Glucocorticoids, Inhaled Review

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FDA-Approved Indications

Drug	Manufacturer	Indication(s)
Glucocorticoids		
beclomethasone inhalation aerosol (QVAR™)[1]	Teva	• Maintenance treatment of asthma as prophylactic therapy (see indicated ages below for each product) • For asthma patients requiring systemic corticosteroid administration to reduce or eliminate the need for oral systemic corticosteroids <u>Indicated Ages</u> • QVAR is for use in patients age five years and older • Pulmicort Flexhaler is for use in patients age six years and older • Pulmicort Respules are used in patients age 12 months to eight years • Aerobid and Aerobid-M are for use in patients age six years and older • Flovent HFA and Flovent Diskus are for use in patients age four years and older • Asmanex is for use in patients age four years and older
budesonide inhalation powder (Pulmicort Flexhaler®)[2]	AstraZeneca	
budesonide inhalation suspension (Pulmicort Respules®)[3]	generic	
flunisolide inhalation aerosol (Aerobid®, Aerobid-M®)[4]	Forest	
fluticasone inhalation powder (Flovent Diskus®)[5]	GlaxoSmithKline	
fluticasone inhalation aerosol (Flovent HFA®)[6]	GlaxoSmithKline	
mometasone furoate inhalation powder (Asmanex® Twisthaler)[7]	Schering-Plough	
ciclesonide inhalation aerosol (Alvesco®)[8]	Sepracor	• Maintenance treatment of asthma as prophylactic therapy in adult and adolescent patients 12 years of age and older
Glucocorticoid/Bronchodilator combinations		
budesonide / formoterol inhalation aerosol (Symbicort®)[9]	AstraZeneca	• Treatment of asthma in patients 12 years of age and older • Maintenance treatment of airflow obstruction in patients with COPD including chronic bronchitis and emphysema
fluticasone / salmeterol inhalation powder (Advair® Diskus)[10]	GlaxoSmithKline	• Treatment of asthma in patients four years of age and older • Maintenance treatment of airflow obstruction in COPD including chronic bronchitis and emphysema (250/50 only). • To reduce COPD exacerbations in patients with a history of exacerbations (250/50 only)
fluticasone / salmeterol inhalation aerosol (Advair® HFA)[11]	GlaxoSmithKline	• Treatment of asthma in patients 12 years of age and older
mometasone / formoterol inhalation aerosol (Dulera®)[12]	Schering	• Treatment of asthma in patients 12 years of age and older

** According to the manufacturer, the promotion and manufacturing of Azmacort was discontinued in December 2009 to comply with the Montreal Protocol which calls for the elimination of certain chlorofluorocarbon (CFC)-containing medical products.[13]*

For asthma therapy, the combination products budesonide/formoterol (Symbicort), fluticasone/salmeterol (Advair Diskus, Advair HFA), and mometasone/formoterol (Dulera) should only be prescribed for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a long-acting $beta_2$ agonist. These combination products are not indicated for the relief of acute bronchospasms.

Overview

Asthma

The National Asthma Education and Prevention Program (NAEPP) has defined asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role.[14] In susceptible individuals, inflammation may cause recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. These episodes are usually associated with airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an increase in bronchial hyper-responsiveness to a variety of stimuli. An estimated 20 million Americans suffer from asthma, which accounts for approximately one-quarter (two million) of all emergency room visits in the United States each year.[15]

Studies have demonstrated the efficacy of glucocorticoids or inhaled corticosteroids (ICS) in improving lung function, reducing symptoms, reducing frequency and severity of exacerbations, and improving the quality of life (QoL) of patients with asthma.[16,17,18,19,20] The 2007 National Heart, Lung, and Blood Institute, National Institutes of Health (NHLBI, NIH) and Global Initiative for Asthma (GINA) state that inhaled glucocorticoids are currently the most effective anti-inflammatory medications for the treatment of persistent asthma.[21,22] However, there is marked individual variability of responsiveness to ICS and because of this and the recognized poor adherence to treatment with ICS, many patients will require higher doses to achieve full therapeutic benefit. To reach clinical control, add-on therapy with another class of controller is preferred over increasing the dose of ICS. There is, however, a clear relationship between the dose of ICS and the prevention of severe acute exacerbations of asthma. Therefore, some patients with severe asthma may benefit from long-term treatment with higher doses of ICS. An updated guideline is also available for the treatment of asthma in pregnancy.[23]

The 2009 GINA guidelines recommend a classification defined in terms of three levels of control: controlled, partly controlled, or uncontrolled.[24] A stepwise treatment approach is offered to achieve control using the patient's current level of control as the baseline. If the patient is not controlled on the current regimen, treatment should be stepped up until control is achieved. If control is maintained for at least three months on the current regimen, treatment can be stepped down to the lowest step and dosage that maintains control.

Levels of Asthma Control from 2009 GINA guidelines[25]

Characteristic	Controlled (all of the following)	Partly controlled (any present in past week)	Uncontrolled
Daytime symptoms	Twice or less per week	> Two times per week	Three or more features of partly controlled asthma in any week
Limitations of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/rescue treatment	Twice or less per week	> Two times per week	
Lung function (PEF or FEV1)	Normal	<80% predicted or personal best	
Exacerbations	None	One or more per year	One in any week

Stepwise Approach to Asthma Control from 2009 GINA guidelines[26]

	Adults and children six years of age and older
Step 1	As-needed reliever medication Recommended: rapid acting beta$_2$-agonist Alternatives: inhaled anticholinergic, short-acting oral beta$_2$-agonist or short-acting theophylline
Step 2	One controller AND an as-needed reliever medication Recommended controller: low-dose ICS Alternative controller: leukotriene modifier
Step 3	One or two controllers AND an as-needed reliever medication Recommended for adolescents and adults: low-dose ICS AND a long-acting beta$_2$-agonist (LABA) Recommended for children but particularly children five years of age and younger: medium-dose ICS Alternative controllers: medium- or high-dose ICS, OR low-dose ICS PLUS leukotriene modifier, OR low-dose ICS PLUS sustained release theophylline
Step 4	Two or more controllers AND an as-needed reliever medication Recommended: medium- or high-dose ICS PLUS LABA Alternative controllers: leukotriene modifier OR sustained release theophylline
Step 5	Additional controller options AND an as-needed reliever medication Recommended controllers for patients who remain severely uncontrolled on Step 4 medications: Oral corticosteroids Anti-IgE treatment [omalizumab – (Xolair®)]

The NAEPP Expert Panel Report-3 (EPR-3) report released in 2007 also recommends a similar classification of asthma severity and control, to guide in the initiation and adjustment of therapy, respectively.[27] Asthma severity and control are defined in terms of two domains, impairment and risk. The distinction between these domains emphasizes the need to consider separately asthma's effects on quality of life and functional capacity on an ongoing basis (e.g., in the

present) and the risks it presents for adverse events in the future, such as exacerbations and progressive loss of pulmonary function.

Stepwise Approach for Managing Persistent Asthma from the NAEPP Expert Panel Report-3 [28]

Severity of asthma	**Adults and children ≥ 12 years**
Step 6 Persistent Asthma	high-dose ICS + LABA + oral corticosteroid Consider omalizumab for patients who have allergies
Step 5 Persistent Asthma	high-dose ICS + LABA Consider omalizumab for patients who have allergies
Step 4 Persistent Asthma	medium-dose ICS + LABA Alternative: Medium-dose ICS + either LTRA, theophylline, or zileuton (Zyflo)
Step 3 Persistent Asthma	low-dose ICS + LABA OR medium-dose ICS Alternative: Low-dose ICS + either LTRA, theophylline, or zileuton
Step 2 Persistent Asthma	low-dose ICS Alternative: cromolyn, LTRA, nedocromil, or theophylline
Step 1 Intermittent Asthma	no daily medications needed SABA as needed

LABA = long acting $beta_2$-agonist; LTRA = leukotriene receptor antagonist or leukotriene modifier; ICS = inhaled corticosteroid; SABA = short acting $beta_2$-agonist

All asthma patients should have a short-acting $beta_2$-agonist inhaler for use on an as-needed basis.

Stepwise Approach for Managing Persistent Asthma from the NAEPP Expert Panel Report-3[29]

Severity of asthma	Children from birth to four years of age	Children five to 11 years of age
Step 6 Persistent Asthma	high-dose ICS + LABA OR montelukast (Singulair®) + oral corticosteroid	high-dose ICS + LABA + oral corticosteroid Alternative: high-dose ICS + LTRA OR theophylline + oral corticosteroids
Step 5 Persistent Asthma	high-dose ICS + LABA OR montelukast	high-dose ICS + LABA Alternative: high-dose ICS + LTRA OR theophylline
Step 4 Persistent Asthma	medium-dose ICS + LABA OR montelukast	medium-dose ICS + LABA Alternative: medium-dose ICS + LTRA OR theophylline
Step 3 Persistent Asthma	medium-dose ICS	low-dose ICS + LABA OR LTRA OR theophylline OR medium-dose ICS
Step 2 Persistent Asthma	low-dose ICS Alternative: cromolyn or montelukast	low-dose ICS Alternative: cromolyn, LTRA, nedocromil, or theophylline
Step 1 Intermittent Asthma	no daily medications needed SABA as needed	no daily medications needed SABA as needed

LABA = long acting $beta_2$-agonist; LTRA = leukotriene receptor antagonist or leukotriene modifier; ICS = inhaled corticosteroid; SABA = short acting $beta_2$-agonist

COPD

The 2009 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines define chronic obstructive pulmonary disease (COPD) as a preventable and treatable disease in which its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.[30] Between three and seven million Americans are currently diagnosed with COPD and it is estimated that the actual number of Americans with COPD exceeds 16 million.[31]

Bronchodilator therapy (e.g., beta$_2$-agonists, anticholinergics, methylxanthines) is central to symptom management in COPD, and the inhaled route is preferred. Most studies indicate that the existing medications for COPD do not modify the long-term decline in lung function, although there is limited evidence that regular treatment with long-acting beta$_2$-agonists, inhaled corticosteroids (ICS), and its combination can decrease the rate of decline of lung function.[32] Therefore, pharmacotherapy for COPD is mainly used to decrease symptoms and/or complications. The GOLD guidelines recommend the addition of ICS to long-acting bronchodilator therapy, such as long-acting beta$_2$-agonists (LABA), for patients with severe to very severe COPD. An inhaled glucocorticoid in combination with a long-acting beta agonist is more effective than the individual components in reducing exacerbations and improving lung function and health status. Available combinations include budesonide/formoterol (Symbicort), fluticasone/salmeterol (Advair), and mometasone/formoterol (Dulera). All three products are FDA-approved for use in the treatment of asthma and the maintenance treatment of COPD.

Pharmacology[33,34,35,36,37,38,39,40,41,42,43]

Corticosteroids suppress the cytokine generation, recruitment of airway eosinophils, and release of inflammatory mediators. These agents thereby block late-phase reaction to allergens, reduce airway hyperresponsiveness, and inhibit inflammatory cell migration and activation.[44] Because systemic corticosteroids have a high incidence of adverse reactions, inhaled corticosteroids are preferred for asthma.

Advair is a combination product containing a long-acting beta$_2$-agonist, salmeterol DPI (Serevent) and a corticosteroid, fluticasone. Symbicort is a combination product containing a long-acting beta$_2$-agonist, formoterol, and an inhaled corticosteroid (ICS), budesonide. Dulera is a combination product containing the long-acting beta$_2$-agonist, formoterol and the ICS, mometasone. Both, formoterol and salmeterol selectively bind to the beta$_2$-receptors in the bronchial smooth muscle, leading to bronchial relaxation and a decrease in the release of mediators of immediate hypersensitivity from mast cells.

Delivery and Deposition

The selection of a delivery system is a critical factor in determining clinical success of inhaled corticosteroid therapy. Delivery systems can significantly affect both topical and systemic activity of inhaled corticosteroids.[45,46] Poor inhaler technique has been reported in up to 89 percent of patients.[47]

Metered dose inhalers (MDIs) are pressurized spray inhalers, available in suspension and solution, for which the user has to press down on the metal canister to release the medicine and then inhale. MDIs deliver approximately 15 to 35 percent of the administered dose to the lungs. Spacer chambers can be attached to MDIs to make them easier to use by people who find it hard to coordinate the press-and-breathe action. When using the spacer, the user can take several breaths to inhale the medicine, which is held in the chamber, so that it is more likely that the proper amount of medicine will reach the airways. There are currently two inhalers that are still in the chlorofluorocarbons (CFC) MDI formulation, Azmacort and Aerobid/Aerobid M. Azmacort has been discontinued effective December 31, 2009; however some product may still be available. The last date for Aerobid to be manufactured, sold, or dispensed was June 30, 2011.[48]

Dry-powder inhalers (DPIs) are breath-actuated devices that release the medicine in the form of a dry powder when the user breathes in. Although DPIs minimize the potential difficulties in coordinating the press-and-breathe action of the MDI, these delivery systems tend to result in more dosage variations than MDIs at low inspiratory flow rates (less than 20 L/min).

Nebulizer therapy is not the recommended form of administration for most patients.[49] It is considered inferior to an MDI with spacer because of the inconvenience, decreased drug deposition, higher risk of side effects and potentially higher cost. It may be considered an alternative in cases where patients lack the coordination to use the MDI with spacer particularly in the very young and the very old.

Pharmacokinetics[50,51,52,53,54,55,56,57,58,59,60]

Several comparative studies have demonstrated that, when given in equipotent anti-inflammatory doses, fluticasone (Flovent) and budesonide (Pulmicort) have less systemic effect, as measured by plasma cortisol, than the other agents.[61,62,63,64,65] There is, however, considerable intersubject variability in the rate of absorption of these agents from the lungs.[66]

The NAEPP guidelines provide information regarding the relative potencies and dosages of each of the available agents.[67] It should be noted that these are not the FDA-approved doses, but rather those doses shown to be clinically effective and recommended by the NHLBI.

Mometasone (Asmanex) for pediatrics and ciclesonide (Alvesco) were approved after the release of the 2007 NAEPP report and are therefore not contained in the following comparative chart. However, beginning with the 2008 GINA guidelines, information on these products are included.

***NAEPP Expert Panel Report-3 Estimated Comparative Daily Dosages for Inhaled Corticosteroids (mcg/day)*[68,69]**

Drug	Adults and Children ≥12 Years of Age			Children (five to 11 years of age)		
	Low-dose	Medium-dose	High-dose	Low-dose	Medium-dose	High-dose
beclomethasone HFA (QVAR)	80-240	240-480	>480	80-160	>160-320	>320
budesonide DPI (Pulmicort)	180-600	>600-1,200	>1,200	180-400	>400-800	>800
budesonide inhaled suspension (Pulmicort Respules)	n/a	n/a	n/a	0.5 mg (ages 5 to 8 years)	1 mg (ages 5 to 8 years)	2 mg (ages 5 to 8 years)
flunisolide MDI (Aerobid, -M)	500-1,000	1,000-2,000	>2,000	500-750	1,000-1,250	>1,250
fluticasone HFA MDI (Flovent HFA)	88-264	264-440	>440	88-176	>176-352	>352
mometasone DPI (Asmanex Twisthaler)	200	400	>400	n/a	n/a	n/a
triamcinolone MDI (Azmacort)	300-750	>750-1,500	>1,500	300-600	>600-900	>900

n/a= not available

Most of these agents are recommended for twice daily use. The exceptions to this are mometasone (Asmanex DPI), which can be dosed once daily, and triamcinolone (Azmacort MDI), which is usually given three to four times daily, although some patients may respond to twice daily dosing.

GINA Guidelines for Equipotent Dosages of Inhaled Corticosteroids (mcg/day)[70]

Drug	Adults			Children		
	Low-dose	Medium-dose	High-dose	Low-dose	Medium-dose	High-dose
beclomethasone MDI (QVAR)	200-500	>500-1,000	>1,000-2,000	100-200	>200-400	>400
budesonide DPI (Pulmicort)	200-400	>400-800	>800-1,600	100-200	>200-400	>400
budesonide respules (Pulmicort Respules)	--	--	--	250-500	>500-1,000	>1,000
ciclesonide MDI (Alvesco)	80-160	>160 - 320	>320 – 1,280	80-160	>160 - 320	>320
flunisolide MDI (Aerobid, -M)	500-1,000	>1,000-2,000	>2,000	500-750	>750-1,250	>1,250
fluticasone MDI (Flovent)	100-250	>250-500	>500-1,000	100-200	>200-500	>500
mometasone DPI (Asmanex)	200-400	>400-800	>800-1,200	100-200	>200-400	>400
triamcinolone MDI (Azmacort)	400-1,000	>1,000-2,000	>2,000	400-800	>800-1,200	>1,200

Onset of Action

Drug	Onset of action	Maximum benefit
Glucocorticoids		
beclomethasone MDI (QVAR)[71]	one to two weeks	three to four weeks
budesonide DPI (Pulmicort Flexhaler)[72]	24 hours	one to two weeks
budesonide suspension (Pulmicort Respules)[73]	two to eight days	four to six weeks
ciclesonide MDI (Alvesco)[74]	--	four weeks or longer
flunisolide MDI (Aerobid)[75]	one to four weeks	--
fluticasone MDI (Flovent HFA)[76]	24 hours – variable time to onset	one to two weeks or longer
fluticasone powder for inhalation (Flovent Diskus)[77]	24 hours – variable time to onset	one to two weeks or longer
mometasone DPI (Asmanex)[78]	one to 2.5 hours	one to two weeks or longer
triamcinolone MDI (Azmacort)[79]	one week	two weeks or longer
Glucocorticoids/Bronchodilator combinations		
budesonide/formoterol MDI (Symbicort)[80]	15 minutes for asthma, 5 minutes for COPD	two weeks or longer
fluticasone/salmeterol DPI (Advair Diskus)[81]	30 – 60 minutes	one week or longer
fluticasone/salmeterol MDI (Advair HFA)[82]	30 – 60 minutes	one week or longer
mometasone/formoterol MDI (Dulera)[83]	variable	one week or longer

Contraindications/Warnings[84,85,86,87,88,89,90,91,92,93,94]

All of these agents are contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

A black box warning exists for all long-acting beta agonists (e.g., salmeterol and formoterol) as well as all combination products that contain them [e.g., fluticasone/salmeterol (Advair HFA, Advair Diskus), budesonide/formoterol (Symbicort), mometasone/formoterol (Dulera)]. For Advair Diskus, Advair HFA, Symbicort, and Dulera, the boxed warning, Risk of Asthma-Related Deaths, states the following:

- Long-acting beta$_2$-adrenergic agonists increase the risk of asthma-related deaths. A U.S. study showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus three out of 13,179 patients on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigate the increased risk of asthma-related death from LABAs. Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

- When treating patients with asthma, Advair Diskus, Advair HFA, Symbicort, and Dulera should be prescribed for only those patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue Advair, Symbicort, or Dulera) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use Advair Diskus, Advair HFA, Symbicort, or Dulera for patients whose asthma is adequately controlled on low or medium dose ICS.

Risk Evaluation and Mitigation Strategy

The REMS for the products that contain a long-acting beta agonist includes a medication guide, a detailed communication plan and annual assessments related to the potential adverse effects associated with their use.

Drug Interactions[95,96,97,98,99,100,101,102,103,104,105]

The main route of metabolism for many corticosteroids is via the cytochrome P450 isoenzyme 3A4. Inhibitors of CYP3A4 (ritonavir, ketoconazole, itraconazole, clarithromycin, erythromycin) may increase the plasma concentration of ICS. Fluticasone (Flovent) use in combination with ritonavir has been associated with systemic corticosteroid effects such as Cushing's syndrome and adrenal suppression.

Products containing salmeterol or formoterol (Advair Diskus, Advair HFA, Dulera, Symbicort):

- These agents should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within two weeks of discontinuation of such agents, because the action of the long-acting $beta_2$ agonist, on the cardiovascular system may be potentiated by these agents.
- Concomitant treatment with xanthine derivatives or diuretics may potentiate any hypokalemic effect of the LABA.

Adverse Effects

Drug	Cough	Headache	Nausea	Oral candidiasis	Pharyngitis	Upper respiratory infection
Glucocorticoids						
beclomethasone MDI (QVAR)[106]	1-3	12	1	0	8	9
budesonide DPI (Pulmicort Flexhaler)[107]	nr	nr	1.8	1.3	2.7	2.2
budesonide suspension (Pulmicort Respules)[108]	5-9	≥3	nr	nr	≥3	34-38
ciclesonide MDI (Alvesco)[109]	< 1	4.9-11	< 1	< 1	7-10.5	4.1-8.7
flunisolide MDI (Aerobid, Aerobid-M)[110]	3-9	25	25	3-9	1-3	25
fluticasone powder for inhalation (Flovent Diskus)[111]	1-5	2-14	1-8	<1-9	3-22	14-21
fluticasone MDI (Flovent HFA)[112]	4-6	5-11	reported	2-5	1-3	16-18
mometasone DPI (Asmanex)[113]	nr	20-22	1-3	4-6	8-13	8-15
triamcinolone MDI (Azmacort)[114]	reported	7-21	nr	reported	7-25	nr
Glucocorticoid/Bronchodilator Combinations						
budesonide/ formoterol MDI (Symbicort)[115]	reported	6.5-11.3	reported	1.4-6	7.3-10.5	3.5-10.5
fluticasone/ salmeterol DPI (Advair Diskus)[116]	3-6	12-13	4-6	1-4	10-13	21-27
fluticasone/ salmeterol MDI (Advair HFA)[117]	reported	21	5	1-3	nr	16
mometasone/ formoterol MDI (Dulera)[118]	nr	2.0-4.5	nr	0.7-0.8	4.7	nr

Adverse effects are reported as a percentage. Adverse effects are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

In 2010, the FDA issued new recommendations on the safe use of long-acting beta$_2$-agonists in the treatment of asthma, which applies to the combination products of budesonide/formoterol (Symbicort), mometasone/formoterol (Dulera), and fluticasone/salmeterol (Advair Diskus, Advair HFA).[119] The FDA recommends against the use of long-acting beta$_2$-agonists without the use of an asthma controller medication such as an ICS. Also, long-acting beta$_2$-agonists should be used for the shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved, and used long-term only in patients whose asthma is not adequately controlled on asthma controller medications. The REMS for long-acting beta$_2$-agonists will include a revised Medication Guide written specifically for patients, and a plan to educate healthcare professionals about the appropriate use of long-acting beta$_2$-agonists. In addition, the FDA is requiring the manufacturers to conduct additional clinical trials to further evaluate the safety of LABAs when used in combination with ICS.

Special Populations[120,121,122,123,124,125,126,127,128,129,130]

Pediatrics

Safety and effectiveness of fluticasone/salmeterol (Advair HFA), budesonide/formoterol (Symbicort), mometasone/formoterol (Dulera), and ciclesonide (Alvesco) in children under age 12 have not been proven. Safety and effectiveness of triamcinolone (Azmacort), budesonide (Pulmicort Flexhaler), and flunisolide (Aerobid, Aerobid-M) in children less than six years have not been proven. Beclomethasone (QVAR) in children less than five years has not been proven safe or effective. Fluticasone/salmeterol (Advair Diskus) and fluticasone (Flovent HFA, Flovent Diskus) in children younger than four years have not been proven safe or effective. Mometasone (Asmanex) is approved for maintenance treatment of asthma as prophylactic therapy for children age four years and older.

Budesonide respules (Pulmicort Respules) are indicated specifically for children between twelve months and eight years of age.

Pregnancy

All products in this category are Pregnancy Category C except budesonide (Pulmicort), which is Pregnancy Category B.

Hepatic Impairment

Close monitoring of patients using fluticasone/salmeterol (Advair) or budesonide/formoterol (Symbicort) who have hepatic impairment is recommended due to accumulation of both active ingredients.

Dosages

Drug	Adult doses		Pediatric doses		Availability
	Initial	Maximum	Initial	Maximum	
Glucocorticoids					
beclomethasone MDI (QVAR)[131]	40 -80 mcg twice daily (previous bronchodilator use alone) 40 -160 mcg twice daily (previous inhaled corticosteroid therapy)	320 mcg twice daily	40 mcg twice daily	80 mcg twice daily	40 mcg and 80 mcg MDI with HFA propellant (100 actuations per canister)
budesonide DPI (Pulmicort Flexhaler)[132]	360 mcg twice daily	720 mcg twice daily	180 mcg twice daily	360 mcg twice daily	90 mcg and 180 mcg DPI (60 and 120 actuations per canister, respectively) Dose counter available for all strengths
budesonide suspension (Pulmicort Respules)[133]	--	--	Prior bronchodilator alone: 500 mcg once daily or 250 mcg twice daily Prior ICS: 500 mcg once daily or 250 to 500 mcg twice daily Prior oral glucocorticoid: 500 mcg twice daily or 1000 mcg once daily		250, 500, 1,000 mcg per 2 mL Respule® via jet nebulizer

Dosages (continued)

Drug	Adult doses		Pediatric doses		Availability
	Initial	Maximum	Initial	Maximum	
Glucocorticoids					
ciclesonide MDI (Alvesco)[134]	80 mcg twice daily (patients who received bronchodilator alone)	160 mcg twice daily	12 years and older: 80 mcg twice daily (patients who received bronchodilator alone)	160 mcg twice daily	80 mcg or 160 mcg MDI with HFA propellant (80 mcg is available as 60 actuations per canister) (160 mcg MDI is available as 60 actuations per canister) Dose counter available for all strengths
	80 mcg twice daily (patients who received inhaled corticosteroid)	320 mcg twice daily	12 years and older: 80 mcg twice daily (patients who received inhaled corticosteroid)	320 mcg twice daily	
	320 mcg twice daily (patients who received oral corticosteroids)	320 mcg twice daily	12 years and older: 120 mcg twice daily (patients who received oral corticosteroid)	320 mcg twice daily	
flunisolide MDI (Aerobid, Aerobid-M)[135]	500 mcg twice daily	1,000 mcg twice daily	500 mcg twice daily	500 mcg twice daily	250 mcg MDI with three CFC propellants (100 actuations per canister)
fluticasone MDI (Flovent HFA)[136]	88 mcg twice daily (patients who received bronchodilator alone) 88-220 mcg twice daily (patients who used inhaled corticosteroids) 440 mcg twice daily (patients who used oral corticosteroids)	440 mcg twice daily 440 mcg twice daily 880 mcg twice daily	four to 11 years: 88 mcg twice daily	four to 11 years: 88 mcg twice daily	44, 110, 220 mcg MDI with HFA propellant (120 actuations per canister) Dose counter available for all strengths

Dosages (continued)

Drug	Adult doses		Pediatric doses		Availability
	Initial	**Maximum**	**Initial**	**Maximum**	
Glucocorticoids					
fluticasone powder for inhalation (Flovent Diskus)[137]	100 mcg twice daily (patients who received bronchodilators alone)	500 mcg twice daily	four to 11 years: 50 mcg twice daily (when prior therapy is with bronchodilator alone or inhaled corticosteroid)	four to 11 years: 100 mcg twice daily	50 mcg, 100 mcg, 250 mcg blister units (60 blisters per pack) Dose counter available for all strengths
	100-250 mcg twice daily (patients who used inhaled corticosteroids)	500 mcg twice daily			
	500-1,000 mcg twice daily (patients who used oral corticosteroids)	1,000 mcg twice daily			
mometasone DPI (Asmanex Twisthaler)[138]	220 mcg daily in evening (if on bronchodilator alone or inhaled corticosteroid) or 440 mcg twice daily (if on oral corticosteroid)	440 mcg daily (single or divided doses) or 880 mcg daily	12 years and older: 220 mcg daily in evening (if on bronchodilator alone or inhaled steroid) or 440 mcg twice daily (if on oral corticosteroid) 4 to 11 years of age: 110 mcg once daily in the evening	12 years and older: 440 mcg daily (single or divided doses) or 880 mcg daily 4 to 11 years of age: 110 mcg once daily in the evening	110 & 220 mcg DPI (Available in 100 & 200 actuations per unit, respectively) Dose counter available for all strengths

Dosages (continued)

Drug	Adult doses		Pediatric doses		Availability
	Initial	Maximum	Initial	Maximum	
Glucocorticoids					
triamcinolone MDI (Azmacort)[139]	150 mcg three to four times daily or 300 mcg twice daily	1,200 mcg daily	75-150 mcg three to four times daily or 150-300 mcg twice daily	900 mcg daily	60 mg per 20 gram canister Note: 200 mcg from the valve and 75 mcg from the spacer mouthpiece per actuation (240 actuations per canister) A check-off chart is including in the Patient Medication Information to track the number of inhalations used
Glucocorticoid/Bronchodilator Combinations					
budesonide/formoterol MDI (Symbicort)[140]	two inhalations twice daily of 80 mcg/ 4.5 mcg or 160 mcg/ 4.5 mcg	two inhalations twice daily of 160 mcg/ 4.5 mcg	12 years and older: 2 inhalations twice daily of 80 mcg/ 4.5 mcg or 160 mcg/ 4.5 mcg	12 years and older: 2 inhalations twice daily of 160 mcg/ 4.5 mcg	80/4.5 and 160/4.5 mcg/actuation MDI with HFA propellant (120 actuations per canister) Dose counter available for all strengths
fluticasone/salmeterol DPI (Advair Diskus)[141]	100 mcg/ 50 mcg twice daily to 500 mcg/ 50 mcg twice daily	500 mcg/ 50 mcg twice daily	4-11 years 100 mcg/ 50 mcg twice daily	--	100/50, 250/50 and 500/50 mcg/actuation Diskus® DPI (60 blisters) Dose counter available for all strengths
fluticasone/salmeterol MDI (Advair HFA)[142]	two inhalations of 45 mcg/ 21 mcg twice daily or 115 mcg/21 mcg twice daily or 230 mcg/ 21 mcg twice daily	two inhalations of 230 mcg/ 21 mcg twice daily	12 years and older: two inhalations of 45 mcg/ 21 mcg twice daily or 115 mcg/ 21 mcg twice daily or 230 mcg/ 21 mcg twice daily	12 years and older: two inhalations of 230 mcg/ 21 mcg twice daily	45/21, 115/21 and 230/21 mcg/actuation MDI with HFA propellant (120 actuations per canister) Dose counter available for all strengths

Drug	Adult doses		Pediatric doses		Availability
	Initial	Maximum	Initial	Maximum	
Glucocorticoid/Bronchodilator Combinations					
mometasone/formoterol MDI (Dulera) [143] The recommended starting dosages are based on prior asthma therapy	For medium dose ICS: two inhalations of 100 mcg/5 mcg twice daily For high dose ICS: two inhalations of 200 mcg/5 mcg twice daily	For medium dose ICS: two inhalations of 100 mcg/5 mcg twice daily For high dose ICS: two inhalations of 200 mcg/5 mcg twice daily	For medium dose ICS: two inhalations of 100 mcg/5 mcg twice daily For high dose ICS: two inhalations of 200 mcg/5 mcg twice daily	For medium dose ICS: two inhalations of 100 mcg/5 mcg twice daily For high dose ICS: two inhalations of 200 mcg/5 mcg twice daily	100/5 and 200/5 mcg per actuation Dose counter available for all strengths

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Asthma

beclomethasone MDI (QVAR) versus fluticasone/salmeterol DPI (Advair)

In an evaluation of step-down therapy, 39 patients with uncontrolled moderate to severe asthma were treated with beclomethasone MDI 1,000 mcg twice daily for four weeks and then randomized to medium-dose beclomethasone MDI 200 mcg twice daily or low-dose fluticasone/salmeterol DPI 100/50 mcg twice daily for eight weeks in a double-blind, double-dummy, parallel-group design.[144] The primary outcome was the provocative dose of methacholine producing a 20 percent fall in forced expiration volume in the first second (FEV_1)

(methacholine PD20). Secondary outcomes were lung function, surrogate inflammatory markers, diary card responses, QoL, and safety. There was a 0.9 doubling dose improvement in methacholine PD20 comparing asthma before versus after beclomethasone. Beclomethasone maintained this improvement, whereas fluticasone/salmeterol produced a further improvement, amounting to a significant 1.1 doubling dose difference at eight weeks for fluticasone/salmeterol versus beclomethasone. Suppression of plasma and urinary cortisol and serum osteocalcin levels occurred with beclomethasone DPI, but values returned to baseline levels within one month of beclomethasone or fluticasone/salmeterol administration.

budesonide/formoterol MDI (Symbicort) versus budesonide DPI (Pulmicort)

A double-blind, randomized, 12-week study conducted in 619 patients ages 12 and older with mild to moderate asthma to evaluate the efficacy and tolerability of once-daily budesonide/formoterol versus once-daily budesonide in patients stable with twice-daily budesonide/formoterol.[145] After an initial four to five weeks of two inhalations twice daily budesonide/formoterol 80 mcg/4.5 mcg (daily dose of 320 mcg/18 mcg), stable patients were randomized to one of four treatment groups. These groups included: two inhalations of twice daily of budesonide/formoterol 80 mcg/4.5 mcg (daily dose 320 mcg/18 mcg); two inhalations once daily in the evening of budesonide/formoterol 160/4.5 mcg or 80/4.5 mcg (daily dose of 320 mcg/9 mcg or 160/4.5 mcg); or two inhalations once daily of budesonide 160 mcg (daily dose of 320 mcg). All budesonide/formoterol groups maintained significantly more favorable evening pre-dose FEV_1, morning PEF, daytime/nighttime asthma symptoms, nighttime rescue medication use, and rescue medication-free days versus budesonide. Variables evaluated during the end of the once-daily dosing interval included evening pre-dose FEV_1, evening PEF, daytime asthma symptoms, and daytime rescue medication use. They significantly favored twice-daily budesonide/formoterol versus all treatments. Twice-daily budesonide/formoterol demonstrated significantly more favorable results for symptom-free and asthma control days versus all treatments and awakening-free nights versus budesonide. Asthma Quality of Life Questionnaire and Asthma Control Questionnaire results significantly favored twice-daily budesonide/formoterol versus budesonide ($p \leq 0.018$). All treatments were well tolerated.

A double-blind, randomized, 12-week multicenter study was conducted in 521 patients ages six to 15 years with mild/moderate persistent asthma to assess the efficacy and tolerability of once-daily budesonide/formoterol MDI versus budesonide MDI (primary) and twice-daily budesonide/formoterol MDI (secondary) in children/adolescents with asthma who have been stabilized with twice-daily budesonide/formoterol MDI.[146] Patients had been stabilized during a four to five week run-in with two inhalations twice daily of budesonide/formoterol 40/4.5 mcg inhalations (160/18 mcg daily). These patients were randomized to either continue on the stabilization regimen, to receive a reduced dose of two inhalations once every evening of daily budesonide/formoterol 80/4.5 mcg (160/9 mcg daily), or two inhalations once every evening of budesonide 80 mcg (160 mcg daily). The once or twice daily regimens of budesonide/formoterol were more effective than budesonide for evening peak expiratory flow (primary variable) at the end of the 24 hour once daily dosing interval ($p \leq 0.027$). Twice-daily budesonide/formoterol demonstrated better efficacy versus once daily treatments for evening pre-dose FEV_1 ($p \leq 0.011$), versus budesonide for daytime/nighttime rescue medication ($p \leq 0.023$), and versus once-daily budesonide/formoterol for daytime rescue medication (last 12 hours of once-daily dosing) ($p = 0.032$). There were no significant between-group differences for daytime/nighttime asthma symptoms, nighttime awakenings attributed to asthma, or health-related quality of life. Fewer patients experienced asthma worsening based on predefined criteria with twice-daily budesonide/formoterol (8.2 percent) versus once-daily budesonide (15.5

percent) (p=0.036) or once-daily budesonide/formoterol (19.6 percent) (p=0.002). All treatments were well tolerated.

budesonide/formoterol MDI (Symbicort) versus budesonide DPI (Pulmicort) versus formoterol MDI (Foradil) versus budesonide (Pulmicort) + formoterol (Foradil) versus placebo

A 12-week, randomized, double-blind, double-dummy, placebo-controlled study was conducted to compare the efficacy and safety of budesonide/formoterol to each of its individual ingredients [budesonide, formoterol, or budesonide + formoterol] as well as to placebo.[147] Five hundred ninety-six patients ages 12 years and older with moderate to severe persistent asthma and previously receiving an inhaled corticosteroid were placed on budesonide 160 mcg twice daily. After two weeks, they were randomized to budesonide/formoterol 160/4.5 mcg twice daily; budesonide 160 mcg twice daily + formoterol 4.5 mcg twice daily; budesonide 160 mcg twice daily; formoterol 4.5 mcg twice daily; or placebo twice daily. The primary efficacy endpoints were mean change from baseline of FEV_1 and mean change from baseline in 12-hour FEV_1. The results were similar in the budesonide/formoterol and the budesonide + formoterol groups in all measures. The budesonide/formoterol group showed greater improvement in FEV_1 ($p \leq 0.049$) than the individual budesonide, formoterol, and placebo. Also, fewer patients on budesonide/formoterol experienced worsening asthma symptoms ($p \leq 0.025$). All of the treatments were well tolerated with similar safety profiles.

A 12-week, randomized, double-blind, double-dummy, placebo-controlled, multicenter trial of 596 adult patients (ages 12 and older) with moderate to severe persistent asthma was conducted to evaluate patient reported outcomes (PROs) related to asthma therapy.[148] Patients received budesonide 160 mcg twice daily for the first two weeks. They were then randomized to receive two inhalations twice daily of one of five treatment arms: budesonide/formoterol 160/4.5 mcg; budesonide 160 mcg plus formoterol DPI 4.5 mcg; budesonide 160 mcg; formoterol DPI 4.5 mcg; or placebo. PROs were assessed in 553 patients 18 years or older using the standardized Asthma Quality of Life Questionnaire (AQLQ[S]), Medical Outcomes Survey (MOS) Sleep Scale, Patient Satisfaction With Asthma Medication (PSAM) questionnaire, diary data, and global assessments. Patients receiving budesonide/formoterol reported significantly greater improvements from baseline on the AQLQ(S) and asthma control variables (based on symptoms and rescue medication use; all $p<0.001$) versus placebo. Clinically important improvements (increase of≥ 0.5 points) from baseline to end of treatment in AQLQ(S) overall scores were achieved by 43.6 percent of patients receiving budesonide/formoterol versus 22.6 percent of patients receiving placebo (p=0.001). The MOS Sleep Scale scores generally showed no differences among treatment groups. Patients receiving budesonide/formoterol had significantly greater PSAM questionnaire scores and better outcomes on physician-patient global assessments at end of treatment versus placebo (all $p \leq 0.001$).

budesonide/formoterol MDI (Symbicort) versus budesonide (Pulmicort) versus formoterol (Foradil) versus placebo

A 12-week, multicenter, double-blind, randomized, placebo-controlled, double-dummy study was conducted in 480 patients age 12 years or older with mild to moderate persistent asthma treated with inhaled corticosteroids for four weeks or more and with an FEV_1 of 60 to 90 percent.[149] After a two-week washout period, patients received either budesonide/formoterol 80/4.5 twice daily (n=123), budesonide 80 mcg twice daily (n=121), formoterol 4.5 mcg twice daily (n=114), or placebo (n=122). At the end of treatment, greater increases in FEV_1 occurred in the budesonide/formoterol group versus all of the other groups (0.37 versus 0.23, 0.17, and 0.03 L, respectively; $p<0.005$). Fewer patients receiving budesonide/formoterol withdrew due to

worsening asthma versus the formoterol (42.1 and 18.4 percent) and placebo (56.6 versus 32.8 percent) groups. However, the results were similar, according to the authors, with respect to worsening asthma between the budesonide/formoterol and budesonide groups (21.5 versus 6.6 percent). The authors determined that in adults and adolescents with mild to moderate persistent asthma that twice daily budesonide/formoterol resulted in improved pulmonary function versus its component ingredients alone. All of the study drugs were well tolerated.

fluticasone (Flovent) versus fluticasone/salmeterol (Advair)

A one-year, randomized, stratified, double-blind, parallel-group study of 3,421 patients with uncontrolled asthma compared fluticasone and fluticasone/salmeterol in achieving guideline-based measures of control: totally and well-controlled asthma.[150] Treatment was stepped-up until total control was achieved (or maximum 500 mcg corticosteroid twice a day). Significantly more patients in each stratum (previously corticosteroid-free, low- and moderate-dose corticosteroid users) achieved control with fluticasone/salmeterol than fluticasone. Total control was achieved across all strata in 31 percent versus 19 percent of patients after dose escalation ($p<0.001$) and 41 percent versus 28 percent of patients at one year for fluticasone/salmeterol and fluticasone, respectively. Asthma became well controlled in 63 percent versus 50 percent after dose escalation ($p<0.001$) and in 71 percent versus 59 percent of patients at one year. Control was achieved more rapidly and at a lower corticosteroid dose with fluticasone/salmeterol versus fluticasone. Across all strata, 68 percent and 76 percent of the patients receiving fluticasone/salmeterol and fluticasone, respectively, were on the highest dose at the end of treatment. Exacerbation rates (0.07-0.27 per patient per year) and improvement in health status were significantly better with fluticasone/salmeterol.

A multicenter, randomized, double-blind, four-week, parallel group trial of 248 pediatric patients (ages four to 17 years old) with persistent asthma was conducted to evaluate the effectiveness of fluticasone/salmeterol 100 mcg/50 mcg compared to fluticasone 100 mcg for the prevention of airflow limitation triggered by standardized exercise challenge.[151] Exercise challenge tests were performed during screening and approximately eight hours after administration of the blinded study medication on treatment day 28. After four weeks of therapy, both treatments provided protection following exercise challenge. The protection estimated by the maximal fall in FEV_1 was significantly better for fluticasone/salmeterol (9.5 +/- 0.8 percent) compared with fluticasone propionate alone (12.7 +/- 1.1 percent, $p=0.021$). Statistically significant differences were not observed for asthma rescue-free days and asthma symptom-free days.

A randomized, double-blind, controlled study was performed in children with asthma ages four to 11 years old to compare the addition of salmeterol 50 mcg to fluticasone 100 mcg with doubling the dose to fluticasone 200 mcg in improving lung function (functional residual capacity (FRC) and FEV_1. [152] Patients were randomized after a two-week run-in period receiving fluticasone 100 mcg twice daily to either combination salmeterol/fluticasone 50 mcg/100 mcg twice daily or fluticasone 200 mcg twice daily for six weeks. Lung function was measured before run-in, at randomization, after three weeks, at the end of a six-week treatment, and after the 48-hour washout. Symptom scores and rescue medication use were recorded throughout the study. Thirty-five children entered the run-in and 24 were randomized. All children showed an improvement in FRC. After adjusting for age, gender, and baseline FRC, children receiving the combination had a significantly greater improvement in FRC compared with those receiving the higher dose flluticasone (adjusted means ratio [95 percent confidence interval {CI}], 0.81 [0.68-0.97]; $p=0.021$). There was a significant interaction between treatment and gender (FRC, adjusted geometric mean [95 percent CI] combination versus fluticasone: boys, 1.25 [1.1-1.41] [n=7] versus 1.87 [1.61-2.17] [n=5]; girls, 1.29 [1.1-1.52] [n = 5] versus 1.29 [1.13-1.47] [n=7];

p=0.008). There were no differences in FEV_1 symptoms or rescue medication use between the groups. Addition of salmeterol provides greater improvement in FRC than doubling the dose of fluticasone in children with moderate/severe persistent asthma.

A multicenter, randomized, parallel-group, double-blind study was performed comparing fluticasone/salmeterol 50/100 mcg twice a day and fluticasone 200 mcg twice a day during a 26 week period to evaluate if the combination is non-inferior regarding symptom control and the effects on asthma control and lung function in children with symptomatic asthma.[153] For children with symptomatic asthma despite low to moderate doses of inhaled corticosteroids, evidence is still lacking whether to add a long-acting bronchodilator or to increase the dose of inhaled corticosteroids. A total of 158 children age six to 16 years old, still symptomatic on fluticasone 100 mcg twice daily were included in a four-week run-in period. The percentage of symptom-free days during the last 10 weeks of the treatment period did not differ between treatment groups (per protocol analysis: adjusted mean difference 2.6 percent; 95 percent confidence interval, -8.1 to 13.4). Both groups showed substantial improvements of about 25 percentage points in symptom-free days (both p<0.001 from baseline). Lung function measurements (FEV_1, FVC, PEF rate, and maximal expiratory flow) did not differ between groups except for a slight advantage in maximal expiratory flow in the fluticasone/salmeterol group at one week. No differences were found between fluticasone and fluticasone/salmeterol regarding exacerbation rates, adverse events, or growth.

<u>fluticasone DPI (Flovent) versus salmeterol DPI (Serevent) versus fluticasone/salmeterol DPI (Advair)</u>

A 12-week, randomized, double-blind study was conducted in patients 12 years and older (n=267) with persistent asthma who were symptomatic while taking as-needed, short-acting $beta_2$-agonists alone.[154] Treatments were administered twice daily via the fluticasone/salmeterol Diskus device: salmeterol 50 mcg; low-dose fluticasone 100 mcg; or fluticasone 100 mcg with salmeterol 50 mcg. At end point, fluticasone/salmeterol were significantly (p≤0.02) more effective than the individual agents used alone in improving morning and evening peak expiratory flow rate and asthma symptoms. In addition, fluticasone and salmeterol effectively reduced rescue albuterol use (p≤0.04).

<u>fluticasone/salmeterol DPI (Advair) versus budesonide/formoterol MDI (Symbicort)</u>

A multicenter, parallel group, double-blind, double-dummy, randomized 24-week study was designed to compare the efficacy of salmeterol/fluticasone propionate combination 50/250 mcg one inhalation twice daily with formoterol/budesonide combination 6/200 mcg two inhalations twice daily in patients (n=1,391) with persistent asthma, currently receiving 1,000-2,000 mcg/day of inhaled corticosteroids.[155] The primary endpoint, mean rate of all exacerbations over 24 weeks, was similar in both treatment groups (p=0.571). A reduction in the rate of exacerbations over time was observed in both treatment groups. Overall, there was a 30 percent lower annual rate of moderate/severe exacerbations in the salmeterol/fluticasone group compared with the formoterol/budesonide group (95% CI, 0-49%, 52 percent reduction versus one percent increase; p=0.059). Similar improvements in lung function, asthma symptoms and rescue medication usage were seen with both treatments and both were well tolerated.

<u>mometasone furoate DPI (Asmanex) versus placebo</u>

A 12-week, multicenter, double-blind, parallel-group, placebo-controlled study evaluating two dosing regimens of mometasone (100 mcg every evening and 100 mcg twice daily) in 296 children ages four to 11 years of age with asthma and prior use of inhaled corticosteroids.[156]

The primary efficacy variable was the change in FEV_1 from baseline to endpoint. The average change in FEV_1 for the group receiving a daily dose was 4.73 points while the group receiving a twice daily dose was 5.52 points ($p \leq 0.002$). The active treatments did not differ from placebo in adverse event reporting.

mometasone furoate DPI (Asmanex) versus budesonide DPI (Pulmicort) versus placebo

An eight-week, multicenter, placebo-controlled, double-blind, double-dummy study was conducted in 262 patients (12 years of age or older) with moderate persistent asthma to compare the safety and efficacy of once daily mometasone DPI to budesonide DPI and placebo.[157] Patients were randomized to once daily morning treatment with mometasone 440 mcg, low-dose budesonide 400 mcg, or placebo. The primary efficacy endpoint was percent change in FEV_1 from baseline to the final evaluable visit. At endpoint, the FEV_1 was significantly greater ($p<0.01$) in the mometasone group (8.9 percent) than both the budesonide group (2.1 percent) and placebo group (-3.9 percent). Secondary efficacy variables including morning and evening PEF rates, albuterol use, percentage of asthma symptom-free days, and physician-evaluated response to therapy were also significantly improved at endpoint in the mometasone group compared with both the placebo and budesonide groups ($p<0.05$). Both active treatments were well tolerated.

mometasone/formoterol MDI (Dulera) versus mometasone (Asmanex) versus formoterol (Foradil) versus placebo

A 26-week, placebo-controlled trial evaluated 781 patients 12 years of age and older with persistent asthma that were not well controlled on medium doses of inhaled corticosteroids.[158] The study compared mometasone/formoterol MDI 100 mcg/5 mcg, mometasone furoate MDI 100 mcg, formoterol fumarate MDI 5 mcg and placebo; each administered as two inhalations twice daily. All other maintenance therapies were discontinued. The $FEV1_{AUC\ (0\text{-}12hr)}$ was assessed as a co-primary efficacy endpoint to evaluate the contribution of the formoterol component. Patients receiving the combination mometasone/formoterol had significantly higher increases from baseline at week 12 in mean $FEV_{1AUC\ (0\text{-}12\ hr)}$ compared to mometasone furoate and placebo (both $p<0.001$). These differences were maintained through week 26. Clinical deterioration in asthma or reductions in lung function was another primary endpoint to evaluate the contribution of mometasone furoate. Deteriorations in asthma were defined as any of the following: a 20 percent decrease in FEV_1; a 30 percent decrease in PEF on two or more consecutive days; emergency treatment, hospitalization, or treatment with systemic corticosteroids or other asthma medications not allowed per protocol. Fewer patients who received the combination mometasone/formoterol (30 percent) reported an event compared to patients who received formoterol (54 percent) ($p<0.001$).

mometasone/formoterol MDI (Dulera) versus mometasone (Asmanex) versus formoterol (Foradil) versus placebo

A 12-week double-blind trial evaluated 728 patients ages 12 years and older with persistent asthma who were uncontrolled on high dose inhaled corticosteroids.[159] This study compared mometasone/formoterol 200 mcg/5 mcg with mometasone/formoterol 100 mcg/5 mcg and mometasone furoate 200 mcg, each administered as two inhalations twice daily by metered dose inhalation aerosols. All other maintenance therapies were discontinued. Patients receiving either mometasone/formoterol dosages had significantly greater increases from baseline at day one in mean $FEV_{1AUC\ (0\text{-}12\ hr)}$ compared to mometasone furoate. The difference was maintained over 12 weeks of therapy. Mean change in trough FEV_1 from baseline to week

12 was also assessed to evaluate the relative contribution of mometasone furoate to the combination product. A greater numerical increase in the mean trough FEV_1 was observed for the higher strength mometasone/formoterol compared to the lower strength mometasone/formoterol and mometasone monotherapy. Clinical deterioration in asthma or reduction in lung function was assessed as an additional endpoint. Fewer patients who received either strength mometasone/formoterol (12 percent for each group) compared to mometasone furoate (18 percent) alone reported an event.

ciclesonide MDI (Alvesco) versus budesonide DPI (Pulmicort)

A 12-week, multicenter, randomized study to compare the efficacy of ciclesonide to budesonide enrolled 544 patients ages 12 to 75 years.[160] Patients were randomized to receive inhaled ciclesonide 80 or 320 mcg daily or budesonide 200 mcg twice daily for 12 weeks. The study was designed in a double-blind manner with respect to the ciclesonide dose and open-label for budesonide because a placebo for budesonide was not available. Efficacy and tolerability assessments were performed at baseline and weeks four, eight, and twelve. The primary end point was the change from baseline in FEV_1 at 12 weeks. Secondary endpoints included changes from baseline in morning peak expiratory flow (PEF), asthma symptom scores, and rescue medication use. The results of this study in patients with primarily mild to moderate asthma suggest that patients using either dose of ciclesonide (80 or 320 mcg daily) had similar improvements in pulmonary function, control of asthma symptoms, and reduced need for rescue medications as those patients who received budesonide 200 mcg twice daily.

ciclesonide MDI (Alvesco) versus fluticasone (Flovent)

A 12-week, double-blind, parallel-group study compared the efficacy and safety of once daily ciclesonide and twice daily fluticasone in patients ages 12 to 75 years with persistent asthma.[161] Patients were randomized to once daily ciclesonide 80 mcg (n=278), ciclesonide 160 mcg (n=271), or twice daily fluticasone 88 mcg (n=259). Significant improvements from baseline were seen in all three treatment groups for FEV_1, asthma symptom scores, and rescue medication use (all $p<0.0001$). Asthma exacerbation rates were low. Adverse event reporting indicated good tolerability of all treatments.

COPD

budesonide/formoterol (Symbicort) versus budesonide (Pulmicort) versus formoterol (Foradil) versus placebo

In a 12-month, randomized, double-blind, placebo-controlled, parallel-group study in 812 adults (mean age 64 years, mean FEV_1 36 percent), patients with moderate to severe COPD received two inhalations twice daily of either budesonide/formoterol 160/4.5 mcg, budesonide 200 mcg, formoterol 4.5 mcg, or placebo.[162] Severe exacerbations and FEV_1 were the primary variables. Other variables including peak expiratory flow (PEF), COPD symptoms, health-related quality of life (HRQL), mild exacerbations, use of reliever $beta_2$-agonist, and safety variables were recorded. Budesonide/formoterol reduced the mean number of severe exacerbations per patient per year by 24 percent versus placebo and 23 percent versus formoterol. For patients receiving budesonide/formoterol, FEV_1 increased by 15 percent versus placebo and nine percent versus budesonide. Morning PEF improved significantly on day one versus placebo and budesonide. After one week, morning PEF was improved versus placebo, budesonide, and formoterol. Improvements in morning and evening PEF versus comparators were maintained over 12 months. Budesonide/formoterol decreased all symptom scores and use of reliever

beta$_2$-agonists significantly versus placebo and budesonide, and improved HRQL versus placebo. All treatments were well tolerated.

The SHINE trial was a six-month, double-blind, multicenter trial that evaluated the efficacy and tolerability of budesonide/formoterol in 1,704 patients ages 40 years and older with moderate to very severe COPD.[163] Patients were randomized to receive twice-daily treatment with two inhalations of budesonide/formoterol 160/4.5 mcg or 80/4.5 mcg, budesonide 160 mcg + formoterol 4.5 mcg, budesonide 160 mcg, formoterol 4.5 mcg, or placebo. Primary outcomes measures included pre-dose and one-hour post-dose FEV_1 over the six month treatment period. Budesonide/formoterol 160/4.5 mcg twice a day (320/9 mcg) improved both pre-dose and one-hour post-dose FEV_1 compared to either of the components alone or placebo ($p \leq 0.039$ for all). At the lower dose of 80/4.5 mcg twice a day (160/9 mcg), there was significantly greater improvement in pre-dose FEV_1 and one-hour post-dose FEV_1 compared with budesonide and placebo ($p \leq 0.002$ for all), but not compared to formoterol. Budesonide/formoterol had a safety profile comparable with that of the monocomponents and placebo.

budesonide/formoterol (Symbicort) versus fluticasone/salmeterol (Advair) versus salbutamol versus placebo

In a double-blind, double-dummy, crossover study, 90 patients (age 40 years and older; FEV_1 30 to 70 percent) were randomized to a single dose (two inhalations) of budesonide/formoterol 160/4.5 mcg, fluticasone/salmeterol 250/25 mcg, salbutamol 100 mcg, or placebo on four visits.[164] Outside the United States albuterol is known as salbutamol. The primary end-point was change in FEV_1 five minutes after drug inhalation; secondary end-points included inspiratory capacity (IC) and perception of onset of effect. Budesonide/formoterol significantly improved FEV_1 at five minutes compared with placebo ($p<0.0001$) and fluticasone/salmeterol ($p=0.0001$). Significant differences were first observed at three minutes. Onset of effect was similar with budesonide/formoterol and salbutamol. Improvements in FEV_1 following active treatments were superior to placebo after 180 minutes (all $p<0.0001$); both combinations were better than salbutamol at maintaining FEV_1 improvements ($p \leq 0.0001$) at 180 minutes. Active treatments improved IC at 15 and 185 minutes compared with placebo ($p<0.0001$). Maximal IC was greater with budesonide/formoterol than fluticasone/salmeterol ($p=0.0184$) at 65 minutes. Patients reported a positive response to the perceptions of the onset of effect question shortly after receiving active treatments (median time to onset was five minutes for active treatments versus 20 minutes for placebo), with no significant difference between active treatments. Budesonide/formoterol has an onset of bronchodilatory effect in patients with COPD and reversible airway obstruction that is faster than fluticasone/salmeterol and similar to salbutamol.

fluticasone DPI (Flovent) versus salmeterol DPI (Serevent) versus fluticasone/salmeterol DPI (Advair)

In a double-blind, parallel-group, placebo-controlled study, 1,465 patients with COPD were randomized to receive salmeterol 50 mcg twice daily, high-dose fluticasone 500 mcg twice daily, fluticasone/salmeterol 500/50 mcg twice daily, or placebo.[165] After 12 months, all active treatments improved lung function, symptoms, and health status and reduced use of rescue medication and frequency of exacerbations. Combination therapy improved pretreatment FEV_1 significantly more than did placebo (treatment difference 133 mL, 95% CI, 105 to 161, $p<0.0001$), salmeterol (73 mL, 95% CI, 46 to 101, $p<0.0001$), or fluticasone alone (95 mL, 95% CI, 67 to 122, $p<0.0001$). Combination treatment produced a clinically significant improvement in health status and the greatest reduction in daily symptoms. All treatments were well tolerated with no difference in the frequency of adverse events, bruising, or clinically significant falls in serum cortisol concentration.

Clinical Trials: Safety

There is concern that prolonged treatment with high doses of inhaled corticosteroids may have a detrimental effect on bone mineral density (BMD), cause ocular toxicity, suppress the adrenal/pituitary axis, and inhibit vertical growth.

budesonide (Pulmicort Respules) versus reference treatments

Pooled safety data from budesonide inhalation suspension studies (n=2,356) found there were small differences in short-term growth velocity between children who received budesonide inhalation suspension and those who received reference treatment in two of five trials that evaluated this variable.[166] No posterior subcapsular cataracts were reported in any study. The frequencies of oropharyngeal events and infection with budesonide inhalation suspension were comparable with those of reference treatments. No increased risk of varicella or upper respiratory tract infection was apparent, and budesonide inhalation suspension did not cause significant adrenal suppression in studies assessing this variable.

Data from the inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study evaluated the safety of once-daily budesonide use over three years in patients aged five to 66 years with mild, persistent asthma (n=7,221).[167] The most commonly reported events included respiratory infections, rhinitis, pharyngitis, bronchitis, viral infections, and sinusitis. Fewer asthma-related, serious adverse events were reported with budesonide (2.2 percent) compared with placebo (3.8 percent). Oral candidiasis was reported more frequently with budesonide (1.2 percent) than with placebo (0.5 percent).

A further analysis of the START trial was conducted to determine whether severe asthma exacerbations are associated with a persistent decline in lung function.[168] This study was a three-year, randomized, double-blind trial that enrolled 7,165 patients (five to 66 years of age) with persistent asthma. There were 315 patients who experienced at least one severe asthma exacerbation, of which 305 were analyzable, 190 in the placebo group and 115 in the budesonide group. In the placebo group, the change in post-bronchodilator FEV_1 percent predicted from baseline to the end of the study, in patients who did or did not experience a severe exacerbation was -6.44 percent and -2.43 percent, respectively ($p<0.001$). A significant difference was seen in both children and in adults, but not in adolescents. In the budesonide group, the change in the post-bronchodilator FEV_1 percent predicted in patients who did or did not experience a severe exacerbation was -2.48 percent and -1.72 percent, respectively ($p=0.57$). The difference in magnitude of reduction afforded by budesonide, in patients who experienced at least one severe asthma-related event compared with those who did not, was statistically significant ($p=0.042$). Severe asthma exacerbations are associated with a more rapid decline in lung function. Treatment with low doses of inhaled corticosteroid is associated with an attenuation of the decline.

fluticasone (Flovent) versus placebo

A randomized, double-blind, placebo-controlled study of 160 patients with asthma who had minimal previous exposure to corticosteroids was performed to evaluate the effects of treatment with fluticasone versus placebo on bone, hypothalamic-pituitary-adrenal (HPA) axis function, and the eyes in patients with asthma.[169] Patients received low-dose fluticasone at 88 mcg twice daily, high-dose fluticasone at 440 mcg twice daily, or placebo twice daily for two years. Long-term treatment with 88 mcg of fluticasone twice daily was comparable to placebo in all skeletal, ophthalmic, and HPA axis function assessments. Treatment with fluticasone at 440 mcg twice

daily resulted in no significant effects on bone mineral density and a statistically significant, but not clinically important, temporary reduction in cortisol production.

fluticasone MDI (Flovent) versus budesonide MDI (Pulmicort)

Forty children (age one to three years) with mild asthma were studied in a three-way crossover, randomized, placebo-controlled, double-blind trial.[170] Treatment with medium-dose fluticasone MDI 200 mcg twice daily was compared with low-dose budesonide MDI 200 mcg twice daily and placebo, all given via a spacer device. Systemic steroid activity was assessed after one and four weeks of treatment by measured increase in lower-leg length. The increases in lower-leg length during placebo, budesonide, and fluticasone treatments were 85, 45, and 34 mcm/day, respectively. Compared to placebo, the growth in lower-leg length was significantly reduced from both corticosteroid treatments. The differences between budesonide and placebo (40 mcm/day) and between fluticasone and placebo (51 mcm/day) were statistically significant. The difference between the two active treatment groups, fluticasone and budesonide, was not statistically significant.

fluticasone/salmeterol DPI (Advair) and fluticasone DPI (Flovent)

A randomized, multicenter, double-blind, active-controlled, parallel-group study in 203 children with persistent asthma who were symptomatic during inhaled corticosteroid therapy were examined to compare the safety of twice-daily treatment of inhaled fluticasone/salmeterol with that of fluticasone alone.[171] The subjects received either fluticasone/salmeterol (100/50 mcg) or low-dose fluticasone (100 mcg) alone twice daily for 12 weeks. The results of the study showed that the safety profile of fluticasone/salmeterol was comparable to that of fluticasone alone with the overall incidence of adverse events being 59 percent for fluticasone/salmeterol and 57 percent for fluticasone. The changes in heart rate, blood pressure, and laboratory variables were infrequent and similar between both groups, and no patients had clinically significant abnormal electrocardiographic findings during treatment. The incidence of withdrawals within the study due to asthma exacerbations was two percent in the fluticasone/salmeterol group and five percent in the fluticasone group. Therefore, the study concluded that in children with persistent asthma, fluticasone/salmeterol twice daily was well tolerated, with a safety profile similar to that of fluticasone used alone.

budesonide DPI (Pulmicort) versus fluticasone DPI (Flovent)

The systemic effects of high-dose budesonide 1,600 mcg/day and high-dose fluticasone 1,500 mcg/day were compared in a randomized, double-blind, cross-over study of 60 adult patients with moderate to severe asthma not controlled on high-dose beclomethasone or budesonide.[172] HPA axis suppression of the two treatment groups was assessed by morning serum cortisol and 12-hour nocturnal urinary cortisol excretion measured at the end of each treatment period. Neither treatment produced significant suppression of either parameter compared to baselines. The ratio between the AUC serum cortisol measured after fluticasone treatment and after budesonide treatment was 0.99, indicating equivalent effects on the HPA axis. Two exacerbations of acute asthma occurred during budesonide treatment and none during fluticasone treatment. Both treatments were well tolerated.

Bone Mineral Density and Fracture

Several studies have been performed to evaluate the relative effects of the various agents on bone mass and metabolism.

A multicenter, double-blind, parallel-group study randomized 69 adults with mild to moderate asthma to treatment with medium or high doses of fluticasone or beclomethasone.[173] After one year, there was no loss of trabecular or integral bone in the distal radius or tibia in any of the patients.

In a randomized, double-blind, placebo-controlled trial, the authors recruited 412 current smokers or recent quitters with mild to moderate COPD.[174] They used inhaled triamcinolone 600 mcg or placebo twice daily. Femoral neck and lumbar spine BMD were measured at baseline and again after one and three years. Serum osteocalcin was measured at baseline, three months, one year, and three years. After three years, BMD at the femoral neck decreased 1.78 percent more with inhaled corticosteroid than with placebo ($p<0.001$). More participants in the inhaled corticosteroid group experienced six percent or more loss of femoral neck BMD ($p=0.002$). Lumbar spine BMD increased in the placebo group by 0.98 percent but decreased by 0.35 percent in the inhaled corticosteroid group (a difference of -1.33 percent, $p=0.007$). Changes in osteocalcin did not correlate with changes in BMD. Fractures, lost height, or osteoporosis diagnoses were not increased among inhaled corticosteroid users compared with placebo users.

Linear Growth

Evidence on growth velocity and height over an extended time period is available from the Childhood Asthma Management Program (CAMP) trial that compared budesonide with nedocromil and placebo in 1,041 children followed for four to six years.[175] A difference consistent with the above magnitude occurred during the first year of the study. However, in long-term follow up, the difference in growth velocity was not maintained, and all groups had similar growth velocity at the end of treatment. There was still a one centimeter difference between the study groups at the end of treatment. A slight difference in bone age suggests the potential for catch-up for the inhaled corticosteroid group. An ancillary study of the CAMP trial demonstrated that low-dose budesonide 400 mcg/day over a three-year period had no effects on HPA axis function in children with mild to moderate asthma.[176] Growth in children taking corticosteroids by any route should be carefully monitored.

Meta-Analyses

In 2007, a meta-analysis of randomized trials in children and adults was completed comparing fluticasone to either beclomethasone or budesonide in the treatment of chronic asthma.[177] Two reviewers independently assessed articles for inclusion and methodological quality. Seventy-one studies (14,602 participants) representing 74 randomized comparisons met the inclusion criteria. When compared at a fluticasone-to-budesonide or beclomethasone dose ratio of 1:2, fluticasone produced a significantly greater end of treatment FEV_1 [0.04 L (95% CI, 0 to 0.07 L)], and end of treatment and change in morning PEF. However, there was no significant change in FEV_1 or evening PEF. This applied to all drug doses, age groups, and delivery devices. No difference between fluticasone and beclomethasone or budesonide was seen for trial withdrawals. Fluticasone led to fewer symptoms and less rescue medication use. There was a greater likelihood of pharyngitis with fluticasone when compared to budesonide or beclomethasone with no difference in the likelihood of oral candidiasis. When comparing the doses of these agents in a dose ratio of 1:1, fluticasone produced a statistically significant difference in morning PEF, evening PEF, and FEV_1 over both budesonide and beclomethasone. The effects on exacerbations were mixed. There were no significant differences in the incidence of hoarseness, pharyngitis, candidiasis, or cough at the equivalent dose ratio.

A meta-analysis of published and unpublished literature evaluated the impact of long-term inhaled corticosteroid use on bone density in adult patients with asthma or COPD.[178] The authors found that long-term use was not associated with significant changes in bone density.

Data from the United Kingdom based General Practice Research Database have been evaluated to determine whether children or adolescents exposed to inhaled corticosteroids are at a higher risk of having bone fractures compared with non-exposed individuals.[179] The authors concluded that they were not.

In 2010, a meta-analysis of randomized, controlled trials (RCTs) that compared the strategy of increasing the daily dose of inhaled corticosteroids (ICS) to continuing the same ICS dose in the home management of asthma exacerbations in children or adults with persistent asthma who receive daily maintenance ICS.[180] Five RCTs (four parallel-group and one cross-over) involving a total of 1,250 patients (28 children and 1,222 adults) with mild to moderate asthma were included. The mean daily baseline ICS dose was 555 mcg (range 200 mcg to 795 mcg) and the mean daily ICS dose achieved following the increase was 1,520 mcg (range 1,000 mcg to 2,075 mcg), in beclomethasone dipropionate equivalents. Three parallel-group studies in adults (two doubling and one quadrupling; mean achieved daily dose of 1,695 mcg with a range of 1,420 to 2,075 mcg), involving 1,080 patients contributed data to the primary outcome. There was no significant reduction in the need for rescue oral corticosteroids when patients were randomized to the increased dose of ICS compared to the stable maintenance dose groups (OR 0.85, 95 percent CI 0.58 to 1.26). Statistically, there was no significant difference in the overall risk of non-serious adverse events associated with the increased ICS dose strategy, but the wide confidence interval prevents a firm conclusion. No serious adverse events were reported.

In 2011, a meta-analysis that compared two or more doses of inhaled corticosteroids (ICS) in pediatric patients (age three to 18 years) with persistent asthma was published to assess the dose-response relationship including benefits and harms of ICS in children with persistent asthma. [181] A Medline search was conducted for articles published between 1950 and August 2009. Main outcomes of this analysis included morning and evening PEF, FEV_1, asthma symptom score, β_2 agonist use, withdrawal because of lack of efficacy, and adverse events. Meta-analyses were performed to compare moderate (300-400 mcg daily) with low (≤200 mcg daily beclomethasone-equivalent) doses of the ICS. Fourteen RCTs that included 5,768 asthmatic children that evaluated five different ICS were included in the analysis. The pooled standardized mean difference from six trials revealed a small but statistically significant increase of moderate over low doses in improving FEV_1 (standardized mean difference: 0.11 [95 percent confidence interval: 0.01-0.21]) among children with mild-to-moderate asthma. There was no significant difference between two doses in terms of other efficacy outcomes. Local adverse events were uncommon, and there was no evidence of dose-response relationship at low-to-moderate doses.

Summary

The 2007 National Heart, Lung, and Blood Institute, National Institutes of Health (NHLBI, NIH) and Global Initiative for Asthma (GINA) both utilize a classification of level of asthma control to guide asthma therapy and state that ICS are currently the most effective anti-inflammatory medications for the treatment of persistent asthma.

Bronchodilator therapy is central to symptom management in COPD and the inhaled route is preferred. The GOLD guidelines recommend the addition of ICS to long-acting bronchodilator therapy, such as long-acting beta$_2$-agonists (LABA), for patients with severe to very severe

COPD.

When used in equivalent dosages, efficacy among all inhaled corticosteroids is similar. There are differences among the agents in dosage frequency and the number of inhalations needed for each dose. Most of these agents are recommended for twice daily use. The exceptions to this are mometasone (Asmanex Twisthaler DPI), which can be dosed once daily, and triamcinolone (Azmacort MDI), which is usually given 3-4 times daily, although some patients may respond to twice daily dosing. Also, there are two agents that act as prodrugs, ciclesonide (Alvesco) and beclomethasone (QVAR). They are both converted either during absorption (QVAR) or by esterases in the lung (Alvesco).

The use of a combination long acting beta agonist and an inhaled corticosteroid (ICS) [e.g., salmeterol/fluticasone (Advair), formoterol/budesonide (Symbicort), formoterol/mometasone (Dulera)] in a single inhaler is effective in the treatment of asthma and reduces asthma exacerbations. Salmeterol/fluticasone and formoterol/budesonide are also indicated for the maintenance treatment of airflow obstruction in patients with COPD, formoterol/mometasone is not approved for this indication.

In 2010, the FDA issued new recommendations on the safe use of long-acting beta$_2$-agonists in the treatment of asthma, which applies to the combination products of budesonide/formoterol (Symbicort), mometasone/formoterol (Dulera), and fluticasone/salmeterol (Advair Diskus, Advair HFA). The FDA recommends against the use of long-acting beta$_2$-agonists without the use of an asthma controller medication such as an ICS. Also, long-acting beta$_2$-agonists should be used for the shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved, and used long-term only in patients whose asthma is not adequately controlled on asthma controller medications.

When selecting an agent for an individual patient, consideration must be given to the characteristics of the particular delivery device and the necessary technique for its use. This is particularly important for the very young and the very old. For children under five years of age, an MDI with a spacer and an optional face mask or mouthpiece may be preferable. If this is not effective, consideration could be given towards nebulizer therapy or a DPI is an alternative for individuals, young and old, who cannot use MDIs due to an inability to coordinate hand and press devices.

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