Inhaled Corticosteroids/Long-Acting Beta$_2$-Agonists (ICS/LABA)

ICS/LABA: *Class Overview*				
Indication	***MOA***	***Common Side Effects (>3% reported frequency)***	***Warnings/Precautions***	***Counseling Points***
- Treatment of asthma, for indicated ages. - Maintenance treatment of airflow obstruction and reducing exacerbations in patients with COPD. **NOT INDICATED FOR THE RELIEF OF ACUTE BRONCHOSPASM[1]**	- ICS have been shown to have multiple anti-inflammatory effects that contribute to their efficacy in asthma, including inhibiting both inflammatory cells and release of inflammatory mediators. - LABA: Long-acting Beta$_2$-agonists act locally in the lung as bronchodilators.	Headache Upper RTI Back pain Nasal congestion Nausea/vomiting Oral candidiasis Sinusitis	- BBW: LABA monotherapy increase risk of asthma-related death - Hypersensitivity reactions: angioedema, rash, urticaria - Localized infection: Candida albicans infection of the mouth and throat - Immunosuppression: potential worsening of existing infections - Paradoxical bronchospasm - Adrenal suppression/Cushing's - Decrease in bone mineral density - Eye disorders: changes in vision - Growth effects: reduction in growth velocity in pediatrics	- Treat acute asthma exacerbations with an inhaled, SABA (such as albuterol). - Rinsing the mouth with water without swallowing after inhalation is advised to help reduce the risk of thrush - The use of DPI inhalers is contraindicated in patients with severe hypersensitivity to milk proteins (avoid if lactose-intolerant)

[1] RED BOOK Online. IBM Micromedex. Truven Health Analytics/IBM Watson Health; 2020

ICS/LABA: *Available Medications*

Name (Brand)	Dosage Forms	Product Image	FDA-Approved Indicated Age	Dosage Strengths (per puff)	AWP COST ($)[1]	Formulary (Y/N)
Budesonide and formoterol fumarate (Symbicort)	HFA		6+	80 mcg ICS/4.5 mcg LABA 160 mcg ICS/4.5 mcg LABA	382.54 437.26	**Y**
Fluticasone furoate and vilanterol (Breo)	Ellipta (DPI)		18+	100 mcg ICS/25 mcg LABA 200 mcg ICS/25 mcg LABA	434.17 434.17	**N**
Fluticasone propionate and salmeterol (AirDuo)	RespiClick (DPI)		12+	55 mcg ICS/14 mcg LABA 113 mcg ICS/14 mcg LABA 232 mcg ICS/14 mcg LABA	384.28 384.28 384.28	**N**
Fluticasone propionate and salmeterol (Advair)	HFA		12+	45 mcg ICS/21 mcg LABA 115 mcg ICS/21 mcg LABA 230 mcg ICS/21 mcg LABA	317.05 472.72 621.72	**Y**
	Diskus (DPI)		4+	100 mcg ICS/50 mcg LABA 250 mcg ICS/50 mcg LABA 500 mcg ICS/50 mcg LABA	317.05 393.93 518.10	**N**
Mometasone furoate and formoterol fumarate (Dulera)	HFA		5+	50 mcg ICS/5 mcg LABA 100 mcg ICS/5 mcg LABA 200 mcg ICS/50 mcg LABA	373.62 373.62 373.62	**Y**

[1] Traditionally, ICS/LABA has been classified as a controller therapy for asthma and has not been used for relief during acute exacerbations. However, newer studies suggest that the utilization of SMART therapy (using low-dose ICS/formoterol) in patients with mild asthma results in a significant reduction of asthma exacerbations, lower average ICS dose, and an improvement in daily asthma symptoms when compared with patients on SABA alone or maintenance ICS therapy (*Beasley et al, NEJM 2019; Hardy et al, Lancet 2019*).

LABA: *Pharmacokinetics*[1,2]

Name	Available ICS Combination Formulations	Particle Size[3,4,5] (µm)	Onset (minutes)	DDI/ Metabolism	Active Metabolite	Serum t ½ (h)	Protein binding (%)	PO Bioavailability (%)	Lung delivery (%)	Vd (L)	Systemic CL (L/hr)	Renal Excretion (%)
Formoterol Fumarate	Symbicort Dulera	1.5	10	3A4 2D6 2C	16a-hydroxyprednisolone 6B-hydroxybudesonide	7-10	46-58	6-13	34	240	150	59-62
Vilanterol	Breo	1.8	10	3A4	N/A	16	93.9	<2	27.3	661	108	70
Salmeterol	Advair AirDuo	0.7 – 3.3	5	3A4	17β carboxylic acid	5.5	96	<1	~40	177-316	392	25

[1] Black Box Warning: LABA monotherapy increases the risk of asthma-related deaths. LABA is only indicated for the treatment of asthma if it used in combination with medications such as ICS.

[2] Medications delivered via inhalation are directly delivered to the target organ, typically yielding high pulmonary efficacy with minimal systemic side effects. However, the efficacy of inhaled drugs depends on pulmonary-specific pharmacokinetic processes and the ability for the drug particles to deposit throughout the lungs. This table reflects the relevant pharmacokinetic parameters for inhaled formulations. Particle size determines the likelihood of the drug depositing in the lungs (0.5 – 5 um) or in the oropharyngeal region ($\geq$ 5 um): smaller particles (0.5 – 3 um) typically deposit peripherally in the lungs, such as alveolar space, and larger particles (3-5 um) typically deposit in the upper conducting airways. The particle size and associated site of deposition impacts the drug's absorption into the lungs, onset of action, systemic clearance, and oral bioavailability. Due to differences in surface area, perfusion, and epithelial thickness, absorption of inhaled drugs is generally faster in the alveoli (the deposition site for smaller particles) and slower in the conducting airways (the deposition site for larger particles), which impacts the drug's time to onset. Moreover, mucociliary clearance is fastest in the larger conducting airways, ultimately clearing larger drug particles the most quickly and allowing smaller particles a longer duration. Generally, high systemic clearance and a low oral bioavailability is key to minimizing systemic exposure of inhaled formulations. An inhaled drug with a high oral bioavailability implies absorption of swallowed particles that deposited in the conducting airways or oropharyngeal region instead of depositing in the alveolar space, which is the optimal deposition site for maximal absorption and airway selectivity. Similarly, inhaled drugs with low systemic clearance have higher systemic exposure and are associated with poor airway selectivity.

[3] Park CS, et al. *Allergy Asthma Immunol Res*. 2017;9(2):99-100.

[4] Ciciliani AM, et al. Int J Chron Obstruct Pulmon Dis. 2017 May 26;12:1565-1577.

[5] Kelly HW, et al. *Annals of Allergy, Asthma & Immunology*. 2001;87(6):482-487.

ICS/LABA: *Comparative Dosing (mcg/day)*[1]

Name (Brand)	Dosage Forms	Children <12 years			Adults/Adolescents ≥12 years			Max Daily Dose	Clinical Pearls
		Low	Medium	High	Low	Medium	High		
Budesonide formoterol fumarate (Symbicort)	**HFA**	***6-12 yrs:*** 320/18	N/A	N/A	320/18	640/18	N/A	640/18	- Prime before using for the first time with **2** sprays - If not used for >1 week, prime by spraying **2** sprays into the air, away from the face
Fluticasone furoate and vilanterol (Breo)	**Ellipta (DPI)**	N/A	N/A	N/A	100/25*	100/25*	200/25*	200/25	
Fluticasone propionate and salmeterol (AirDuo)	**Respi Click (DPI)**	N/A	N/A	N/A	110/28	226/28	464/28	464/28	- Do not use with spacer/volume holding chamber
Fluticasone propionate and salmeterol (Advair)	**HFA**	N/A	N/A	N/A	180/84	460/84	920/84	920/84	- Prime before using for the first time with **4** sprays - If not used for >4 week, prime by spraying **2** sprays into the air, away from the face
	Diskus (DPI)	N/A	***4-11 yrs:*** 200/100	N/A	200/100	500/100	1000/100	1000/100	
Mometasone furoate and formoterol fumarate (Dulera)	**HFA**	N/A	N/A	***5-12 yrs:*** 200/20 (Max daily)	400/20	400/20	800/20	800/20	- Prime before using for the first time with **4** sprays - If not used for >5 days, prime by spraying **4** sprays into the air, away from the face

* = Only FDA-approved for ages ≥ 18 years, benefits include once-daily dosing

[1] Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2020.