

Texas Vendor Drug Program

Drug Use Criteria: Aerosolized Agents - Metered-Dose Inhalers (MDIs): Beta₂ Agonists (long-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.

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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. Salmeterol is FDA-approved in adults and children four years of age and older and is also FDA-approved for use to acutely prevent exercise-induced bronchospasm (EIB) on an as-needed basis. 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. 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. Indacaterol (Arcapta[®]) and olodaterol (Striverdi[®] Respimat[®]) are newer LABAs FDA-approved for use as maintenance therapy COPD, but neither has received an indication for use in asthma. LABAs combined with ICS are FDA-approved for use in adults and children as asthma maintenance therapy: fluticasone propionate/salmeterol metered aerosol (Advair[®] HFA) and mometasone/formoterol inhalation aerosol (Dulera[®]) are FDA-approved for use as maintenance therapy for asthma in patients 12 years of age and older, while fluticasone propionate/salmeterol inhalation powder (Advair Diskus[®]) is FDA-approved for use in asthma maintenance in patients 4 years of age and older. A newer fluticasone/salmeterol inhalation powder (AirDuo RespiClick[®]) that provides additional dosage strengths has been approved for use in asthma patients 12 years and older. Budesonide/formoterol inhalation aerosol (Symbicort[®]) and Advair Diskus[®] are FDA-approved for use in adults as COPD maintenance therapy. The newer combination agents, fluticasone/vilanterol (Breo[®] Ellipta[®]), umeclidinium/vilanterol (Anoro[®] Ellipta[®]), glycopyrrolate/formoterol (Bevespi Aerosphere[®]), indacaterol/glycopyrrolate (Utibron[®] Neohaler[®]), and tiotropium/olodaterol (Stiolto[®] Respimat[®]) are indicated for use in adults as maintenance therapy for COPD but are not FDA-approved for use in asthma. Additionally, a triple therapy inhaler containing fluticasone, umeclidinium and vilanterol (Trelegy[®] Ellipta[®]) has now been approved for COPD management to treat airway obstruction and reduce exacerbations.

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: Monotherapy

Treatment Indication	Drug Name	Dosage Form/ Strength	Maximum Recommended Dosage
chronic obstructive pulmonary disease (COPD)	indacaterol maleate (Arcapta® Neohaler®)	inhalation capsules: 75 mcg/capsule	1 actuation once daily; total dose = 75 mcg/day
COPD	olodaterol hydrochloride (Striverdi® Respimat®)	inhalation aerosol: 2.5 mcg/actuation	2 actuations once daily; total dose = 5 mcg/day
asthma	salmeterol (Serevent® Diskus®)	inhalation powder: 50 mcg/inhalation	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

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. 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. Advair® HFA, AirDuo Resplick®, and Dulera® are FDA-approved for asthma management only.

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

Treatment Indication	Drug Name	Dosage Form/ Strength	Maximum Recommended Dosage
asthma	budesonide/ formoterol (Symbicort®)	inhalation aerosol: 80 mcg/4.5 mcg/ inhalation	4 actuations/day (2 actuations twice daily); total dose = 320 mcg/18 mcg/day
asthma		inhalation aerosol: 160 mcg/4.5 mcg/ inhalation	4 actuations/day (2 actuations twice daily); total dose = 640 mcg/18 mcg/day
chronic obstructive pulmonary disease (COPD)			4 actuations/day (2 actuations twice daily); total dose = 640 mcg/18 mcg/day
asthma	fluticasone propionate/ salmeterol xinafoate (Advair® HFA)	inhalation aerosol: 45 mcg fluticasone/21 mcg salmeterol/ inhalation	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
asthma	fluticasone propionate/ salmeterol (Advair Diskus®)	inhalation powder: 100 mcg fluticasone/50 mcg salmeterol/ inhalation	2 actuations/day in divided doses (1 actuation twice daily); total dose = 200 mcg/100 mcg/day
asthma		inhalation powder: 250 mcg fluticasone/50 mcg salmeterol/ inhalation	2 actuations/day in divided doses (1 actuation twice daily); total dose =500 mcg/100 mcg/day
COPD			2 actuations/day in divided doses (1 actuation twice daily); total dose =500 mcg/100 mcg/day

Treatment Indication	Drug Name	Dosage Form/ Strength	Maximum Recommended Dosage
asthma		inhalation powder: 500 mcg fluticasone/50 mcg salmeterol/ inhalation	2 actuations/day in divided doses (1 actuation twice daily); total dose = 1000 mcg/100 mcg/day
asthma	fluticasone propionate/ salmeterol (AirDuo RespiClick®)	inhalation powder: 55 mcg fluticasone/14 mcg salmeterol/ inhalation	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
COPD	fluticasone furoate/ umeclidinium/ vilanterol (Trelegy® Ellipta®)	inhalation powder: 100 mcg/ 62.5 mcg/ 25 mcg/inhalation	1 actuation/day; total dose = 100 mcg/62.5 mcg/ 25 mcg/day
asthma	fluticasone furoate/ vilanterol (Breo® Ellipta®)	inhalation powder: 100 mcg fluticasone/25 mcg vilanterol/ inhalation	1 actuation/day; total dose = 100 mcg/25 mcg/day
		inhalation powder: 200 mcg fluticasone/25 mcg vilanterol/ inhalation	1 actuation/day; total dose = 200 mcg/25 mcg/day
COPD		inhalation powder: 100 mcg fluticasone/25 mcg vilanterol/ inhalation	1 actuation/day; total dose = 100 mcg/25 mcg/day
COPD	glycopyrrolate/ formoterol (Bevespi Aerosphere®)	inhalation aerosol: 9 mcg glycopyrrolate/ 4.8 mcg formoterol/ actuation	4 actuations/day in two divided doses (2 actuations twice daily); total dose = 36 mcg/19.2 mcg/day

Treatment Indication	Drug Name	Dosage Form/ Strength	Maximum Recommended Dosage
COPD	indacaterol/ glycopyrrolate (Utibron® Neohaler®)	inhalation capsule: 27.5 mcg indacaterol/15.6 mcg/capsule	2 capsules/day in divided doses (1 capsule inhaled twice daily); total dose = 55 mcg/31.2 mcg/day
asthma	mometasone/ formoterol (Dulera®)	inhalation aerosol: 100 mcg mometasone/5 mcg formoterol/ inhalation	for patients on medium- dose inhaled corticosteroids: 4 actuations/day in divided doses (2 actuations twice daily); total dose = 400 mcg/20 mcg/day
		inhalation aerosol: 200 mcg mometasone/ 5 mcg formoterol/ inhalation	patients on high-dose inhaled corticosteroids: 4 actuations/day in divided doses (2 actuations twice daily); total dose = 800 mcg/20 mcg/day
COPD	tiotropium/ olodaterol (Stiolto® Respimat®)	inhalation aerosol: 2.5 mcg tiotropium/2.5 mcg olodaterol/ inhalation	2 actuations once daily (total dose = 5 mcg/5/mcg/day
COPD	umeclidinium/ vilanterol (Anoro® Ellipta®)	inhalation powder: 62.5 mcg umeclidinium/25 mcg vilanterol/ inhalation	1 actuation/day; total dose = 62.5 mcg/25 mcg/day

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

1.2 Pediatrics

The safety and efficacy of inhalational salmeterol in children less than 4 years of age have not been established. Indacaterol and olodaterol are not approved for use in children as safety and efficacy of these agents have not been established in the pediatric population. Similarly, the glycopyrrolate/formoterol, indacaterol/glycopyrrolate, 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.

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. 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: Monotherapy

Drug Name	Dosage Form/ Strength	Patient Age/Maximum Recommended Dosage
salmeterol (Serevent® Diskus®)	inhalation powder: 50 mcg/inhalation	Greater than or equal to 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

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
		Greater than or equal to 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	Greater than or equal to 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	Greater than or equal to 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	Greater than or equal to 12 years of age: 4 actuations/day in divided doses (2 actuations twice daily); total dose = 460 mcg/84 mcg/day

Drug Name	Dosage Form/ Strength	Patient Age/Maximum Recommended Dosage
	inhalation aerosol: 230 mcg/21 mcg/ inhalation	Greater than or equal to 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	Greater than or equal to 12 years of age: 2 actuations/day (1 actuation twice daily); total dose = 200 mcg/100 mcg/day
	inhalation powder: 250 mcg/50 mcg/ inhalation	Greater than or equal to 12 years of age: 2 actuations/day (1 actuation twice daily); total dose = 500 mcg/100 mcg/day
	inhalation powder: 500 mcg/50 mcg/ inhalation	Greater than or equal to 12 years of age: 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	Greater than or equal to 12 years of age: 2 actuations/day in divided doses (1 actuation twice daily); total dose = 110 mcg/28 mcg/day
	113 mcg fluticasone/14 mcg salmeterol/ inhalation	Greater than or equal to 12 years of age: 2 actuations/day in divided doses (1 actuation twice daily); total dose = 226 mcg/28 mcg/day
	232 mcg fluticasone/14 mcg salmeterol/ inhalation	Greater than or equal to 12 years of age: 2 actuations/day in divided doses (1 actuation twice daily); total dose = 464 mcg/28 mcg/day
mometasone/ formoterol (Dulera®)	inhalation aerosol: 100 mcg/5 mcg/ inhalation	Greater than or equal to 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

Drug Name	Dosage Form/ Strength	Patient Age/Maximum Recommended Dosage
	200 mcg/5 mcg/ inhalation	Greater than or equal to 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

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

2 Duration of Therapy

Unlike other available short-acting selective beta₂-agonists, salmeterol possesses a longer duration of bronchodilation of at least 12 hours which allows for twice daily dosing. Salmeterol does not exhibit immediate pharmacologic activity due to its delayed onset of action. The onset of effective bronchodilation is approximately 10-20 minutes, with the time to maximum effect approaching one hour. This delayed onset has been attributed to slower receptor binding by salmeterol. Therefore, salmeterol administered either alone or in combination with fluticasone propionate is not effective in the treatment of acute asthmatic attacks but is reserved for use as preventive asthma therapy. Patients should **never** receive salmeterol as treatment for acute bronchospasm due to the delayed onset of action (10-20 minutes) attributed to this agent. Deaths have been reported when patients mistakenly used salmeterol to combat acute bronchospasm. Similarly, indacaterol, olodaterol, and vilanterol possess longer durations of bronchodilation allowing for once daily dosing and should also never be used to manage acute bronchospasm; these agents are only indicated for use as maintenance therapy in COPD.

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. Indacaterol and indacaterol/ glycopyrrolate have capsules that are inserted into the inhaler device; dose number is determined by accompanying capsule number and number of inhalations 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) +
indacaterol inhalation capsule~	30	30
salmeterol dry powder inhaler* <ul style="list-style-type: none"> • 60 blisters • 28 blisters 	<ul style="list-style-type: none"> • 60 • 28 	<ul style="list-style-type: none"> • 30 • 14

olodaterol inhalation aerosol~

60

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 greater than or equal to 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) +
budesonide/formoterol inhalation aerosol# <i>80 mcg/4.5 mcg/inhalation</i>	60 120	15 30
<i>160 mcg/4.5 mcg/inhalation</i>	60 120	15 30
fluticasone propionate/ salmeterol xinafoate inhalation aerosol^ <i>45 mcg fluticasone/21 mcg salmeterol / inhalation</i>	120 60	30 15
<i>115mcg fluticasone/21 mcg salmeterol/ inhalation</i>	120 60	30 15

Drug	# of Actuations Per Canister	Days Supply (based on maximum dose per day) ⁺
<i>230 mcg fluticasone/21 mcg salmeterol/ inhalation</i>	120 60	30 15
fluticasone propionate/salmeterol inhalation powder* <i>100 mcg fluticasone/50 mcg salmeterol/ inhalation:</i>		
14 blisters	14	7
60 blisters	60	30
<i>250 mcg fluticasone/50 mcg salmeterol/ inhalation:</i>		
14 blisters	14	7
60 blisters	60	30
<i>500 mcg fluticasone/50 mcg salmeterol/ inhalation:</i>		
14 blisters	14	7
60 blisters	60	30
fluticasone/salmeterol inhalation powder^ <i>55 mcg/14 mcg/actuation (0.45 g canister)</i>	60	30
<i>113 mcg/14 mcg/actuation (0.45 g canister)</i>	60	30
<i>232 mcg/14 mcg/actuation (0.45 g canister)</i>	60	30
fluticasone furoate/ umeclidinium/ vilanterol inhalation powder~ <i>100 mcg/62.5 mcg/25 mcg/actuation</i>		
28 blisters <i>(one strip contains fluticasone, one strip contains umeclidinium and vilanterol)</i>	14	14
60 blisters <i>(one strip contains fluticasone, one strip contains umeclidinium and vilanterol)</i>	30	30
fluticasone furoate/vilanterol inhalation powder~ <i>100 mcg/25 mcg/actuation</i>		
28 blisters <i>(one strip contains fluticasone, one strip contains vilanterol)</i>	14	14
60 blisters <i>(one strip contains fluticasone, one strip contains vilanterol)</i>	30	30

Drug	# of Actuations Per Canister	Days Supply (based on maximum dose per day) ⁺
200 mcg/25 mcg/actuation 28 blisters (one strip contains fluticasone, one strip contains vilanterol)	14	14
60 blisters (one strip contains fluticasone, one strip contains vilanterol)	30	30
glycopyrrolate/formoterol inhalation aerosol ⁻ 9 mcg/4.8 mcg/actuation	120 28	30 7
indacaterol/glycopyrrolate inhalation capsule ⁻ 60 blisters 6 blisters	60 6	30 3
mometasone furoate/formoterol inhalation aerosol [^] 100 mcg/5 mcg/inhalation	120 60	30 15
200 mcg/5 mcg/inhalation	120 60	30 15
tiotropium/ olodaterol inhalation aerosol ⁻ 2.5 mcg/ 2.5 mcg/inhalation	60 28	30 14
umeclidinium/vilanterol inhalation powder ⁻ 14 blisters 60 blisters	7 30	7 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 Greater than or equal to 4 years of age
- # Budesonide/formoterol indicated for children Greater than or equal to 6 years of age
- ^ Fluticasone/salmeterol inhalation aerosol and fluticasone/salmeterol inhalation powder as AirDuo[®] RespiClick as well as mometasone/formoterol inhalation aerosols only indicated for children Greater than or equal to 12 years of age

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 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	major (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, 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	3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level ⁺
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 (DrugReax) 2-major (CP)
beta ₂ -agonists	QTc interval-prolonging medications (e.g., class I, III anti-arrhythmics, 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	contraindicated (vilanterol) DrugReax) 1-severe, 2-major, 3-moderate (CP)
beta ₂ -agonists	TCA	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 (DrugReax) 3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level ⁺
salmeterol, ICS	strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, clarithromycin)	salmeterol, ICS extensively CYP3A4 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 (DrugReax) 2-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	3-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	major (DrugReax)

- + CP = Clinical Pharmacology
- COPD = chronic obstructive pulmonary disease
- ECG = electrocardiogram
- MAOIs = monoamine oxidase inhibitors
- TCAs = tricyclic antidepressants

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13. Fluticasone/salmeterol inhalation aerosol (Advair® HFA) package insert. GlaxoSmithKline, February 2019.

14. Fluticasone/salmeterol inhalation powder (Advair Diskus®) package insert. GlaxoSmithKline, January 2019.
15. Fluticasone/vilanterol inhalation powder (Breo® Ellipta™) package insert. GlaxoSmithKline, January 2019.
16. Fluticasone/umeclidinium/vilanterol inhalation powder (Trelegy® Ellipta®) package insert. GlaxoSmithKline, January 2019.
17. Glycopyrrolate/formoterol inhalation aerosol (Bevespi Aerosphere®) package insert. AstraZeneca, June 2017.
18. Indacaterol/glycopyrrolate inhalation capsule (Utibron® Neohaler®) package insert. Novartis, January 2018.
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