day in divided doses (2 actuations twice daily); total dose = 320 mcg/18 mcg/day
	inhalation aerosol: 160 mcg/4.5 mcg/inhalation	≥ 12 years of age: 4 actuations/day in divided doses (2 actuations twice daily); total dose = 640 mcg/18 mcg /day
fluticasone propionate/ salmeterol xinafoate (Advair HFA®)	inhalation aerosol: 45 mcg/21 mcg/ inhalation	≥ 12 years of age: 4 actuations/day in divided doses (2 actuations twice daily); total dose = 180 mcg/84 mcg/day
	inhalation aerosol: 115 mcg/21 mcg/ inhalation	≥ 12 years of age: 4 actuations/day in divided doses (2 actuations twice daily); total dose = 460 mcg/84 mcg/day
	inhalation aerosol: 230 mcg/21 mcg/ inhalation	≥ 12 years of age: 4 actuations/day in divided doses (2 actuations twice daily); total dose = 920 mcg /84 mcg/day
fluticasone propionate/ salmeterol (Advair Diskus®)	inhalation powder: 100 mcg/50 mcg/ inhalation	4-11 years of age: 2 actuations/day (1 actuation twice daily); total dose = 200 mcg/100 mcg/day
	inhalation powder: 100 mcg/50 mcg/ inhalation	≥ 12 years of age: 2 actuations/day (1 actuation twice daily); total dose = 200 mcg/100 mcg/day

Drug Name	Dosage Form/ Strength	Patient Age/Maximum Recommended Dosage
	inhalation powder: 250 mcg/50 mcg/ inhalation	<i>≥ 12 years of age:</i> 2 actuations/day (1 actuation twice daily); total dose = 500 mcg/100 mcg/day
	inhalation powder: 500 mcg/50 mcg/ inhalation	<i>≥ 12 years of age:</i> 2 actuations/day (1 actuation twice daily); total dose = 1000 mcg/100 mcg/day
fluticasone propionate/salmeterol (AirDuo RespiClick®)	inhalation powder: 55 mcg fluticasone/14 mcg salmeterol/ inhalation	<i>≥ 12 years of age:</i> 2 actuations/day in divided doses (1 actuation twice daily); total dose = 110 mcg/28 mcg/day
	113 mcg fluticasone/14 mcg salmeterol/ inhalation	<i>≥ 12 years of age:</i> 2 actuations/day in divided doses (1 actuation twice daily); total dose = 226 mcg/28 mcg/day
	232 mcg fluticasone/14 mcg salmeterol/ inhalation	<i>≥ 12 years of age:</i> 2 actuations/day in divided doses (1 actuation twice daily); total dose = 464 mcg/28 mcg/day
fluticasone propionate/salmeterol (AirDuo Digihaler®)	55 mcg fluticasone/14 mcg salmeterol/ inhalation	<i>≥ 12 years of age:</i> 2 actuations/day in divided doses (1 actuation twice daily); total dose = 110 mcg/28 mcg/day
	inhalation powder: 113 mcg fluticasone/14 mcg salmeterol/ inhalation	<i>≥ 12 years of age:</i> 2 actuations/day in divided doses (1 actuation twice daily); total dose = 226 mcg/28 mcg/day
	inhalation powder: 232 mcg fluticasone/14 mcg salmeterol/ inhalation	<i>≥ 12 years of age:</i> 2 actuations/day in divided doses (1 actuation twice daily); total dose = 464 mcg/28 mcg/day
mometasone/formoterol (Dulera®)	inhalation aerosol: 50 mcg/5 mcg/ inhalation	<i>5-11 years of age:</i> 4 actuations/day in divided doses (2 actuations twice daily); total dose = 200 mcg/ 20 mcg/ day

Drug Name	Dosage Form/ Strength	Patient Age/Maximum Recommended Dosage
	100 mcg/5 mcg/ inhalation	<p>≥ 12 years of age: patients on medium-dose inhaled corticosteroids: 4 actuations/day in divided doses (2 actuations twice daily); total dose = 400 mcg/20 mcg/day</p>
	200 mcg/5 mcg/ inhalation	<p>≥ 12 years of age: patients on high-dose inhaled corticosteroids: 4 actuations/day in divided doses (2 actuations twice daily); total dose = 800 mcg/20 mcg/day</p>

Number of maximum actuations per day based on dose of salmeterol and formoterol, and independent of inhaled corticosteroid dose.

2 Duration of Therapy

Generally, LABAs should only be used as maintenance therapy. Recent guideline updates recommend the combined use of formoterol and budesonide as maintenance and rescue therapy for most patients with asthma, including the use of this combination as needed.¹²

For maintenance therapy, daily administration of LABAs alone or in combination with ICS is warranted in asthma and COPD. Formoterol combination products, olodaterol monotherapy and combination products, salmeterol monotherapy and combination products, and vilanterol combination products are metered-dose inhalers designed to deliver a set number of inhalations based on the canister size as well as the medication prescribed. Tables 5 and 6 summarize the number of inhalations available LABA and LABA combination products provide, respectively, and the days' supply per inhaler or blister package based on the maximum dose allowed per day (see Tables 1 through 4). Excessive use may be identified based on refill frequency. Inappropriate supply of salmeterol metered-dose inhalers, salmeterol/fluticasone blister packages, formoterol blister packages, budesonide/formoterol metered-dose inhalers, or mometasone/formoterol metered-dose inhalers will be monitored by reviewing excessive refills.

Table 5. Days' Supply for Available Long-Acting Beta2-Adrenergic Metered Dose Inhalers (Adult and Pediatric Patients) - Monotherapy

Drug	# of Actuations Per Canister	Days' Supply (based on maximum dose per day) ⁺
salmeterol dry powder inhaler* 60 blisters	60	30
olodaterol inhalation aerosol~	60	30

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

*Salmeterol inhalation powder, alone or in combination with fluticasone, may be used in children ≥ 4 years of age

Table 6. Days' Supply for Available Long-Acting Beta2-Adrenergic Metered Dose Inhalers (Adult and Pediatric Patients) – Combination Therapy

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/formoterol inhalation aerosol# 80 mcg/4.5 mcg/inhalation	120	30
160 mcg/4.5 mcg/inhalation	120	30
budesonide/ glycopyrrolate/ formoterol fumarate 160 mcg/9 mcg/4.8 mcg/inhalation	120	30
fluticasone propionate/salmeterol xinafoate inhalation aerosol^ 45 mcg fluticasone/21 mcg salmeterol/ inhalation	60 120	15 30
115 mcg fluticasone/21 mcg salmeterol/ inhalation	60 120	15 30
230 mcg fluticasone/21 mcg salmeterol/ inhalation	60 120	15 30

Drug	# of Actuations Per Canister	Days' Supply (based on maximum dose per day)⁺
fluticasone propionate/salmeterol inhalation powder* 100 mcg fluticasone/50 mcg salmeterol/ inhalation: 60 blisters	60	30
250 mcg fluticasone/50 mcg salmeterol/ inhalation: 60 blisters	60	30
500 mcg fluticasone/50 mcg salmeterol/ inhalation: 60 blisters	60	30
fluticasone/salmeterol inhalation powder^ 55 mcg/14 mcg/actuation (0.45 g canister)	60	30
113 mcg/14 mcg/actuation (0.45 g canister)	60	30
232 mcg/14 mcg/actuation (0.45 g canister)	60	30
fluticasone furoate/ umeclidinium/ vilanterol inhalation powder~ 100 mcg/62.5 60 blisters (one strip contains fluticasone, one strip contains umeclidinium and vilanterol)	30	30
200 mcg/62.5 mcg/25 mcg/actuation 60 blisters (one strip contains fluticasone, one strip contains umeclidinium and vilanterol)	30	30
fluticasone furoate/vilanterol inhalation powder~ 100 mcg/25 mcg/actuation 60 blisters (one strip contains fluticasone, one strip contains vilanterol)	30	30
200 mcg/25 mcg/actuation 60 blisters (one strip contains fluticasone, one strip contains vilanterol)	30	30
glycopyrrolate/formoterol inhalation aerosol~ 9 mcg/4.8 mcg/actuation	120	30
mometasone furoate/formoterol inhalation aerosol^ 50 mcg/5 mcg/inhalation'	120	30
100 mcg/5 mcg/inhalation	120	30

Drug	# of Actuations Per Canister	Days' Supply (based on maximum dose per day) ⁺
200 mcg/5 mcg/inhalation	120	30
tiotropium/ olodaterol inhalation aerosol~ 2.5 mcg/ 2.5 mcg/inhalation	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

~not indicated for use in children

*Salmeterol inhalation powder, alone or in combination with fluticasone, may be used in children ≥ 4 years of age

#Budesonide/formoterol indicated for children ≥ 6 years of age

^Fluticasone/salmeterol inhalation aerosol and fluticasone/salmeterol inhalation powder as AirDuo® RespiClick and AirDuo Digihaler® as well as mometasone/formoterol inhalation aerosols only indicated for children ≥ 12 years of age

[!]Mometasone furoate/ formoterol 50 mcg/ 5mcg/ inhalation is approved for children 5 years of age and older

3 Duplicative Therapy

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

Current literature does not support the adjunctive use of multiple LABAs for prevention and control of asthma symptoms. Concomitant LABA use will be reviewed as clinical evidence does not validate improved outcome with conjunctive therapy.

4 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 LABAs and combination products are summarized in Table 7. 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 7. Key Drug-Drug Interactions for Inhaled LABAs and Combination Products

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	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 (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level⁺
beta ₂ -agonists	diuretics, xanthine derivatives (e.g., theophylline), corticosteroids	potential for worsening of hypokalemia and/or ECG changes with beta ₂ -agonist concurrent administration, especially with high beta ₂ -agonist doses	administer combination cautiously, although common for xanthines and steroids to be administered adjunctively with beta ₂ -agonists; monitor potassium levels as necessary	moderate (CP)
beta ₂ -agonists	MAOIs (including linezolid)	concurrent administration 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 (CP)
beta ₂ -agonists	QTc interval-prolonging medications (e.g., class I, III anti-arrhythmic, ziprasidone, dolasetron)	concurrent administration may increase risk of cardiotoxicity (e.g., life-threatening arrhythmias, cardiac arrest) due to potential for additive QTc interval prolongation and, rarely, torsades de pointes	administer combination cautiously	moderate (CP)
beta ₂ -agonists	TCAs	concurrent administration may potentiate effects on cardiovascular system and increase risk of adverse events	cautiously administer together, including within 2 weeks of TCA discontinuation; monitor patients and observe for changes in blood pressure, heart rate and ECG	moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level ⁺
salmeterol, ICS	strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, clarithromycin)	salmeterol, ICS extensively metabolized; conjunctive administration may increase salmeterol, ICS serum levels and potential for increased adverse cardiovascular effects (salmeterol), steroid adverse effects (ICS)	avoid combination, if possible; if combination necessary, monitor for salmeterol, ICS adverse effects and adjust therapy as necessary	major (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	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	moderate (CP)

⁺CP = *Clinical Pharmacology*

COPD = *chronic obstructive pulmonary disease*; ECG = *electrocardiogram*; MAOIs = *monoamine oxidase inhibitors*; TCAs = *tricyclic antidepressants*

5 References

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8. Fluticasone/salmeterol inhalation powder (AirDuo RespiClick®) package insert. Teva Pharmaceuticals, **September 2022**.
9. Fluticasone/salmeterol inhalation powder (AirDuo Digihaler®) package insert. Teva Pharmaceuticals, **April 2022**.
10. Budesonide/formoterol fumarate inhalation aerosol (Symbicort®) package insert. AstraZeneca, July 2019.
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13. Umeclidinium/vilanterol inhalation powder (Anoro® Ellipta®) package insert. GlaxoSmithKline, **October 2022**.
14. Glycopyrrolate/formoterol inhalation aerosol (Bevespi Aerosphere®) package insert. AstraZeneca, November 2020.
15. Tiotropium/olodaterol (Stiolto® Respimat®) package insert. Boehringer-Ingelheim Pharmaceuticals, Inc., **November 2021**.
16. Fluticasone/umeclidinium/vilanterol inhalation powder (Trelegy® Ellipta®) package insert. GlaxoSmithKline, **December 2022**.
17. Aclidinium/ formoterol fumarate powder (Duaklir Pressair®) metered dose inhaler package insert. Circassia Pharmaceuticals, Inc., **January 2022**.
18. **Budesonide/ Glycopyrrolate/ formoterol fumarate inhalation aerosol (Breztri Aerosphere®) package insert. January 2022.**
19. **Fluticasone/salmeterol inhalation powder (Wixela Inhub®) package insert. Mylan Pharmaceuticals, Inc., August 2022.**