Beta$_2$ Adrenergic Agents –Long Acting Review

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FDA-Approved Indications

Drug	Manufacturer	Reversible Bronchospasm		Prevention of Exercise-Induced Broncho-constriction	COPD	Age (years)
		Prevention and Treatment	Relief			
Long Acting Inhalation Agents						
arformoterol inhalation solution (Brovana®)[1]	Sepracor	--	--	--	X	≥18
formoterol inhalation solution (Perforomist™)[2]	Dey	--	--	--	X	≥18
formoterol DPI (Foradil®)[3]	Schering	X	--	X		5-11
		X	--	X	X	≥12
salmeterol DPI (Serevent® Diskus)[4]	GlaxoSmithKline	X	--	X	X	≥4
Oral Agents						
albuterol extended-release oral tablets[5]	generic	--	X	--	--	≥6

DPI=dry powder inhaler COPD = Chronic Obstructive Pulmonary Disease

Arformoterol (Brovana) and formoterol (Perforomist) are not indicated for the treatment of acute deteriorations of COPD or the management of asthma.

Overview

Beta$_2$-agonist bronchodilators are used for the treatment and prevention of bronchospasm associated with asthma, prophylaxis of exercise-induced bronchospasm (EIB), and in the treatment of chronic obstructive pulmonary disease (COPD).

Asthma

The mainstay of asthma therapy is the use of inhaled corticosteroids and long acting beta$_2$-agonists (LABAs) as controller medications.[6] These agents lead to improvements in lung function and symptoms and reduce the need for short-acting beta$_2$-agonists for quick relief. Long acting beta$_2$-agonists are not to be used as monotherapy for controlling asthma. While the corticosteroid reduces inflammation, the long-acting beta$_2$-agonist acts principally to dilate the airways by relaxing airway smooth muscle. The latest guidelines from the National Heart Lung and Blood Institute recommend that for patients over age five years with moderate persistent asthma or asthma not controlled by low-dose corticosteroids that consideration be given for use of a combination of inhaled corticosteroids and long acting beta$_2$-agonists or for increasing the dose of inhaled corticosteroids. For patients with severe persistent asthma, a combination of a long acting beta$_2$-agonist and an inhaled corticosteroid is recommended. For exercise-induced

bronchospasm, long acting beta$_2$-agonists may be used for prevention; however, it is noted that frequent or chronic use may disguise poorly controlled persistent asthma.

In November 2007, the National Asthma Education and Prevention Panel released a summary of the third report of the Expert Panel (EPR-3) that emphasizes the importance of asthma control and identifies asthma severity as the intrinsic intensity of the disease process. The recommendation from EPR-3 is to assess severity to initiate therapy and assess control to adjust therapy in patients as young as five years of age.

In November 2006, the GINA guidelines for asthma management were updated to reflect a change in focus from asthma severity to asthma control.[7] Asthma control is defined as no or minimal daytime symptoms, no limitations of activity, no nocturnal symptoms, no or minimal need for rescue medications, normal or near normal lung function, and no exacerbations. A five-step treatment approach is introduced in this guideline that offers flexibility to step up treatment if control is lost or to step down treatment when asthma is controlled. These new guidelines suggest treatment with short acting beta$_2$-agonists only on an as needed basis particularly if patients experience only occasional daytime symptoms of short duration. When symptoms are more frequent and/or worsen periodically, patients require regular controller therapy.

COPD

Bronchodilator medications are central to the symptomatic management of COPD.[8,9,10,11] They improve emptying of the lungs, tend to reduce dynamic hyperinflation at rest and during exercise, and improve exercise performance. [12] They are given either on an as needed basis for relief of persistent or worsening symptoms or on a regular basis to prevent or reduce symptoms. Regular bronchodilation with these drugs does not modify the decline of lung function in mild COPD or the prognosis of the disease.[13] The principal bronchodilator treatments are beta$_2$-agonists, anticholinergics, and theophylline. These may be given either as monotherapy or preferably, in combination with the inhaled agents. While short-acting beta$_2$-agonists can be used on an as needed basis in mild COPD, regular treatment with a long-acting agent is required as the disease progresses.[14]

In December 2006, the updated GOLD guidelines were released and state that beta$_2$-agonist bronchodilators are among the principal treatments for symptomatic management of COPD.[15] The guidelines also state that regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators.

Pharmacology

Beta-agonists stimulate adenyl cyclase, the enzyme that catalyzes the formation of cyclic-3'5' adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity, especially from mast cells. The beta$_2$-agonists relieve reversible bronchospasm by relaxing the smooth muscles of the bronchioles in conditions associated with asthma, COPD, or bronchiectasis. Bronchodilation may additionally facilitate expectoration.

Although there are both beta$_1$ and beta$_2$ receptors in the heart, the latter are more predominant in the lungs, where they serve as the primary adrenergic receptors in bronchial smooth muscle. In order to reduce cardiac toxicities (e.g., tachyarrhythmias), the use of beta$_2$ specific agonists is

preferred in the treatment of bronchospasm. To further reduce cardiac toxicities, non-systemic dosage forms given by inhalation are preferred to oral dosage forms.

Pharmacokinetics

Drug	Relative ß$_2$ Specificity	Onset of Action (minutes)	Duration of Action (hours)
Long Acting Inhalation Agents			
arformoterol inhalation solution (Brovana)[16]	ß$_2$ >>> ß$_1$	7-20	12
formoterol inhalation solution (Perforomist)[17]	ß$_2$ >>> ß$_1$	11-13	12
formoterol DPI (Foradil)[18]	ß$_2$ >>> ß$_1$	5-15	12
salmeterol DPI (Serevent Diskus)[19]	ß$_2$ >>> ß$_1$	30-48	12
Oral Agents			
albuterol extended-release tablets (Vospire ER)[20]	ß$_2$ >> ß$_1$	30	12

Contraindications/Warnings[21,22,23,24]

In 2003, the FDA updated the safety information for products containing salmeterol (Serevent). The new 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 (Serevent) in the large, placebo-controlled Salmeterol Multicenter Asthma Research Trial (SMART). In the prematurely stopped study, only the single component agent, salmeterol (Serevent), was administered. Post-hoc analysis indicates that the risk of these serious reactions was significantly higher in African-Americans. The FDA did indicate that the benefits of salmeterol (Serevent) in patients with COPD or asthma outweigh the risks.[25]

In 2006, the FDA requested that manufacturers of the long-acting beta-$_2$ agonists salmeterol (Serevent, Advair) and formoterol (Foradil), update their product labeling to alert health care professionals and patients that these medicines may increase the chance of severe asthma episodes, and death when those episodes occur. Newer products, arformoterol inhalation (Brovana) and formoterol inhalation (Perforomist), also have the same warnings in the labeling.

The long acting beta$_2$-agonists should not be initiated in patients who are acutely deteriorating with COPD or for acute symptoms; a short acting beta-agonist bronchodilator should be used for acute symptoms. The long acting beta$_2$-agonists should be used with caution in patients with cardiovascular or convulsive disorders, thyrotoxicosis, or with sensitivity to sympathomimetic drugs.

Arformoterol (Brovana) is contraindicated in patients with a known hypersensitivity to arformoterol, racemic formoterol (Foradil) or any of its components.

Drug Interactions[26,27,28,29]

Monoamine Oxidase (MAO) Inhibitors and Tricyclic Antidepressants

All long acting beta$_2$-agonists should be administered with extreme caution to patients being treated with MAO inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Allow two weeks after discontinuation of MAO inhibitors before initiating therapy with agents in this category.

Beta-Adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as arformoterol (Brovana), salmeterol (Serevent), and formoterol (Foradil, Perforomist), but may also produce severe bronchospasm in patients with asthma or COPD. Therefore, patients with asthma or COPD should not normally be treated with beta-blockers. However, under certain circumstances, such as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma or COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non-potassium-sparing diuretics. Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists.

Adverse Effects

Drug	Headache	Nausea/ Vomiting	Nervousness	Palpitations	Tachycardia	Tremor
Long Acting Inhalation Agents						
arformoterol inhalation solution (Brovana)[30]	<2	reported	<2	<2	<2	< 2
formoterol inhalation solution (Perforomist)[31]	nr	4.9/2.4 (2.6/1.8)	nr	nr	nr	nr
formoterol DPI (Foradil)[32]	reported	reported	reported	reported	reported	1.9 (0.4)
salmeterol DPI (Serevent Diskus)[33]	13 (9)	1 - 3	1 - 3	reported	reported	reported
Oral Agents						
albuterol extended release tablets (Vospire ER)[34]	18.8	4.2	8.5	2.4	2.7	24.2

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses. nr = not reported.

Special Populations[35,36,37,38]

Pediatrics

Formoterol (Foradil) has been studied in children ages five and older for the prevention and treatment of asthma and prevention of EIB; recommended dosage is the same as for older children. Salmeterol (Serevent) is indicated for the prevention and treatment of asthma and prevention of EIB in children as young as four years.

The safety and effectiveness of arformoterol (Brovana) and formoterol (Perforomist) have not been established in children.

Pregnancy

All agents in this category are Pregnancy Category C.

Dosages

Drug	Usual Adult Dosage	Prevention of EIB	Usual Pediatric Dose	Availability
Long Acting Inhalation Agents				
arformoterol inhalation solution (Brovana)[39]	15 mcg twice daily	--	--	15 mcg/2 mL inhalation solution
formoterol inhalation solution (Perforomist)[40]	20 mcg every 12 hours	--	--	20 mcg/2 mL inhalation solution
formoterol DPI (Foradil)[41]	1 inhalation every 12 hrs	1 inhalation 15 minutes prior to exercise	Ages 5 years and up: 1 inhalation every 12 hrs	12 mcg per inhalation
salmeterol DPI (Serevent Diskus)[42]	1 inhalation every 12 hrs	1 inhalation 30 minutes before exercise; not to administer a second dose within 12 hours	Ages 4 years and up: 1 inhalation every 12 hrs	50 mcg per inhalation
Oral Agents				
albuterol extended-release tablets (Vospire ER)[43]	4-8 mg every 12 hrs	--	4 mg every 12 hrs	4 mg, 8 mg tablets

An FDA Public Health Advisory was issued in March 2008 to highlight the correct use of formoterol (Foradil) capsules which are to be used in the Aerolizer device. These capsules should not be swallowed.[44]

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed, www.ifpma.org/clinicaltrials and review of information sent by manufacturers. Search strategy included the 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.

The newest product to this category, formoterol inhalation solution (Perforomist) only has placebo-controlled data available at this time.

ASTHMA

albuterol MDI (Proventil, Ventolin) versus formoterol DPI (Foradil)

Formoterol DPI 12 mcg twice daily was compared to albuterol MDI 180 mcg four times daily and placebo in a total of 1,095 patients with mild-to-moderate asthma in two twelve-week, multicenter, randomized, double-blind, parallel group studies.[45] The results of both studies showed that formoterol inhalation powder resulted in significantly greater postdose bronchodilation, as measured by serial forced expiratory volume in one second (FEV_1) for 12 hours postdose, throughout the study period. Compared with placebo and albuterol, patients treated with formoterol demonstrated improvement in the secondary efficacy endpoints of improved combined and nocturnal asthma symptom scores, fewer nighttime awakenings, fewer nights in which patients used rescue medication, and higher morning and evening peak expiratory flow (PEF).

A study compared the efficacy and tolerability of formoterol DPI 12 mcg and 24 mcg twice-daily with albuterol MDI 180 mcg four times daily and placebo.[46] A total of 484 adolescents and adults (ages 12-75 years) with mild-to-moderate asthma completed this 12-week, multicenter, double-blind, double-dummy, placebo-controlled, parallel-group study. For the primary efficacy variable, FEV_1, both formoterol 12 and 24 mcg were statistically superior to placebo at all time points on all test days ($p \leq 0.017$) and to albuterol at most time points on all test days ($p \leq 0.001$). The onset of improvement in FEV_1 was rapid, with 15 percent increase within five minutes in 57, 71, and 65 percent of formoterol 12 mcg, formoterol 24 mcg, and albuterol patients, respectively. Formoterol was also superior to placebo and albuterol in terms of secondary efficacy variables: FEV_1, AUC, percentage of predicted FEV_1, forced vital capacity (FVC), asthma symptom scores, and peak expiratory flow rate (PEFR). Formoterol and albuterol were both well-tolerated.

In a double-dummy, four-way crossover study, 17 adult and adolescent asthmatic patients received single doses of formoterol DPI 12 and 24 mcg, albuterol MDI 180 mcg, and placebo.[47] Exercise challenge tests were conducted at 15 minutes and at four, eight, and 12 hours postdose. Compared with placebo, both doses of formoterol produced significantly greater inhibition of FEV_1 decreases at all time points ($p<0.01$). There were no significant differences in efficacy measures between the two formoterol doses throughout the study. The exercise-induced decrease in FEV_1 after albuterol treatment was significantly reduced compared with placebo only at 15 minutes after dosing ($p<0.05$). Formoterol and albuterol exhibited a similar rapid onset of action (<15 minutes), but formoterol continued to protect patients against EIB for at least 12 hours ($p<0.01$), whereas albuterol was no longer clinically effective by the four hour exercise challenge test.

formoterol DPI (Foradil) versus salmeterol DPI (Serevent) versus terbutaline MDI (Brethine)

Twenty-five subjects with asthma and a history of EIB were enrolled in a double-blind, double-dummy, placebo-controlled, randomized, four-period crossover study.[48] Exercise challenge was performed after 12 days at five, 30, or 60 minutes after inhalation of a single dose of formoterol DPI 12 mcg, salmeterol DPI 50 mcg, terbutaline MDI 500 mcg, or placebo. Exercise-induced bronchoconstriction did not differ significantly between the active treatments at five, 30, or 60 minutes postdose. In contrast, the onset of bronchodilation was slower after salmeterol (Serevent) compared to terbutaline ($p<0.05$) and formoterol ($p<0.05$), both of which showed a similar time course. At all time points between five and 60 minutes, formoterol provided significantly greater bronchodilation than salmeterol ($p<0.05$).

COPD

arformoterol (Brovana) versus salmeterol (Serevent)

A 12-week, double-blind, randomized, double-dummy, placebo-controlled trial in the United States compared arformoterol and salmeterol in 717 COPD patients.[49] Patients were randomized to arformoterol 15 mcg twice daily, 25 mcg twice daily, or 50 mcg daily via nebulizer, salmeterol 42 mcg twice daily via MDI or placebo. Groups were similar at baseline and had a mean baseline FEV_1 of 1.2 L (41 percent predicted). Mean improvement in trough FEV_1 over 12 weeks was significantly greater with all three arformoterol doses (15 mcg twice daily, +16.9 percent; 25 mcg twice daily, +18.9 percent; 50 mcg daily, +14.9 percent) and for salmeterol (+17.4 percent) relative to placebo (+6.0 percent; $p<0.001$). There were significantly greater improvements in the mean percentage change in FEV_1 $AUC_{(0\text{-}12h)}$ from the predose value over 12 weeks (arformoterol 15 mcg twice daily, 12.7 percent; 25 mcg twice daily, 13.9 percent; 50 mcg daily, 18.9 percent; salmeterol, 9.8 percent) versus placebo (2.7 percent; $p\leq0.001$); all doses of arformoterol were statistically different from salmeterol for this end point ($p\leq0.024$). Adverse effects and COPD exacerbations (defined as worsening respiratory status requiring a change in medication or an unscheduled provider visit) were similar in frequency across groups including placebo.

arformoterol (Brovana) versus salmeterol DPI (Serevent) versus placebo

Data were pooled from two, identical, 12-week, double-blind, randomized trials to determine the effect of nebulized arformoterol on airway function in adult patients with COPD.[50] Patients were randomized to one of the following treatment groups: arformoterol 15 mcg twice daily (n=147), 25 mcg twice daily (n=149) or 50 mcg daily (n=147); salmeterol 42 mcg twice daily (n=146); or placebo (n=150). The improvement in trough FEV_1 over 12 weeks was greater for arformoterol and salmeterol versus placebo. The arformoterol groups showed an 11.4 percent (15 mcg); 15.4 percent (25 mcg); and 10.9 percent (50 mcg), respectively. The salmeterol group had an 11.6 percent improvement. Also, after 12 weeks, 78 to 87 percent of arformoterol patients had at least a 10 percent increase in FEV_1 compared to 56 percent for the salmeterol and 44 percent for the placebo groups. This study was conducted and funded by the manufacturer of arformoterol (Brovana).

albuterol MDI versus formoterol DPI (Foradil) versus salmeterol DPI (Serevent)

A crossover, randomized, double-blind, placebo-controlled study was carried out on 20 COPD patients.[51] Patients underwent pulmonary function testing and dyspnea evaluation in basal condition and five, 15, 30, 60 and 120 minutes after bronchodilator (albuterol, formoterol, or salmeterol) or placebo administration. The results indicated that in COPD patients with decreased baseline inspiratory capacity, there was a much greater increase of inspiratory capacity after bronchodilator administration, which correlated closely with the improvement of dyspnea sensation at rest.

formoterol DPI (Foradil) versus salmeterol DPI (Serevent)

Researchers compared the effects of single doses of formoterol DPI 12 and 24 mcg and salmeterol DPI 50 and 100 mcg in a randomized, double-blind, placebo-controlled, crossover study of 47 patients with moderate-to-severe COPD.[52] The primary efficacy parameter was the area under the curve of FEV_1 in the first hour after drug inhalation in the morning. The

estimates of treatment difference in absolute terms (0.086 L; p=0.0044) and percentage change from predose baseline (7.8 percent; p=0.0021) were greater for formoterol than for salmeterol.

comparison of inhaler systems

The American College of Chest Physicians (ACCP) and the American College of Allergy, Asthma, and Immunology (ACAAI) have issued joint evidence-based guidelines for selecting aerosol delivery devices for use in asthma or COPD.[53] The authors compared the efficacy and adverse effects of treatment using nebulizers versus pressurized MDIs with or without a spacer/holding chamber versus DPIs as delivery systems for beta$_2$-agonists, anticholinergic agents, and corticosteroids in several commonly encountered clinical settings and patient populations. The authors conclude that devices used for the delivery of bronchodilators and steroids can be equally efficacious.

Meta-analyses

A systematic review of pertinent randomized, controlled, clinical trials was undertaken using MEDLINE, EmBase, and the Cochrane Library databases to determine if a difference in efficacy and adverse effects exists between the various aerosol delivery devices (MDI versus DPI versus nebulizers) used in the management of asthma and COPD exacerbations.[54] A total of 254 outcomes were tabulated. Of the 131 studies that met the eligibility criteria, only 59 (primarily those that tested beta$_2$-agonists) proved to have useable data. None of the pooled meta-analyses showed a significant difference between devices in any efficacy outcome in any patient group for each of the clinical settings that was investigated. The adverse effects that were reported were minimal and were related to the increased drug dose that was delivered. Each of the delivery devices provided similar outcomes in patients using the correct technique for inhalation.

Additionally, a meta-analysis of 19 trials with 33,826 patients examined the effects of LABAs in patients with asthma.[55] Although the meta-analysis suggested a 3.5-fold greater risk for asthma-related deaths in patients using LABAs, it did not distinguish the impact of baseline asthma severity, medication adherence or pharmacogenomics. This meta-analysis is also criticized because 78 percent of the study population came from the SMART trial where only 47 percent of the patients were receiving an inhaled corticosteroid. Long-acting beta$_2$-agonists are more appropriate for routine use than the short-acting agents.

A systematic review examined the benefit or detriment on the primary outcome of asthma control with the regular use of long acting beta$_2$-agonists compared with placebo, in populations in which only some patients were taking inhaled corticosteroids and in populations not using inhaled corticosteroids.[56] A total of 67 studies (n=42,333) of at least four weeks duration comparing long acting beta$_2$-agonists given twice daily with placebo were included in the analysis. Salmeterol was studied in 50 trials and formoterol in 17 trials. Twenty-four studies did not permit the use of inhaled corticosteroids, and forty permitted inhaled corticosteroids. In these studies, between 22 percent and 92 percent of subjects, were taking inhaled corticosteroids, with a median of 62 percent. Long acting beta$_2$-agonists were associated with benefits compared to placebo for morning peak expiratory flow (PEF), evening PEF and FEV_1. They were associated with significantly fewer symptoms, less use of rescue medication and higher quality of life scores. This was true whether patients were taking long acting beta$_2$-agonists in combination with inhaled corticosteroids or not. Adverse effects such as headache, throat irritation, tremor and nervousness were more frequent with long acting beta$_2$-agonists.

Summary

Formoterol (Foradil) and salmeterol (Serevent) are two long acting, inhaled, beta$_2$-agonist bronchodilators. The main difference between the two is that formoterol has an earlier onset of action. A recent study indicates that, while both of these long-acting agents attenuate the response to short-acting beta$_2$-agonists, salmeterol (Serevent) may have a more pronounced effect.[57] Whether this translates to a clinically significant effect is unknown. The black box warning recently added to all long acting beta agonists may discourage the use of these agents, especially in the African-American population.

Arformoterol (Brovana) and formoterol (Perforomist) are long-acting beta agonists for nebulization indicated for the twice-daily, long-term maintenance treatment of bronchoconstriction in patients with COPD, which includes chronic bronchitis and emphysema. The nebulized form may prove beneficial for patients who have difficulty synchronizing breath and actuation using the other existing long-acting beta agonists available as dry powder inhalers (Foradil and Serevent). There are no comparative data to suggest that arformoterol (Brovana) or formoterol (Perforomist) are superior in efficacy or safety to the other agents. None of the long acting beta agonists have demonstrated an impact on delaying the progression of disease or improving survival of patients with COPD.

Oral dosage forms of albuterol are less desirable than the inhaled forms due to systemic beta-adrenergic stimulation of the former, especially in patients sensitive to these effects, such as those with cardiovascular disease. The extended-release oral dosage forms of albuterol have fewer side effects than immediate-release oral dosage forms, although they are also less effective than inhaled beta$_2$-agonists.

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