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# Inhaled Budesonide/Formoterol Combination

*Jane K. McGavin, Karen L. Goa* and *Blair Jarvis*

Adis International Limited, Auckland, New Zealand

## Contents



## Abstract

▲ Current evidence suggests that the addition of the long acting inhaled $\beta_2$-agonist formoterol to low or moderate doses of the inhaled corticosteroid budesonide is effective in improving lung function and reducing the incidence of asthma exacerbations.

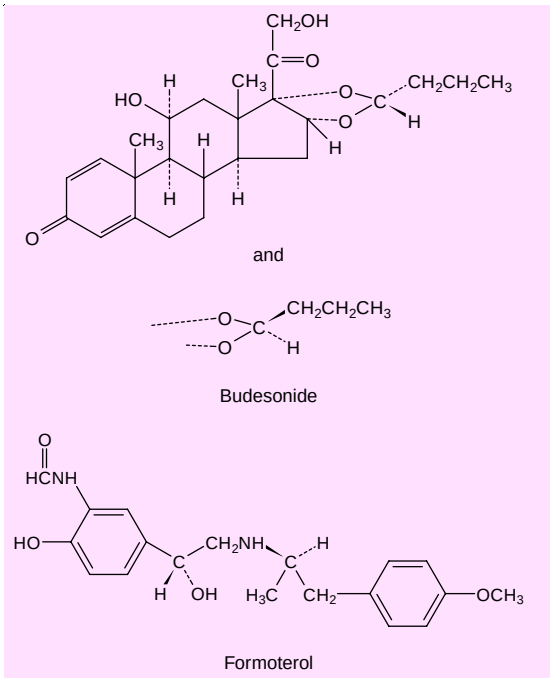
▲ Concurrent use of budesonide with formoterol does not result in any untoward interaction that affects the pharmacodynamic or pharmacokinetic profiles of the individual drugs, or their adverse effect profiles.

▲ The administration of combined budesonide/formoterol is effective in improving morning and evening peak expiratory flow rates in adults with persistent asthma. Control of asthma symptoms is also significantly improved.

▲ In children aged 4 to 17 years, combined budesonide/formoterol is effective in increasing both morning and evening peak expiratory flow rates and significantly improving forced expiratory volume in 1 second ($FEV_1$).

▲ The most commonly encountered adverse effects in clinical trials with combination budesonide/formoterol therapy have been respiratory infection, pharyngitis and coughing. No adverse effects on pulse rate, blood pressure or serum potassium have been reported with combination therapy.

| Features and properties of budesonide/formoterol | |
|---|---|
| **Indications** | |
| Regular treatment of persistent asthma where use of a combination of inhaled corticosteroid therapy plus a bronchodilator is appropriate (focus of this review). Launched in Sweden. | |
| **Mechanism of action** | |
| Antiasthmatic | Combination of a long acting inhaled $\beta_2$-agonist bronchodilator and an inhaled corticosteroid |
| **Dosage and administration** | |
| Available strengths (budesonide/formoterol; μg) | 80/4.5 or 160/4.5 per inhalation |
| Route of administration | Inhalation (via Turbuhaler® dry powder inhaler) |
| Frequency of administration | Once or twice daily |
| **Pharmacokinetic profile** | |
| Time to peak plasma concentration | First peak 0.25 hours, then a second peak at 1.58 hours (formoterol); ≈30 minutes (budesonide) |
| Elimination | 24% excreted in the urine (formoterol); 70% via the kidneys as metabolites (budesonide) |
| Elimination half-life | 1.7 to 2.3 hours (formoterol); 1.5 to 3 hours (budesonide) |
| **Adverse events** | |
| Most frequent | Respiratory infection, pharyngitis, coughing, aggravated asthma, viral infection and rhinitis. |




**Budesonide/formoterol**

A fixed combination of the corticosteroid budesonide and the long acting inhaled $\beta_2$-agonist formoterol has recently become available in 2 different strengths (80/4.5μg and 160/4.5μg per inhalation), delivered via Turbuhaler® dry powder inhaler.

Several studies have investigated the addition of a long acting inhaled $\beta_2$-agonist to low or moderate doses of inhaled corticosteroid as an alternative to increasing the dose of inhaled corticosteroid in patients with poorly controlled asthma. Patients treated with formoterol or salmeterol in addition to low or moderate doses of inhaled corticosteroids showed fewer symptoms and better lung function than patients whose inhaled corticosteroid dosage was increased.[1-3]

The use of such a combination is included in current guidelines for the management of asthma. These recommend the use of a long acting inhaled $\beta_2$-agonist as an adjunct to inhaled corticosteroid therapy for long term control of moderate to severe persistent asthma.[4,5] The rationale for this is 2-fold. Firstly, systemic adverse effects of inhaled corticosteroids are dose-related, and so a strategy that allows for the use of lower dosages of these agents is desirable. Secondly, noncompliance with inhaled drugs (particularly corticosteroids) is a major problem in asthma treatment, therefore a combination of budesonide/formoterol offering the option of a long acting $\beta_2$-agonist and a corticosteroid in 1 device would be expected to improve compliance.[6]

This review focuses on studies of the combination of budesonide plus formoterol administered via Turbuhaler® in patients with asthma. Studies which have examined concurrent treatment with budesonide plus formoterol will also be presented. For the purpose of this review, combination therapy refers to the administration of both budesonide and formoterol via a single Turbuhaler®, and concurrent therapy refers to budesonide and formoterol administered via separate devices.

## 1. Pharmacodynamic Profile

The pharmacodynamic properties of both budesonide and formoterol have previously been reviewed.[7-9] Few data have been published on the pharmacodynamic nature of budesonide and formoterol when administered in combination. However, as clinical trial results show little difference in efficacy between combination and concurrent therapies, it is expected that significant differences would not exist between the 2 therapies.

- Both budesonide and formoterol are moderately lipophilic with rapid onset of action and long duration of effect in the lung. Budesonide uptake is rapid because of a high affinity for the glucocorticoid receptor, leading to high initial saturation of the glucocorticoid receptors.[8] Reversible esterification of budesonide on inhalation prolongs the duration of action in airways and lung tissue, while the moderate lipophilicity of unesterified budesonide limits peripheral tissue retention.[8,10] The onset of bronchodilation with inhalation of formoterol is more rapid than that of salmeterol (another long acting inhaled $\beta_2$-agonist), with a similar duration of effect (up to 24 hours).[11,12]

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• In patients with asthma, inhaled budesonide reduces the number of inflammatory cells and mediators in the airways, inhibits the synthesis and release of cytokines, reduces bronchial hyperresponsiveness to a variety of substances and attenuates both the early and late asthmatic response.[13]

• Formoterol elicits dose-dependent bronchodilation in patients with asthma, as measured by forced expiratory volume in 1 second ($FEV_1$), forced vital capacity (FVC), peak expiratory flow rate (PEF) and specific airways conductance (sGaw).[7] Additionally, formoterol protects against methacholine, histamine and allergen challenges, reduces cold air sensitivity, and has exhibited modest anti-inflammatory effects *in vivo*.

• Formoterol induces $\beta_2$-adrenoceptor down-regulation and subsensitivity.[14,15] In patients taking regular twice daily formoterol with concurrent inhaled corticosteroids, the bronchoprotector or bronchodilator tolerance can be overcome within 2 hours by administration of a bolus of high dose inhaled corticosteroid.[16,17] Sensitisation is influenced by a genetic polymorphism of the $\beta_2$-adrenoceptor; therefore considerable interindividual variability is seen.[16] Moreover, long term bronchodilator action is maintained and rebound bronchial hyperresponsiveness has not been observed with cessation of treatment.[15,18]

• Sputum markers of airway inflammation remained suppressed over 12 months in patients receiving twice daily treatment with budesonide (100μg) and formoterol (12μg), after 4 weeks' pretreatment with high dose budesonide (800μg twice daily).[19] An increase in upper limb tremor compared with baseline values was reported in a group of 10 patients with asthma receiving 400μg budesonide in combination with 12μg formoterol twice daily.[20]

• Comparison of effect of 2 different combination products on $FEV_1$ was evaluated in a randomised, double-blind, placebo-controlled, crossover study in 30 patients with asthma [mean baseline $FEV_1$ = 78% predicted (12% reversibility)].[21] One or 2 inhalations of budesonide/formoterol (160/4.5μg per inhalation) showed a more rapid onset of action than a single inhalation of salmeterol/fluticasone (50/250μg), significantly improving mean $FEV_1$ 3 minutes after baseline and during the 3-hour period thereafter (all $p < 0.001$). Similar increases in $FEV_1$ were seen in patients receiving 1 and 2 doses of budesonide/formoterol.[21]

• The effect of 10 inhalations of either budesonide/formoterol (1600/45μg), formoterol (45μg) or placebo over 1 hour and in addition to maintenance therapy with budesonide/formoterol (320/9μg twice daily) was evaluated in 14 patients in a randomised double-blind, crossover trial. No adverse effects or safety concerns were reported either individually or for the group with respect to mean change in pulse rate (+5.4 beats/min), systolic/diastolic blood pressure (+2.5/–3.3mm Hg), or serum potassium (–0.16 mmol/L).[22]

## 2. Pharmacokinetic Profile

Previously published evaluations have reviewed the available information on the 2 drugs following administration via inhaler.[7,9] No pharmacokinetic data concerning combination budesonide/formoterol have been published.

• Single dose inhalation of formoterol results in an initial peak in serum concentration at 0.25 hours, followed by a second peak at 1.58 hours. The mean plasma elimination half-life ($t_{½\beta}$) has been calculated as 1.7 to 2.3 hours following inhalation, with 24% excreted in the urine within 12 hours.[7]

• Peak plasma concentrations of budesonide are reached ≈30 minutes after inhalation via Turbuhaler®.[23] Systemic availability of budesonide administered via Turbuhaler® was 38%, and pulmonary availability was 32%.[24] The drug has a $t_{½\beta}$ of approximately 1.5 to 3 hours and is rapidly and extensively metabolised by cytochrome P450 in the liver, with approximately 70% eliminated via the kidneys as metabolites.[9,10] Pharmacokinetic parameters observed in children (age 10 to 14 years) following inhalation are similar to those observed

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in adults. However, a shorter plasma half-life has been noted after intravenous dosing.[23]

### Effect of Delivery Device

• Budesonide/formoterol (160/4.5μg) administered in combination via the Turbuhaler® dry powder inhaler was associated with a higher percentage of fine particle deposition *in vitro* than salmeterol/fluticasone propionate (250/50μg) via the Diskus® dry powder inhaler. Approximately 50% of the budesonide/formoterol dose was delivered as particles ≤5μm, compared with approximately 20% of the salmeterol/fluticasone propionate dose.[25] Percentages of fine particle doses delivered were similar for both the combination budesonide/formoterol Turbuhaler®, and for budesonide plus formoterol administered concurrently via separate Turbuhaler® devices.[26]

## 3. Therapeutic Trials

Most studies reviewed in this section refer to combination budesonide/formoterol administered via Turbuhaler® inhaler. Combined budesonide/formoterol has been evaluated in three 12-week randomised, double-blind clinical trials in both adults and children whose asthma was inadequately controlled on inhaled corticosteroids alone.[27-31] Metered doses of budesonide used as a comparator in these studies were equivalent to the delivered dosage of budesonide from the combination.

The rationale for using a combination was provided from evidence suggesting that addition of a long acting $\beta_2$-agonist to an inhaled corticosteroid, in patients with asthma reduced symptoms and improved lung function to a greater extent than in those whose inhaled corticosteroid dose was increased.[1-3].

The Formoterol and Corticosteroids Establishing Therapy (FACET) study, a large multicentre, randomised, double-blind clinical trial, investigated the effect of high (800 μg/day) and low (200 μg/day) dosages of budesonide plus formoterol (24 μg/day) administered concurrently via separate Turbuhaler® devices. The results of this study are also described.[3]

### Adults with Persistent Asthma

• Significant differences in both mean morning (the primary efficacy variable) and evening PEF were noted over 12 weeks in patients receiving twice daily combination budesonide/formoterol therapy (320/9μg) in comparison with those receiving budesonide (400μg metered dose twice daily) alone (fig. 1). This study included 362 patients with moderate to severe persistent asthma [mean baseline $FEV_1$ 74% predicted (22.5% reversibility)] inadequately controlled with inhaled corticosteroids alone (mean dosage = 960 μg/day) who received either combination budesonide/formoterol, concurrent budesonide plus formoterol in the same dosages, or budesonide alone. No differences were observed in lung function in patients treated with budesonide/formoterol administered via a single device, or separately via 2 devices. Both combined and concurrent administration demonstrated similar improved efficacy on morning and evening PEF (all $p < 0.001$) compared with budesonide alone.[27]

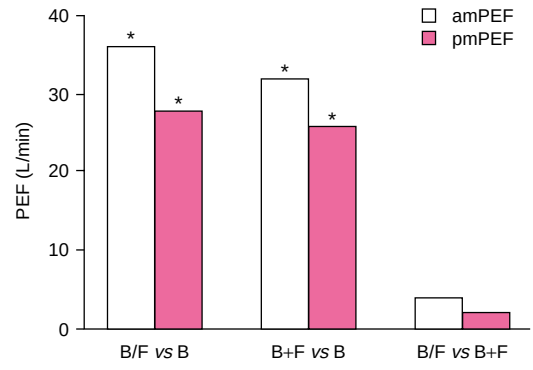


**Fig. 1.** Difference in morning and evening peak expiratory flow rates (amPEF and pmPEF, respectively) between combined budesonide/formoterol (B/F; 320/9μg twice daily) or concurrent B+F (320/9μg twice daily) and B (400μg metered dose twice daily) alone.[27] Results of a multicentre, randomised, double-blind study in 362 patients with moderate to severe persistent asthma (mean forced expiratory volume in 1 second = 74% predicted [22.5% reversibility]). * $p < 0.001$ *vs* comparator.

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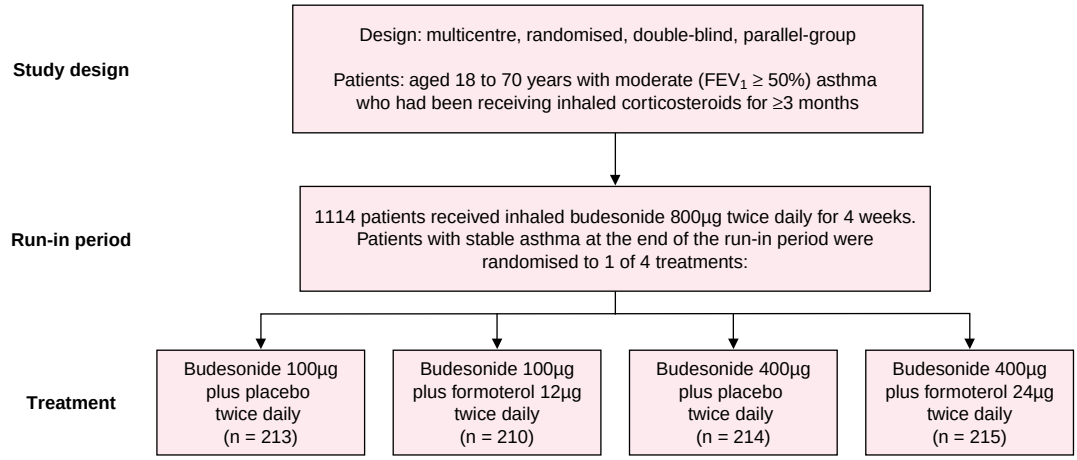


**Fig. 2.** Schematic representation of the design of the Formoterol and Corticosteroids Establishing Therapy (FACET) study.[3]

• In the same study, combination budesonide/formoterol significantly increased the time to first mild exacerbation, corresponding to a 40% decrease in risk compared with budesonide alone ($p = 0.01$). Additionally, the number of asthma-control days (defined as days with no symptoms, rescue medication use or night-time awakenings) increased by 16% ($p < 0.001$) in the combination group compared with budesonide alone. Again, no significant differences were detected between the groups receiving combined or concurrent budesonide and formoterol.[27]

• Average morning and evening PEF were both significantly increased over 12 weeks in adults receiving twice daily treatment with combination budesonide/formoterol compared with those treated with budesonide alone ($p = 0.002$ and $p < 0.001$, respectively). 467 adult patients with mild asthma [mean baseline $FEV_1$ ≈82% predicted (22% reversibility)] who remained symptomatic on low dose corticosteroids alone (mean dosage = 390 µg/day) were randomised to receive either budesonide/formoterol (80/4.5µg) or budesonide alone (200µg metered dose) twice daily. Treatment with the combination also resulted in significantly more asthma control days ($p = 0.02$) and significantly less rescue medication use ($p = 0.025$) than treatment with budesonide monotherapy.[30,31]

• A 12-week double-blind, placebo-controlled clinical trial comparing twice daily concurrent budesonide (800µg) plus formoterol (12µg) treatment with combination salmeterol/fluticasone (50/250µg twice daily) in 428 patients with asthma [$FEV_1$ = 50-85% predicted (≥15% reversibility)] showed identical mean improvements in morning PEF from baseline in the 2 groups [difference = –0.6 (95% CI –9.3,8.1)].[32]

### *The FACET Study*

• Briefly, 852 adult patients with moderate persistent asthma (mean baseline $FEV_1$ 75.8% predicted) that remained stable after high dosage budesonide (800µg twice daily) during a 4-week run-in period, were randomised to receive twice daily budesonide 100µg or 400µg, alone or concurrently with 12µg formoterol, for 12 months (fig. 2). Compared with budesonide monotherapy, the addition of formoterol to budesonide significantly reduced the mean incidence of mild ($p \leq 0.01$, fig.

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3a) and severe exacerbations ($p \leq 0.01$, fig. 3b), the primary efficacy variables in the study. However, an increased dose of budesonide alone was more effective in decreasing severe exacerbations than the addition of formoterol to a low dose of budesonide ($p = 0.03$).[3]

- The addition of formoterol was more effective in increasing PEF than increasing the dose of budesonide, with improvements in morning PEF greatest during the first 3 days of treatment. Absolute values ranged from ≈24 to ≈36.5 L/min (estimated from graphs) in patients treated with the combination, but failed to exceed baseline in recipients of budesonide monotherapy throughout the first 2 weeks of the trial.[3] PEF in patients receiving concurrent budesonide plus formoterol was considerably (i.e. ≥10.9 L/min) greater than baseline throughout the 12-month study while in patients randomised to monotherapy was minimal (i.e. ≤3 L/min).[3]

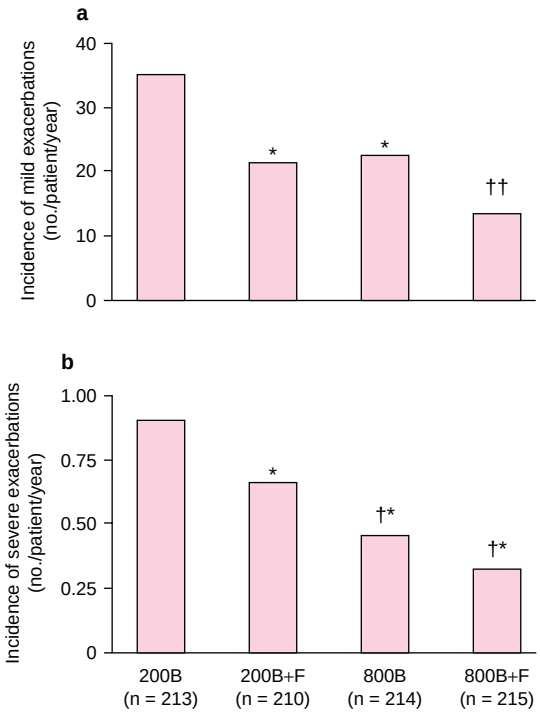


**Fig. 3.** Effect of inhaled concurrent budesonide plus formoterol on (**a**) mild or (**b**) severe exacerbations of asthma. 852 patients with moderate persistent asthma [forced expiratory volume in 1 second ≥50% predicted despite ongoing inhaled corticosteroid treatment (mean dose = 830 μg/day)] received 12 months' treatment with 200 μg/day budesonide (200B), 200 μg/day budesonide + 24 μg/day formoterol (200B+F), 800 μg/day budesonide (800B), or 800 μg/day budesonide + 24 μg/day formoterol (800B+F) in a double-blind, placebo-controlled randomised trial (see fig. 2.).[3] Mild exacerbation = morning peak expiratory flow rate (amPEF) >20% below baseline value, >3 additional inhalations of terbutaline needed over 24 hours compared with baseline, or awakening at night due to asthma; severe exacerbation = requiring oral glucocorticoid treatment, or amPEF >30% below baseline on 2 consecutive days; * $p \leq 0.01$ *vs* 200B, † $p < 0.05$ *vs* 200B+F, †† $p < 0.001$ *vs* 800B.

- Quality of life was assessed via the Asthma Quality of Life Questionnaire in a subset of patients (n = 470) in the FACET study. Overall scores, and those for symptoms, activities, emotions and environment individually improved both clinically (≤ 0.5 units) and statistically significantly during the run-in period ($p < 0.0001$ *vs* baseline) when patients received 1600μg budesonide daily. Further statistically significant improvements over 12 months were seen in the group receiving concurrent budesonide (400μg) plus formoterol (12μg) twice daily ($p = 0.028$); however, scores were maintained in the other 3 groups.[33]

### Children and Adolescents with Persistent Asthma

- The efficacy of twice daily combination budesonide/formoterol (160/9μg) was compared with that of twice daily budesonide alone (160μg) in 286 children aged 4 to 17 years [mean baseline $FEV_1$ 75.0% predicted (21.5% reversibility)], whose asthma was inadequately controlled on inhaled corticosteroids alone (mean dosage = 550 μg/day). The increase in morning PEF from baseline was significantly greater in the group receiving the combination (23 L/min) than in those receiving budesonide alone (11 L/min; $p < 0.001$).[28]
- Significantly greater improvements in $FEV_1$ were noted at week 12 in a subgroup of 81 patients from the same study. The increase in $FEV_1$ after 10 minutes was 6% higher ($p = 0.01$), and the 12-hour average $FEV_1$ was 5% higher ($p = 0.04$), in those receiving combined budesonide/formoterol than in

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those receiving budesonide alone. Additionally, the peak $FEV_1$ was 6% higher ($p = 0.01$) in those receiving combined budesonide/formoterol than in patients given budesonide only.[29]

## 4. Tolerability

• The most commonly reported adverse effects with combination budesonide/formoterol in double-blind randomised trials in both adults and children with persistent asthma were respiratory infection (16%), pharyngitis (6%), coughing (5%), worsening asthma (4%), viral infection (4%) and rhinitis (4%).[27,30,31,34]

• 29 patients withdrew from the FACET study due to adverse effects, 7 of which were due to a pharmacologically predictable event. The proportion of patients reporting adverse effects was similar among the 4 groups. Adverse effects reported were: headache, tremor, tachycardia and oral candidiasis.[3]

## 5. Budesonide/Formoterol: Current Status

In clinical trials in both children and adults with moderate persistent asthma, combined budesonide/formoterol administered in a combination formulation via the Turbuhaler® dry powder inhaler has proven to be more effective in improving lung function than the same dose of budesonide given alone. The time to mild exacerbations was reduced and the number of asthma control days was increased in adults.

In addition, studies in adults given combined budesonide/formoterol 320/9 μg/day and 160/9 μg/day, respectively, have demonstrated similar efficacy to concurrent therapy with the same dosages of the 2 agents given via separate inhalers.

## References


1. Greening AP, Ind PW, Northfield M, et al. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Lancet 1994; 344: 219-24
2. Woolcock A, Lundback B, Ringdal N, et al. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. Am J Respir Crit Care Med 1996; 153: 1481-8
3. Pauwels RA, Löfdahl CG, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group [published erratum appears in N Engl J Med 1998 Jan 8;338(2):139]. N Engl J Med 1997 Nov 13; 337: 1405-11
4. National Institutes of Health. National Asthma Education and Prevention Program Expert Panel Report 2: guidelines for the diagnosis and management of asthma [online]. National Heart, Lung and Blood Institute 1997 July. Available from: URL: http://www.nhlbi.nih.gov/health/prof/lung/asthma/ [Accessed 2000 Dec 14]
5. The British Guidelines on Asthma Management 1995 Review and Position Statement. Thorax 1997; 52 Suppl. 1: 1-21
6. Campbell LM. Once-daily inhaled corticosteroids in mild to moderate asthma: improving acceptance of treatment. Drugs 1999; 58 Suppl. 4: 25-33
7. Bartow R, Brogden RN. Formoterol: an update of its pharmacological properties and therapeutic efficacy in the management of asthma. Drugs 1998 Feb; 2: 303-22
8. Hvizdos KM, Jarvis B. Budesonide inhalation suspension: a review of its use in infants, children and adults with inflammatory respiratory disorders. Drugs 2000; 60 (5): 1-38
9. Boobis A. Comparative physiochemical and pharmacokinetic profiles of inhaled beclomethasone dipropionate and budesonide. Respir Med 1998; 92 Suppl. B: 2-6
10. Edsbacker S. Pharmacological factors that influence the choice of inhaled corticosteroids. Drugs 1999; 58 Suppl. 4: 7-16
11. Rabe K, Jörres R, Nowak D, et al. Comparison of the effects of salmeterol and formoterol on airway tone and responsiveness over 24 hours in bronchial asthma. Am Rev Respir Dis 1993; 147: 1436-41
12. Palmqvist M, Persson G, Lazer L, et al. Inhaled dry-powder formoterol and salmeterol in asthmatic patients: onset of action, duration of effect and potency. Eur Respir J 1997; 10: 2484-9
13. Szefler SJ. Pharmacodynamics and pharmacokinetics of budesonide: a new nebulized corticosteroid. J Allergy Clin Immunol 1999; 104: S175-83
14. Taylor DR, Hancox RJ. Interactions between corticosteroids and β agonists. Thorax 2000; 55: 595-602
15. Lipworth B. Airway subsensitivity with long-acting $\beta_2$-agonists. Is there cause for concern? Drug Saf 1997; 16 (5): 295-308
16. Tan KS, Grove A, McLean A, et al. Systemic corticosteriod rapidly reverses bronchodilator subsensitivity induced by formoterol in asthmatic patients. Am J Respir Crit Care Med 1997 Jul; 156: 28-35
17. Aziz I, Lipworth BJ. A bolus of inhaled budesonide rapidly reverses airway subsensitivity and $\beta_2$-adrenoceptor down-regulation after regular inhaled formoterol. Chest 1999 Mar; 115: 623-8
18. Beasley R, Pearce N, Crane J, et al. β-Agonists: what is the evidence that their use increases the risk of asthma morbidity and mortality? J Allergy Clin Immunol 1999 Aug; 104 Suppl. 2: S18-30
19. Kips JC, O'Connor BJ, Inman MD, et al. A long-term study of the antiinflammatory effect of low-dose budesonide plus formoterol versus high-dose budesonide in asthma. Am J Respir Crit Care Med 2000 Mar; 161 (3 Pt 1): 996-1001
20. Centanni S, Carlucci P, Santus P, et al. Non-pulmonary effects induced by the addition of formoterol to budesonide therapy in patients with mild or moderate persistent asthma. Respiration 2000; 67: 60-4


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21. Palmqvist M, Arvidsson P, Beckman O, et al. Onset of bronchodilation of budesonide/formoterol *vs* salmeterol/fluticasone in single inhalers. Pulm Pharmacol Ther. In press
22. Ankerst J, Persson G, Weibull E. A high dose of budesonide/formoterol in a single inhaler was well tolerated by asthmatic patients [abstract]. World Congress on Lung Health and 10th ERS Annual Congress. Eur Respir J 2000 Aug; 16 Suppl. 31: 33S
23. Astra USA. Pulmicort Turbuhaler (budesonide inhalation powder) prescribing information. Westborough, MA, 1998
24. Thorsson L, Edsbäcker S, Conradson T-B. Lung deposition of budesonide from Turbuhaler is twice that from a pressurized metered-dose inhaler P-MDI. Eur Respir J 1994; 7: 1839-44
25. Granlund KM, Asking L, Lindblad T, et al. An *in-vitro* comparison of budesonide/formoterol and fluticasone/salmeterol in dry powder inhalers [abstract]. World Congress on Lung Health and 10th ERS Annual Congress. Eur Respir J 2000 Aug; 16 Suppl. 31: 455S
26. Lindblad T, Granlund KM, Rollwage U, et al. Characteristics of a dry powder inhaler containing both budesonide and formoterol [abstract]. World Congress on Lung Health and 10th ERS Annual Congress. Eur Respir J 2000 Aug; 16 Suppl. 31: 455S
27. Zetterström O, Buhl R, Mellem H, et al. Symbicort® (budesonide and formoterol in a single inhaler) improves asthma control compared with budesonide alone: a randomised controlled study. Eur Respir J. In press
28. Tal A, Simon G, Vermeulen J, et al. The benefit of the new single inhaler product containing both budesonide and formoterol in asthmatic children [abstract]. World Congress on Lung Health and 10th ERS Annual Congress. Eur Respir J 2000 Aug; 16 Suppl. 31: 384S
29. Vermeulen J, Simon G, Tal A, et al. Improved lung function and rapid control achieved with the new single inhaler product containing both budesonide and formoterol in asthmatic children aged 4-17 years [abstract]. World Congress on Lung Health and 10th ERS Annual Congress. Eur Respir J 2000 Aug; 16 Suppl. 31: 384S
30. Lalloo UG, Malolepszy J, Kozma D, et al. Low-dose Symbicort® (budesonide/formoterol) is more effective than double-dose inhaled corticosteroid in mild asthma [abstract]. XVII International Congress of Allergology and Clinical Immunology; 2000 Oct 15-20; Sydney
31. Lalloo UG, Malolepszy J, Kozma D, et al. Low-dose Symbicort® (budesonide/formoterol) controls exacerbations better than double-dose ICS in mild asthma [abstract]. XVII International Congress of Allergology and Clinical Immunology; Oct 15-20; Sydney
32. Ringdal N, Chuchalin AG, Chovan L, et al. A comparison of Advair™/Seretide™ (salmeterol 50μg/fluticasone propionate 250μg bid) with formoterol 12μg + budesonide 800μg bid in moderate-severe asthma [abstract]. Am J Respir Crit Care Med; 2000: 196
33. Juniper EF, Svensson K, O'Byrne PM, et al. Asthma quality of life during 1 year of treatment with budesonide with or without formoterol. Eur Respir J 1999 Nov; 14: 1038-43
34. Tal A, Vermeulen JH, Vit P, et al. Symbicort® Turbuhaler® provides improved effect in asthmatic children treated with inhaled corticosteroids [poster]. XVII International Congress of Allergology and Clinical Immunology; Oct 15-20; Sydney

Correspondence: *Jane K. McGavin*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz

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