

Glucocorticoids, Inhaled Review

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Glucocorticoids, Inhaled Review

FDA-Approved Indications

Drug	Manufacturer	Indication(s)
Corticosteroids		
beclomethasone inhalation aerosol (QVAR™) ¹	Teva	<ul style="list-style-type: none"> 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 <p><u>Indicated Ages</u></p> <ul style="list-style-type: none"> QVAR is for use in patients age five years and older Pulmicort Flexhaler is for use in patients age six years and older. 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. Azmacort is for use in patients age six years and older.
budesonide inhalation powder (Pulmicort Flexhaler®) ²	AstraZeneca	
flunisolide inhalation aerosol (Aerobid®, Aerobid-M®) ³	Forest	
fluticasone inhalation powder (Flovent Diskus®) ⁴	GlaxoSmithKline	
fluticasone inhalation aerosol (Flovent HFA®) ⁵	GlaxoSmithKline	
mometasone furoate inhalation powder (Asmanex® Twisthaler®) ⁶	Schering-Plough	
triamcinolone inhalation aerosol (Azmacort®) ⁷ *	Abbott	
budesonide inhalation suspension (Pulmicort Respules®) ⁸	AstraZeneca	<ul style="list-style-type: none"> Maintenance treatment of asthma as prophylactic therapy in patients 12 months to eight years of age
ciclesonide inhalation aerosol (Alvesco®) ⁹	Sepracor	<ul style="list-style-type: none"> Maintenance treatment of asthma as prophylactic therapy in patients in adult and adolescent patients 12 years of age and older
Corticosteroid/Bronchodilator combinations		
budesonide / formoterol inhalation aerosol (Symbicort®) ¹⁰	AstraZeneca	<ul style="list-style-type: none"> Maintenance 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) ¹¹	GlaxoSmithKline	<ul style="list-style-type: none"> Maintenance 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) ¹²	GlaxoSmithKline	<ul style="list-style-type: none"> Maintenance treatment of asthma in patients 12 years of age and older

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

Overview

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 one-quarter (two million) of all emergency room visits in the U.S. each year.¹⁵

Studies have demonstrated the efficacy of 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} Based on this evidence, the 2007 National Heart, Lung, and Blood Institute, National Institutes of Health (NHLBI, NIH) Global Initiative for Asthma (GINA) state that “inhaled glucocorticoids are the preferred treatment for patients with persistent asthma at all levels of severity”.^{21,22} To help health care professionals bridge the gap between current knowledge and practice, the NHLBI’s NAEPP has prepared clinical guidelines for the management of asthma.²³ An updated guideline is also available for the treatment of asthma in pregnancy.²⁴

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.²⁵ Between three and seven million Americans are currently diagnosed with COPD, and the true prevalence is probably exceeds 16 million.²⁶

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 beta₂-agonists, inhaled corticosteroids (ICS), and its combination can decrease the rate of decline of lung function.²⁷ Therefore, pharmacotherapy for COPD is mainly used to decrease symptoms and/or complications. The GOLD guidelines recommend the addition of ICS to long-acting beta₂-agonists (LABA), in addition to other treatment options 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. Two available combinations include budesonide/formoterol (Symbicort) and fluticasone/salmeterol (Advair). Both products are FDA-approved for use in the maintenance treatment of asthma and COPD.

**Stepwise Approach for Managing Persistent Asthma from the NAEPP Expert Panel
Report-3²⁸**

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
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 short acting inhaled beta ₂ -agonist (SABA) as needed

LABA = long acting beta₂-agonist

LTRA = leukotriene receptor antagonist or leukotriene modifier

ICS = inhaled corticosteroid

SABA = short acting beta₂-agonist

All asthma patients should have a short-acting beta₂-agonist inhaler for use on an as-needed basis.

Stepwise Approach for Managing Persistent Asthma from the NAEPP Expert Panel Report-3²⁹

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 (Singulair)	high-dose ICS + LABA Alternative: high-dose ICS + LTRA OR theophylline
Step 4 Persistent Asthma	medium-dose ICS + LABA OR montelukast (Singulair)	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 (Singulair)	low-dose ICS Alternative: cromolyn, LTRA, nedocromil, or theophylline
Step 1 Intermittent Asthma	no daily medications needed Short acting Beta ₂ -agonist as needed	no daily medications needed Short acting Beta ₂ -agonist as needed

The 2009 GINA guidelines recommend a classification based on level of asthma control.³⁰ The GINA guidelines offer a stepwise treatment approach to achieving control using the patient's current level of control as the start point. 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. The NAEPP Expert Panel Report-3 report released in 2007 also recommends a similar evaluation of control and adjusting therapy up or down to achieve control.³¹

The GINA guidelines were updated to produce a more streamlined, user-friendly document that emphasizes the importance of asthma control with appropriate treatment. The asthma classification system is defined in terms of three levels of control: controlled, partly controlled, or

uncontrolled. This classification is also recommended to be utilized in conjunction with the assessment of future risk of losing asthma control so that treatment regimen can be appropriately adjusted. Roles of several medications used to treat asthma (e.g. leukotriene modifiers, long-acting beta-agonists, cromones and inhaled glucocorticoids) have evolved since prior versions of the guidelines and have been included in the 2008 update.³² More specifically, use of the long-acting beta₂-agonists only in combination with appropriately dosed inhaled corticosteroids for the treatment of asthma was emphasized.

Levels of Asthma Control from 2009 GINA guidelines³³

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 FEV ₁)	Normal	<80% predicted or personal best	
Exacerbations	None	One or more per year	One in any week

Assessment of Future Risk (risk of exacerbations, instability, rapid decline in lung function, and side-effects)

Features that are associated with increased risk of adverse events in the future include:

Poor clinical control, frequent exacerbations in past year, ever admission to critical care for asthma, low FEV₁, exposure to cigarette smoke, high dose medications.

Stepwise Approach to Asthma Control from 2009 GINA guidelines³⁴

	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 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 AND 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 AND a long-acting beta ₂ -agonist 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 [®])]

Pharmacology

Corticosteroids suppress the cytokine generation, recruitment of airway eosinophils, and release of inflammatory mediators. Corticosteroids block late-phase reaction to allergens, reduce airway hyperresponsiveness, and inhibit inflammatory cell migration and activation.³⁵ Because systemic corticosteroids have a high incidence of adverse reactions, inhaled corticosteroids are preferred for maintenance therapy of asthma.

Advair is a combination product containing a long-acting beta₂-agonist, salmeterol DPI (Serevent) and a corticosteroid, fluticasone. Symbicort is a combination product also containing a long-acting beta₂-agonist, formoterol MDI (Foradil[®]) and a corticosteroid, budesonide. Both selectively bind to the beta₂-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.^{36,37} Poor inhaler technique has been reported in up to 89 percent of patients.³⁸

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 CFC MDI formulation, Azmacort and Aerobid/Aerobid M. Azmacort has discontinued Azmacort effective December 31, 2009; however some product may still be available. There is no date specified for the discontinuation of Aerobid/Aerobid M.

Dry-powder inhalers (DPIs) are breath-actuated devices that release the medicine in the form of a dry powder when the user breathes in. Each manufacturer uses a different brand of DPI for their individual products. 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.³⁹ 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

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.^{40,41,42,43,44} There is, however, considerable intersubject variability in the rate of absorption of these agents from the lungs.⁴⁵

The NAEPP guidelines provide information regarding the relative potencies and dosages of each of the available agents.⁴⁶ 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 is therefore not contained in the following comparative chart. However, the GINA guidelines were updated in 2008.

NAEPP Expert Panel Report-3 Estimated Comparative Daily Dosages for Inhaled Corticosteroids (mcg/day)^{47,48}

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
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

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)⁴⁹

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 (Azmecort)	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
Corticosteroids		
beclomethasone MDI (QVAR) ⁵⁰	one to two weeks	three to four weeks
budesonide DPI (Pulmicort Flexhaler) ⁵¹	24 hours	one to two weeks
budesonide suspension (Pulmicort Respules) ⁵²	two to eight days	four to six weeks
ciclesonide MDI (Alvesco) ⁵³	--	four weeks or longer
flunisolide MDI (Aerobid) ⁵⁴	one to four weeks	--
fluticasone MDI (Flovent HFA) ⁵⁵	24 hours – variable time to onset	one to two weeks or longer
fluticasone powder for inhalation (Flovent Diskus) ⁵⁶	24 hours – variable time to onset	one to two weeks or longer
mometasone DPI (Asmanex) ⁵⁷	one to 2.5 hours	one to two weeks or longer
triamcinolone MDI (Azmecort) ⁵⁸	one week	two weeks or longer
Corticosteroid/Bronchodilator combinations		
budesonide/formoterol MDI (Symbicort) ⁵⁹	15 minutes	two weeks or longer
fluticasone/salmeterol DPI (Advair Diskus) ⁶⁰	30 – 60 minutes	one week or longer
fluticasone/salmeterol MDI (Advair HFA) ⁶¹	30 – 60 minutes	one week or longer

Contraindications/Warnings^{62,63,64,65,66,67,68,69,70,71,72}

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) and budesonide/formoterol (Symbicort)]. For Advair Diskus, Advair HFA and Symbicort, the boxed warning, Risk of Asthma-Related Deaths, states the following:

- Long-acting beta₂-adrenergic agonists may increase the risk of asthma-related deaths. A US 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).
- When treating patients with asthma, Advair Diskus, Advair HFA, or Symbicort should be prescribed for only those patients not adequately controlled on other asthma-controller medications or whose disease severity clearly warrants initiation of treatment with two maintenance therapies.

Drug Interactions^{73,74,75,76,77,78,79,80,81,82,83}

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 inhaled corticosteroids. Fluticasone (Flovent) use in combination with ritonavir has been associated with systemic corticosteroid effects such as Cushing's syndrome and adrenal suppression.

Adverse Effects

Drug	Cough	Headache	Nausea	Oral candidiasis	Pharyngitis	Upper respiratory infection
Corticosteroids						
beclomethasone MDI (QVAR) ⁸⁴	1-3	12	1	0	8	9
budesonide DPI (Pulmicort Flexhaler) ⁸⁵	nr	nr	1.8	1.3	2.7	2.2
budesonide suspension (Pulmicort Respules) ⁸⁶	5-9	≥3	nr	nr	≥3	34-38
ciclesonide MDI (Alvesco) ⁸⁷	< 1	4.9-11	< 1	< 1	7-10.5	4.1-8.7
flunisolide MDI (Aerobid, Aerobid-M) ⁸⁸	3-9	25	25	3-9	1-3	25
fluticasone powder for inhalation (Flovent Diskus) ⁸⁹	1-5	2-14	1-8	<1-9	3-22	14-21
fluticasone MDI (Flovent HFA) ⁹⁰	4-6	5-11	reported	2-5	1-3	16-18
mometasone DPI (Asmanex) ⁹¹	nr	20-22	1-3	4-6	8-13	8-15
triamcinolone MDI (Azmacort) ⁹²	reported	7-21	nr	reported	7-25	nr
Corticosteroid/Bronchodilator Combinations						
budesonide/formoterol MDI (Symbicort) ⁹³	reported	6.5-11.3	reported	1.4-3.2	reported	7.6-10.5
fluticasone/salmeterol DPI (Advair Diskus) ⁹⁴	3-6	12-13	4-6	1-4	10-13	21-27
fluticasone/salmeterol MDI (Advair HFA) ⁹⁵	reported	21	5	1-3	nr	16

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 2006, the FDA updated the safety information for combination products containing salmeterol (Serevent), including fluticasone/salmeterol (Advair Diskus and Advair HFA). Product safety information for formoterol (Foradil) was updated in 2006. The combination product budesonide/formoterol (Symbicort) also has this warning. The labeling for these products contains a boxed warning about a small, but significant, increased risk of life-threatening asthma episodes or asthma related deaths observed in patients taking salmeterol in the recently completed Salmeterol Multicenter Asthma Research Trial (SMART). In the prematurely stopped study, only the single component agent, salmeterol, was administered. Post-hoc analysis indicates that the risk of these serious reactions was significantly higher in African-Americans. The FDA does note that the benefits of salmeterol in patients with COPD or asthma outweigh the risks.⁹⁶

Special Populations^{97,98,99,100,101,102,103,104,105,106,107}

Pediatrics

Safety and effectiveness of fluticasone/salmeterol (Advair HFA), budesonide/formoterol (Symbicort), 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 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 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) who have hepatic impairment is recommended due to accumulation of both active ingredients.

Dosages

Drug	Adult doses		Pediatric doses		Availability
	Initial	Maximum	Initial	Maximum	
Corticosteroids					
beclomethasone MDI (QVAR) ¹⁰⁸	40 -80 mcg twice daily (previous bronchodilator use alone) 40 -160 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) ¹⁰⁹	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) ¹¹⁰	--	--	250-500 mcg twice daily or 250-1,000 mcg once daily	250-500 mcg twice daily or 500-1,000 mcg once daily	250, 500, 1,000 mcg per 2 mL Respule® via jet nebulizer
ciclesonide MDI (Alvesco) ¹¹¹	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	

Dosages (continued)

Drug	Adult doses		Pediatric doses		Availability
	Initial	Maximum	Initial	Maximum	
Corticosteroids					
flunisolide MDI (Aerobid, Aerobid-M) ¹¹²	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) ¹¹³	88 mcg twice daily (patients who received bronchodilator alone)	440 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
	88-220 mcg twice daily (patients who used inhaled corticosteroids)	440 mcg twice daily			
	440 mcg twice daily (patients who used oral corticosteroids)	880 mcg twice daily			
fluticasone powder for inhalation (Flovent Diskus) ¹¹⁴	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			

Dosages (continued)

Drug	Adult doses		Pediatric doses		Availability
	Initial	Maximum	Initial	Maximum	
Corticosteroids					
mometasone DPI (Asmanex Twisthaler) ¹¹⁵	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
triamcinolone MDI (Azmacort) ¹¹⁶	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.

Dosages (continued)

Drug	Adult doses		Pediatric doses		Availability
	Initial	Maximum	Initial	Maximum	
Corticosteroid/Bronchodilator Combinations					
budesonide/formoterol MDI (Symbicort) ¹¹⁷	80 mcg/ 4.5 mcg twice daily to 160 mcg/ 4.5 mcg twice daily	160 mcg/ 4.5 mcg twice daily	12 years and older: 80 mcg/ 4.5 mcg twice daily to 160 mcg/ 4.5 mcg twice daily	12 years and older: 160 mcg/ 4.5 mcg twice daily	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) ¹¹⁸	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) ¹¹⁹	45 mcg/ 21 mcg twice daily 115 mcg/ 21 mcg twice daily 230 mcg/ 21 mcg twice daily	230 mcg/ 21 mcg twice daily	12 years and older: 45 mcg/ 21 mcg twice daily 115 mcg/ 21 mcg twice daily 230 mcg/ 21 mcg twice daily	12 years and older: 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

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.¹²⁰ The primary outcome was the provocative dose of methacholine producing a 20 percent fall in forced expiration volume in the first second (FEV₁) (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 DPI (Pulmicort) versus fluticasone/salmeterol DPI (Advair)

A randomized, double-blind study compared the efficacy and tolerability of low-dose fluticasone/salmeterol 100/50 mcg twice daily with medium-dose budesonide 400 mcg twice daily in 349 patients with symptomatic, mild to moderate asthma.¹²¹ After 12 weeks of treatment, patients in the fluticasone/salmeterol arm had a mean morning peak expiratory flow (PEF) of 426 L/min and evening PEF of 435 L/min compared to 415 L/min and 424 L/min in the budesonide group (p=0.022 and p=0.008, respectively). There were no differences in any other efficacy or tolerability parameters (symptom scores, use of rescue medication, spirometry, and exacerbations).

budesonide DPI (Pulmicort) / formoterol DPI (Foradil) versus fluticasone/salmeterol DPI (Advair)

In the Evaluation of Different Inhaled Combination Therapies (EDICT) trial, medium-dose fluticasone/salmeterol DPI 250/50 mcg twice daily was compared with formoterol DPI 12 mcg twice daily and high-dose budesonide DPI 800 mcg twice daily given concurrently.¹²² The 428 patients in this study had moderate-to-severe, symptomatic asthma and were uncontrolled on existing corticosteroid therapy. This study used a randomized, double-blind, double-dummy, parallel-group design, consisting of a two-week run-in period on current corticosteroid therapy (1,000 to 1,600 mcg/day of beclomethasone or equivalent) and a 12-week treatment period. Improvement in mean morning PEF was similar in both groups and, like mean evening PEF, increased by a clinically significant amount (more than 20 L/min) from baseline in each treatment group. The mean rate of exacerbations was significantly lower in the fluticasone/salmeterol group compared with the budesonide/formoterol group (0.472 versus 0.735, respectively; p<0.001). Patients in the fluticasone/salmeterol group also experienced significantly fewer nocturnal symptoms, with a higher median percentage of symptom-free nights (p=0.04), nights with a symptom score less than two (p=0.03), and nights with no awakenings (p=0.02). Both treatments were well tolerated, with a similar low incidence of adverse events.

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

A double-blind, randomized, parallel-group study was conducted to compare the efficacy and safety of low-dose budesonide/formoterol 80/4.5 mcg twice daily versus low-dose budesonide 200 mcg twice daily in 467 adult patients with mild to moderate asthma not fully controlled on low-dose inhaled corticosteroid use alone.¹²³ Improvements were maintained over the 12 weeks of the study in asthma control days (17 percent increase in budesonide/formoterol patients versus 10 percent in budesonide patients), greater reduction in reliever medication use, and symptom-free days in patients using budesonide/formoterol. Mean PEF after 12 weeks was 378 and 388 in the morning and evening, respectively per budesonide/formoterol group, while the budesonide-alone group was 369 and 381 in the morning and evening, respectively (p=0.002 and p=0.001 for morning and evening, respectively).

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 stabilized with twice-daily budesonide/formoterol.¹²⁴ 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 (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 160 mcg/9 mcg or 80/4.5 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 FEV₁, 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 FEV₁, 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≤0.018). 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.¹²⁵ 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 FEV₁ and mean change from baseline in 12-hour FEV₁. The results were similar in the budesonide/formoterol and the budesonide + formoterol groups in all measures. The budesonide/formoterol group showed greater improvement in FEV₁ (p≤0.049) than the individual budesonide, formoterol, and placebo. Also, fewer patients on budesonide/formoterol experienced worsening asthma symptoms (p≤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.¹²⁶ 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 FEV₁ of 60 to 90 percent.¹²⁷ 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 FEV₁ 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.

budesonide/formoterol MDI (Symbicort) versus formoterol MDI (Foradil) versus terbutaline (Brethine)

In a 12-month, double-blind, parallel-group study of 3,394 patients (aged 12 years or older) maintained on budesonide/formoterol 160/4.5 mcg twice daily, the efficacy and safety of three reliever strategies were compared: terbutaline 0.4 mg daily, formoterol 4.5 mcg daily, and budesonide/formoterol 160/4.5 mcg daily.¹²⁸ The primary outcome was time to first severe exacerbation, defined as an event resulting in hospitalization, ER visit or both, or the need for oral corticosteroids for three days or more. The time to first severe exacerbation was longer with as-needed budesonide/formoterol versus formoterol. The rate of severe exacerbations was 37, 29, and 19 per 100 patients per year with as-needed terbutaline, formoterol, and budesonide/formoterol, respectively. Asthma control days increased to a similar extent in all treatment groups. As-needed formoterol did not significantly improve symptoms compared with as-needed terbutaline. All treatments 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.¹²⁹ 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.¹³⁰ 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 FEV₁ 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.

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.¹³¹ 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 FEV₁ 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.

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 beta₂-agonists alone.¹³² 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 ($p \leq 0.02$) 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 ($p \leq 0.04$).

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

A double-blind, double-dummy study compared the efficacy of stable versus adjusted doses of inhaled corticosteroid plus long-acting beta-agonists. The study was conducted in 688 adult patients with persistent asthma and a mean FEV₁ of 81 percent.¹³³ Initially, patients were randomized to receive either fluticasone/salmeterol 250 mcg/50 mcg one inhalation twice daily or budesonide/formoterol 200 mcg/6 mcg two inhalations twice daily. After four weeks of this stable dosing, 581 patients (about 15 percent discontinuation rate) in both groups continued for an additional 48 weeks on either a stable dose of fluticasone/salmeterol or an adjustable dosing regimen of budesonide/formoterol that required either halving the dose and stepping up or down as indicated by presence or absence of nocturnal awakenings due to asthma, frequency of rescue medication use, and changes in morning PEF. The primary endpoint was the percentage of symptom-free days. Patients receiving stable-dosed fluticasone/salmeterol had a significantly greater percentage of symptom-free days compared to those receiving adjustable budesonide/formoterol (58.8 versus 52.1 percent; $p=0.034$) and experienced fewer emergency room visits/hospitalizations (0.18 versus 0.33; $p=0.008$). Patients in the adjustable budesonide/formoterol group used an average of 1.8 inhalations daily with nearly 83 percent ($n=235$) stepping down to one inhalation daily. The results suggest that there is a minimum daily amount of maintenance therapy necessary to prevent exacerbations in adults with persistent asthma.

In a follow-up study to the CONCEPT trial, the long-term efficacy (including symptom-free days and exacerbations) as well as impact on health-related QoL of the stable-dose regimen of fluticasone/salmeterol and the adjustable maintenance dosing regimen of budesonide/formoterol were evaluated.¹³⁴ A total of 568 patients completed the Asthma Quality of Life Questionnaire (AQLQ) at least once during the study. The mean change from baseline in AQLQ overall score was not significantly greater at 52 weeks with fluticasone/salmeterol than with budesonide/formoterol ($p=0.121$). However, a post hoc regression analysis did identify a statistically significant difference in AQLQ score of a 0.5 point improvement in overall score at both 28 and 52 weeks, respectively ($p=0.038$ and $p=0.009$).

The efficacy of high-dose fluticasone/salmeterol plus a short-acting beta-agonist was compared to budesonide/formoterol.¹³⁵ The study consisted of 2,309 patients aged 12 years old with an FEV₁ 50% of predicted and who experienced an asthma exacerbation in the previous year. Patients were randomized to receive budesonide/formoterol 160/4.5 mcg (two inhalations twice daily and as needed) or fluticasone/salmeterol 500/50 mcg (one inhalation twice daily), plus terbutaline as needed, for six months. Budesonide/formoterol reduced total exacerbations from 31 to 25 events/100 patients/year ($p=0.039$), and exacerbations requiring hospitalization/emergency room treatment from 13 to eight events/100 patients/year ($p=0.046$). The treatments showed no difference in measures of lung function or asthma symptoms and were both well tolerated. Also, the mean dose of inhaled corticosteroid was lower using budesonide/formoterol (792 mcg/day budesonide [1,238 mcg/day beclomethasone dipropionate equivalent]) versus 1,000 mcg/day fluticasone [2,000 mcg/day beclomethasone equivalent] with salmeterol/fluticasone therapy; $p < 0.0001$). In the treatment of uncontrolled asthma, budesonide/formoterol reduces incidence of severe asthma exacerbations and hospitalizations/ER treatment with similar daily symptom control (and less inhaled corticosteroid exposure) compared with sustained fluticasone/salmeterol with short-acting beta-agonist.

mometasone furoate DPI (Asmanex) versus placebo

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.¹³⁶ The primary efficacy variable was the change in FEV₁ from baseline to endpoint. The average change in FEV₁ for the group receiving a daily dose was 4.73 points while the group receiving a twice daily dose was 5.52 points (p<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.¹³⁷ 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 FEV₁ from baseline to the final evaluable visit. At endpoint, the FEV₁ 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.

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.¹³⁸ Patients were randomized to receive inhaled ciclesonide 80 or 320 micrograms daily or budesonide 200 micrograms 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 FEV₁ 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 micrograms daily) had similar improvements in pulmonary function, control of asthma symptoms, and reduced need for rescue medications as those patients who received budesonide 200 micrograms twice daily.

Another study was designed to compare the efficacy and safety of once daily ciclesonide (320 mcg) to once daily budesonide (320 mcg) in patients (n=359) with persistent asthma for 12 weeks after a four to six week pre-treatment period with budesonide.¹³⁹ Patients with an increase in FEV₁ of seven percent were randomized to ciclesonide 320 mcg or budesonide 320 mcg once daily in the morning for 12 weeks. Change in FEV₁ was the primary endpoint and actually decreased in both groups. The authors state that for FEV₁, ciclesonide was noninferior to budesonide (change in FEV₁ 0.18 L versus 0.23 L, respectively). For forced vital capacity (FVC) improvement, ciclesonide was statistically greater than budesonide (0.12 L versus 0.21 L, p=0.010). Asthma symptom scores were comparable; the median percentage of symptom-free days was significantly higher for ciclesonide (43.6 percent) versus budesonide (25.8 percent, p=0.017). Rescue medication use decreased significantly only for ciclesonide patients

($p=0.009$). Frequency of adverse events was low in both groups.

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.¹⁴⁰ 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 FEV₁, 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 FEV₁ 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.¹⁴¹ Severe exacerbations and FEV₁ were the primary variables. Other variables including peak expiratory flow (PEF), COPD symptoms, health-related quality of life (HRQL), mild exacerbations, use of reliever beta₂-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, FEV₁ 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 beta₂-agonists significantly versus placebo and budesonide, and improved HRQL versus placebo. All treatments were well tolerated.

The SHINE was a in 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.¹⁴² 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 FEV₁ over the six month treatment period. Both budesonide/formoterol doses demonstrated a significantly greater improvement from baseline in pre-dose FEV₁ ($p<0.001$) and one-hour post-dose FEV₁ compared with budesonide ($p<0.001$). Budesonide/formoterol 160/4.5 mcg also demonstrated a significant ($p=0.026$) improvement from baseline for pre-dose FEV₁ compared with formoterol. The most common drug-related adverse events were oral candidiasis, dysphonia, a voice disorder, and headache.

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; FEV₁ 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.¹⁴³ Outside the United States albuterol is known as salbutamol. The primary end-point

was change in FEV₁ five minutes after drug inhalation; secondary end-points included inspiratory capacity (IC) and perception of onset of effect. Budesonide/formoterol significantly improved FEV₁ 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 FEV₁ following active treatments were superior to placebo after 180 minutes (all p<0.0001); both combinations were better than salbutamol at maintaining FEV₁ improvements (p≤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.

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.¹⁴⁴ 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).¹⁴⁵ 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.¹⁴⁶ 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 FEV₁ 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 FEV₁ 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.¹⁴⁷ 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.¹⁴⁸ 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.¹⁴⁹ 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.¹⁵⁰ 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.¹⁵¹ 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.¹⁵² 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.¹⁵³ 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.¹⁵⁴ 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.¹⁵⁵ 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 FEV₁ (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 FEV₁ 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 FEV₁ 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.¹⁵⁶ 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.¹⁵⁷ The authors concluded that they were not.

Summary

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 glucocorticoid [e.g. salmeterol/fluticasone (Advair) and formoterol/budesonide (Symbicort)] in a single inhaler is effective in maintaining asthma control and reduces exacerbations. In addition, while the combination may offer the specific benefit of increased compliance with therapy, there is limited ability to titrate the dose of each component independently.

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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