Texas Vendor Drug Program

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

Publication History

1. Developed January 1995.
2. Revised 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.

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.

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1 Dosage

Long-acting, selective beta$_2$-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. Serevent Diskus® (salmeterol) is FDA-approved for asthma in adults and children four years of age and older, and it is also FDA-approved for use to acutely prevent exercise-induced bronchospasm (EIB) on an as-needed basis. 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.

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. Advair Diskus® (fluticasone propionate/salmeterol) inhalation powder is FDA-approved for use in asthma maintenance in patients 4 years of age and older. 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. Symbicort® (budesonide/formoterol) inhalation aerosol and Advair Diskus® (fluticasone propionate/salmeterol) are FDA-approved for use in adults as COPD maintenance therapy. 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.

Anoro Ellipta® (umeclidinium/vilanterol), Bevespi Aerosphere® (glycopyrrolate/formoterol), Utibron® Neohaler® (indacaterol/glycopyrrolate), 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.

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 in September of 2020 it was approved for the maintenance treatment of asthma in patients 18 years of age and older.

Duaklir Pressair® (aclidinium bromide/ formoterol) is a long-acting beta agonist and long-acting muscarinic antagonist combination product that was FDA approved in 2019 for the management of COPD in adults.

In March of 2020 Sunovion Pharmaceuticals announced the discontinuation of Utibron Neohaler® (indacaterol/glycopyrrolate), Seebri Neohaler® (glycopyrrolate), and Arcapta Neohaler® (indacaterol), and these products are no longer available in the United States as of April 1, 2020.

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
COPD	olodaterol hydrochloride (Striverdi Respimat®)	inhalation aerosol: 2.5 mcg/actuation	2 actuations once daily; total dose = 5 mcg/day

Treatment Indication	Drug Name	Dosage Form/ Strength	Maximum Recommended Dosage
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 RespiClick®, AirDuo Digihaler®, 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
COPD	aclidinium bromide/ formoterol fumarate (Duaklir Pressair®)	inhalation powder: 400 mcg/ 12 mcg/ inhalation	2 actuations/day (1 actuation twice daily); total dose = 800 mcg/24 mcg/day
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

Treatment Indication	Drug Name	Dosage Form/ Strength	Maximum Recommended Dosage
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®, Wixela Inhub®)	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
asthma	fluticasone propionate/ salmeterol (AirDuo Digihaler®)	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
asthma	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

Treatment Indication	Drug Name	Dosage Form/ Strength	Maximum Recommended Dosage
COPD			1 actuation/day; total dose = 100 mcg/62.5 mcg/ 25 mcg/day
asthma		inhalation powder: 200 mcg/ 62.5 mcg/ 25 mcg/inhalation	1 actuation/day; total dose = 200 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
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

Treatment Indication	Drug Name	Dosage Form/ Strength	Maximum Recommended Dosage
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 < 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, aclidinium/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.

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	*≥ 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
		≥ 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
	inhalation powder: 250 mcg/50 mcg/ inhalation	*≥ 12 years of age:* 2 actuations/day (1 actuation twice daily); total dose = 500 mcg/100 mcg/day

Drug Name	Dosage Form/ Strength	Patient Age/Maximum Recommended Dosage
	inhalation powder: 500 mcg/50 mcg/ inhalation	*≥ 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	*≥ 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	*≥ 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	*≥ 12 years of age:* 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	*≥ 12 years of age:* 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	*≥ 12 years of age:* 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	*≥ 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: 50 mcg/5 mcg/ inhalation	*5-11 years of age:* 4 actuations/day in divided doses (2 actuations twice daily); total dose = 200 mcg/ 20 mcg/ day
	100 mcg/5 mcg/ inhalation	*≥ 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	*≥ 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 beta$_2$-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. Olodaterol is indicated for use as maintenance therapy in COPD while vilanterol is approved for the maintenance treatment of asthma and 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. 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*	60 120	15 30
160 mcg/4.5 mcg/inhalation	60 120	15 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

Drug	# of Actuations Per Canister	Days' Supply (based on maximum dose per day)+
230 mcg fluticasone/21 mcg salmeterol/ inhalation	60 120	15 30
fluticasone propionate/salmeterol inhalation powder* *100 mcg fluticasone/50 mcg salmeterol/ inhalation:* 14 blisters 60 blisters	 14 60	 7 30
250 mcg fluticasone/50 mcg salmeterol/ inhalation: 14 blisters 60 blisters	 14 60	 7 30
500 mcg fluticasone/50 mcg salmeterol/ inhalation: 14 blisters 60 blisters	 14 60	 7 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 mcg/25 mcg/actuation* 28 blisters *(one strip contains fluticasone, one strip contains umeclidinium and vilanterol)* 60 blisters *(one strip contains fluticasone, one strip contains umeclidinium and vilanterol)*	 14 30	 14 30
200 mcg/62.5 mcg/25 mcg/actuation 28 blisters *(one strip contains fluticasone, one strip contains umeclidinium and vilanterol)* 60 blisters *(one strip contains fluticasone, one strip contains umeclidinium and vilanterol)*	 14 30	 14 30

Drug	# of Actuations Per Canister	Days' Supply (based on maximum dose per day)[+]
fluticasone furoate/vilanterol inhalation powder[~] *100 mcg/25 mcg/actuation* 28 blisters *(one strip contains fluticasone, one strip contains vilanterol)* 60 blisters *(one strip contains fluticasone, one strip contains vilanterol)*	 14 30	 14 30
200 mcg/25 mcg/actuation 28 blisters *(one strip contains fluticasone, one strip contains vilanterol)* 60 blisters *(one strip contains fluticasone, one strip contains vilanterol)*	 14 30	 14 30
glycopyrrolate/formoterol inhalation aerosol[~] *9 mcg/4.8 mcg/actuation*	28 120	7 30
mometasone furoate/formoterol inhalation aerosol[^] *50 mcg/5 mcg/inhalation*[!]	120	30
100 mcg/5 mcg/inhalation	60 120	15 30
200 mcg/5 mcg/inhalation	60 120	15 30
tiotropium/ olodaterol inhalation aerosol[~] *2.5 mcg/ 2.5 mcg/inhalation*	60 10	30 5
umeclidinium/vilanterol inhalation powder[~] 14 blisters *(one strip contains umeclidinium, one strip contains vilanterol)* 60 blisters *(one strip contains umeclidinium, one strip contains vilanterol)*	 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 ≥ 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 beta$_2$-adrenergic agents even though maintenance therapy with LABAs 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. LABAs used in conjunction with frequently administered short-acting beta$_2$-adrenergic drugs (i.e., frequent refill of a short-acting beta$_2$-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	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)
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)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level+
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	contraindicated (vilanterol) DrugReax) 1-severe, 2-major, 3-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 (DrugReax) 3-moderate (CP)
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)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level+
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

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: *March 24, 2021*).
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2021. Available at: http://clinicalpharmacology-ip.com.ezproxy.lib.utexas.edu/. Accessed March 24, 2021.
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