Cost-effectiveness analysis of budesonide/formoterol compared with fluticasone in moderate-persistent asthma

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Summary In this economic evaluation, conducted alongside a randomized, double-blind clinical trial, economic data were collected from 339 patients with moderate-persistent asthma randomized to receive twice-daily, double-blind treatment with budesonide/formoterol 160/4.5 mg in a single inhaler (n = 166) or fluticasone propionate 250 mg (n = 173) for 12 weeks. The mean number of episode-free days (EFD) per patient was significantly greater in the budesonide/formoterol group than the fluticasone group (48.71 compared with 42.34, \( P = 0.0185 \)). Data on medication use, visits to healthcare professionals, and hospitalization were pooled across all six countries and combined with German and Dutch unit cost data to calculate total healthcare costs. Using German unit costs, budesonide/formoterol was associated with significantly lower total healthcare costs per patient over the 12-week period compared with fluticasone (€131 compared with €210, \( P = 0.0043 \)). Using Dutch unit costs, total healthcare costs were slightly numerically lower in the budesonide/formoterol group than the fluticasone group (€102 compared with €104), but the difference did not reach statistical significance. Budesonide/formoterol in a single inhaler is more effective than a higher microgram dose of fluticasone alone. It is cost-neutral and may provide cost-savings in some countries.

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Introduction

Asthma prevalence is high with an estimated 300 million sufferers worldwide,1 imposing a heavy economic burden on society as a whole. The cost of asthma has been calculated at €2.74 billion per year in Germany2 in 1999, and $10.7 billion per year in the USA3 in 1994. Hospitalization and indirect costs (loss of productivity due to being unable to work because of asthma) accounted for substantial costs in both studies, indicating sub-optimal asthma control. Patients with better-controlled asthma have been shown to incur lower costs,4,5 demonstrating that improving the control of asthma could reduce the burden of illness for patients, healthcare systems, and society as a whole.6

International guidelines recommend a stepped approach approach to asthma treatment, titrating maintenance treatment down to the lowest effective dose.7 Inhaled corticosteroids are recommended for all but mild-intermittent asthma, with the addition of a long-acting β2-agonist in patients with persistent asthma who are not adequately controlled on inhaled corticosteroids alone.7 Clinical trials have shown that the addition of the long-acting β2-agonist formoterol to inhaled corticosteroid treatment provides better lung function, better symptom control, and a reduced risk of exacerbations compared with inhaled corticosteroids alone in patients with moderate-to-severe8 and mild-to-moderate9 asthma. In addition, using both a long-acting β2-agonist and an inhaled corticosteroid in a single inhaler has been shown to improve patient adherence to medication,10 which in turn can increase efficacy.11

However, combined therapy has an intrinsically higher unit cost than inhaled corticosteroids alone. To address concerns about possible increased costs, there is a need for economic studies to define the cost and cost-effectiveness of inhaled corticosteroids plus a long-acting β2-agonist compared with inhaled corticosteroids alone. Such information will be of help to physicians and budget holders in deciding on the most appropriate allocation of resources for treating patients whose asthma is not fully controlled by inhaled corticosteroids alone.

Clinical efficacy assessments

The primary clinical efficacy variable was morning peak expiratory flow (PEF). Secondary variables included time to first exacerbation, use of rescue medication, and asthma symptom score. PEF and asthma symptoms were recorded each morning and evening using a diary card. Mild and severe exacerbations were recorded throughout the study. A mild exacerbation was defined as one of the following: awakening due to asthma on two consecutive nights, morning PEF at least 20% below baseline value on two consecutive days, or use of at least four inhalations of reliever medication more
than the baseline mean value on each of two consecutive days (i.e. over a 48-h period). A severe exacerbation was defined as: the need for oral corticosteroids, PEF of at least 30% below baseline on two consecutive days, or discontinuation due to asthma worsening.

Cost and effectiveness assessments

The primary effectiveness variable used in the economic analysis was the number of episode-free days (EFD). An EFD was defined as 24 h without any asthma symptoms, no use of rescue medication, no night-time awakening due to asthma, and morning PEF of at least 80% of baseline. The EFD has been previously recommended as an economically and clinically meaningful effectiveness measure that can be constructed from asthma clinical trial data. The main economic analysis was conducted from the perspective of a healthcare payer, including total healthcare costs only. Secondary analyses were conducted from a societal perspective (also including productivity costs), and from the perspective of a drug budget holder (medication costs only).

Utilization of healthcare resources and days on which the patient was unable to work (employment or home-making) were recorded in the case report forms.

Use of rescue medication and other asthma medication was also recorded. Study medication use was calculated as the intended daily dose strength multiplied by the intended number of days in the study (84 days). Study medication use was thus the same for all patients in a treatment group.

A total of 15 patients in the budesonide/formoterol group, and 20 in the fluticasone group discontinued the clinical study before the end of the 12-week study period; 11 due to disease deterioration (three in the budesonide/formoterol group, eight in the fluticasone group), 10 due to other adverse events (five in each group) and 14 for other reasons (seven in each group). These discontinuations were handled using the patient-year approach, which scales the available data for a patient to represent the nominal study period of 12 weeks, by imputing the patient’s own observed average value on each day after discontinuation. An alternative approach uses group mean imputation by similarly imputing the treatment group average on each day after discontinuation, which gives a greater weight to patients with more days in the study. A sensitivity analysis was conducted using this approach to test the effect of the different calculation methods on the results.

Resource utilization data were pooled across all six countries. However, different countries may have different healthcare systems, different treatment patterns, and cultural differences in healthcare use (e.g. differences in when it is thought appropriate to call a doctor or attend an emergency room), and these may cause different patterns of resource utilization. The resource use data in the present study were tested for the absence of homogeneity using a \( \chi^2 \)-test on the number of physician visits, which was the single most common healthcare contact in the study.

Costs cannot be generalized from one country to another because differences in the price of healthcare interventions and medications vary so greatly between countries. We calculated costs for Germany and The Netherlands by multiplying the pooled resource use data by German or Dutch unit costs, respectively (Table 1). The unit costs were obtained in 2000 in German Marks (DM) and Dutch Guilders (NGL), respectively. As these currencies have now been replaced by the Euro, all costs are presented in Euros (€1 = DM 1.95583 = NGL 2.20371). These two countries were selected a priori because they have shown a strong interest in health economic data, and because unit cost data for the healthcare resources are readily available. Calculating costs for two different countries provides a way of assessing the impact of price differentials on our findings.

Effectiveness data were compared between groups using a Wilcoxon rank sum test. Mean values for cost data were compared using parametric tests (t-test) based on the central limit theorem.

Results

Clinical results

Of the 373 patients enrolled into the study, 344 were randomized. There were 168 patients in the budesonide/formoterol group (42% male), and 176 patients in the fluticasone group (44% male), with a mean age of 42.6 years and 41.8 years, respectively. The groups were well balanced at baseline. The mean duration of asthma was 16.3 years in both groups; mean pre-study steroid use was 591 μg/day in the budesonide/formoterol group, and 597 μg/day in the fluticasone group, and mean pre-study use of reliever medication was 0.9 inhalation/day and 1 inhalation/day, respectively. Mean FEV₁ (% predicted normal) was 77.2 in the
budesonide/formoterol group and 79.2 in the fluticasone group.

The clinical efficacy results are summarized in Table 2. Budesonide/formoterol improved lung function significantly ($P<0.001$) more than fluticasone, significantly ($P = 0.04$) reduced the use of rescue medication, and significantly ($P = 0.04$) increased the time to the first mild exacerbation.14

### Economic results

A total of 339 patients were included in the economic analysis. This differs from the number in the clinical analysis ($n = 344$) as five patients provided no economic data after randomization. The mean number of EFD per patient was significantly higher in the budesonide/formoterol group.
than the fluticasone group (48.71 compared with 42.34, \( P = 0.0185 \)) (Fig. 1).

Average resource utilization across all six countries is shown in Table 3.

German healthcare costs are presented in Fig. 2a and Table 4. Total healthcare costs were significantly \( (P<0.01) \) lower in the budesonide/formoterol group than in the fluticasone group, mainly due to the lower cost for study medication, rescue medication, and hospitalization in the budesonide/formoterol group.

Dutch healthcare costs are presented in Fig. 2b and Table 4. In The Netherlands, there was no statistically significant difference in total healthcare costs. Study medication costs were higher in the budesonide/formoterol group than in the fluticasone group, but this was fully offset by reductions in other cost components, mainly hospitalization and rescue medication. The difference in study medication costs is due to the larger difference in price between the two products in Germany (Table 1).

Taking the perspective of a drug budget holder and looking only at total medication costs, budesonide/formoterol treatment was less costly than fluticasone treatment in Germany (Table 4). In The Netherlands, by contrast, total medication cost per patient over the study period was higher in the budesonide/formoterol group than in the fluticasone group (Table 4). These differences are mainly the result of the difference in prices for the study medications in the two countries (Table 1).

In both countries, productivity costs were lower in the budesonide/formoterol group than in the fluticasone group (Fig. 3), although the differences were not statistically significant. Total costs (healthcare plus productivity costs) were lower in the budesonide/formoterol group than in the fluticasone group in both countries (Table 4), but the difference was only statistically significant in Germany \( (P = 0.025) \).

### Sensitivity analyses

In the test of homogeneity, it was found that the pattern of physician visits was not homogeneous. Israel comprised roughly half of all reported physician visits, in spite of its relatively low number of patients (65 out of 339). There was no evidence of lack of homogeneity when the Israeli patients were excluded. We therefore conducted a sensitivity analysis to determine whether excluding the Israeli data influenced the results. The findings were similar to those of the main analysis (Table 5).

#### Table 3  Mean resource utilization per patient over the study period.

<table>
<thead>
<tr>
<th>Item</th>
<th>Budesonide/formoterol ((n = 166))</th>
<th>Fluticasone ((n = 173))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rescue medication (inhalations)</td>
<td>48.39</td>
<td>68.56</td>
</tr>
<tr>
<td>Hospitalization (general medicine) (days)</td>
<td>0</td>
<td>0.13</td>
</tr>
<tr>
<td>Hospitalization (ICU) (days)</td>
<td>0</td>
<td>0.10</td>
</tr>
<tr>
<td>Emergency room (visits)</td>
<td>0</td>
<td>0.21</td>
</tr>
<tr>
<td>Physician visits ((n))</td>
<td>0.18</td>
<td>0.21</td>
</tr>
<tr>
<td>Nurse visits ((n))</td>
<td>0.01</td>
<td>0</td>
</tr>
<tr>
<td>House calls ((n))</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>Phone calls ((n))</td>
<td>0.11</td>
<td>0.13</td>
</tr>
<tr>
<td>Pharmacy contacts ((n))</td>
<td>0.13</td>
<td>0.11</td>
</tr>
<tr>
<td>Time off work ((days))</td>
<td>0.26</td>
<td>0.78</td>
</tr>
</tbody>
</table>

ICU = intensive care unit.

Time off work: \( >4h = 1 \text{ day}, \leq 4h = 0.5 \text{ day} \). For the unemployed, the cost for time off work was only calculated for a person who stayed home assisting the patient, if applicable.

“Other medication” use is the sum of numerous different therapies and so is not presented here. However, it is included in the cost estimates.

![Figure 1 Mean number of episode-free days per patient during the study period.](image_url)
A further analysis was conducted using the group mean imputation method to handle early discontinuations, instead of the patient-year approach. The findings were similar to those of the main analysis (Table 5).

**Discussion**

According to international guidelines, the goal of asthma treatment is to achieve maximum asthma control (minimal or no symptoms, minimal or no lung function impairment, and minimal risk of exacerbations) and maintain it at the lowest possible dose of controller treatment, usually inhaled corticosteroid. Several studies have found that adding a long-acting $\beta_2$-agonist to a low or moderate dose of inhaled corticosteroid provides more effective asthma control than a higher dose of inhaled corticosteroid alone. Guidelines now recommend that the addition of a long-acting $\beta_2$-agonist to inhaled corticosteroid treatment is preferable to increasing the inhaled corticosteroid dose in patients with moderate- and severe-persistent asthma. The findings of O’Byrne et al. suggest that this might also be a valuable treatment option in patients with mild-to-moderate asthma who are not fully controlled on inhaled corticosteroids alone.

The development of single inhaler devices containing both a long-acting $\beta_2$-agonist, and a corticosteroid provides a convenient treatment option for patients who are judged likely to benefit from combination therapy. Budesonide/formoterol in a single inhaler (160/4.5 mg bid) was significantly more effective than fluticasone propionate (250 mg bid) in improving lung function, reducing the use of reliever medication, and reducing the risk of mild exacerbations in patients with moderate-persistent asthma.

In addition to clinical evidence, information is also needed on the economic effects of switching patients from inhaled corticosteroid monotherapy to inhaled corticosteroid plus long-acting $\beta_2$-agonist in a single inhaler. Many patients remain on monotherapy despite achieving less than optimal control of symptoms, and in a recent survey only 15% of physicians prescribed an additional drug in response to worsening asthma symptoms. There may be many reasons for this apparent reluctance to step up treatment, including misjudgment of the degree of asthma control achieved, concern about medication (especially corticosteroid) side effects, and resistance to increasing the complexity of treatment by adding another inhaler. Concern over possible increases in healthcare cost may also be an issue.

The present economic evaluation provides data that may help physicians and budget holders with a commonly encountered choice: should a patient with moderate-persistent asthma not adequately controlled on inhaled corticosteroids alone receive a higher microgram dose of inhaled corticosteroid or inhaled corticosteroid plus a long-acting $\beta_2$-agonist?

The present study confirms that budesonide/formoterol in a single inhaler was more effective
than fluticasone alone, providing significantly more EFD per patient. This increase in effectiveness was achieved at either no increase or a net saving in healthcare and total costs, depending on the country. Compared with fluticasone, budesonide/formoterol was associated with substantially lower utilization of some resources, such as the mean number of inhalations of rescue medication (48.39 vs. 68.56), and the mean number of days lost from work (0.26 vs. 0.78). Hospitalization and emergency room visits were also lower in the budesonide/formoterol group than the fluticasone group, but the numbers were small.

Using German unit costs, budesonide/formoterol was associated with a significant saving in healthcare costs (€80 per patient over the 12-week study period, $P = 0.0043$). When productivity costs were included, thereby taking a societal perspective, total costs were also significantly lower in the budesonide/formoterol group than in the fluticasone group ($P = 0.0254$). Taking the perspective of a drug budget holder, and looking only at total medication costs, budesonide/formoterol treatment was also less costly than fluticasone treatment (€114 compared with €154), reflecting the fact that Symbicort® Turbuhaler® 160/4.5 μg has a lower acquisition cost than Flifixotide® 250 μg in Germany. Thus, using German cost data, formoterol/budesonide in a single inhaler was both more effective and less costly than fluticasone from all perspectives analyzed, making it the dominant strategy.

In The Netherlands, the acquisition cost of fluticasone is lower than that of budesonide/formoterol, so that the mean cost of study medication was higher in the budesonide/formoterol group than in the fluticasone group. However,
this was completely offset by savings in other medication, and healthcare resource use, so that total healthcare costs were almost identical in the two treatment groups. Productivity and total costs were lower in the budesonide/formoterol group, but this did not reach statistical significance. Using Dutch cost data, budesonide/formoterol provided significantly improved effectiveness with no increase in healthcare or total costs, making it clearly cost-effective compared with fluticasone alone.

The pattern of numerically lower costs for use of healthcare resources and productivity losses observed for the budesonide/formoterol group in both countries is as would be expected from the improved asthma control achieved with combined treatment.

Pooling resource use data from multiple countries to calculate costs is a methodological issue in economic studies. Variations in healthcare systems and treatment patterns may cause problems in generalizing resource use data across countries. In the present study, it was found that patients in Israel were significantly more likely than patients in other countries to contact a physician. The other five countries did not show such differences. Therefore, the results were analyzed with and without the Israeli data to test the sensitivity of the results to this inter-country difference. A further sensitivity analysis was also carried out to test the effect of using two different approaches to handling data from patients who discontinued the study early. Both these analyses showed that the findings of the study were robust to using these alternative methodologies.

A limitation of the present study is its short duration (12 weeks). Asthma is a chronic disease, and the results from a 12-week period may not necessarily reflect the effects in long-term treatment. In particular, a study of this length is unlikely to be able to detect differences in rare (but costly) events such as hospitalizations. It is possible that the economic impact of the reduction in the risk of exacerbations observed in the budesonide/formoterol group may have been underestimated.

The findings of the present study are consistent with other studies investigating the cost-effectiveness of formoterol plus budesonide in asthma. Formoterol plus budesonide in separate inhalers has been shown to be cost-effective compared with budesonide alone, and budesonide/formoterol in a single inhaler has been found to be cost-saving compared with separate inhaler treatment. Other studies have compared the combination of salmeterol and fluticasone at various doses with equivalent microgram doses of fluticasone alone, either by analyzing data collected alongside clinical studies, or by Markov computer modeling. These have consistently found that the combination is more effective than fluticasone alone, although

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Sensitivity analyses.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost item</td>
<td>German costs (Euros)</td>
</tr>
<tr>
<td></td>
<td>Budesonide/formoterol</td>
</tr>
<tr>
<td></td>
<td>(n = 135)</td>
</tr>
<tr>
<td>Mean costs per patient excluding data from Israel</td>
<td></td>
</tr>
<tr>
<td>Total healthcare costs</td>
<td>127</td>
</tr>
<tr>
<td>Productivity costs</td>
<td>19</td>
</tr>
<tr>
<td>Total costs</td>
<td>146</td>
</tr>
<tr>
<td>Mean costs per patient including data from all six countries and using the group mean imputation approach</td>
<td></td>
</tr>
<tr>
<td>Total healthcare costs</td>
<td>133</td>
</tr>
<tr>
<td>Productivity costs</td>
<td>29</td>
</tr>
<tr>
<td>Total costs</td>
<td>163</td>
</tr>
</tbody>
</table>

Totals may not add exactly due to rounding.
associated with higher or similar total healthcare costs. However, differences in dose, country-specific prices, and methodology mean that their findings may not be directly comparable with those of the present study.

The present study shows that budesonide/formoterol in a single inhaler is more effective than a higher microgram dose of fluticasone alone. It is cost-neutral and may provide cost-savings in some countries. These results indicate that when a patient is not adequately controlled on inhaled corticosteroids alone and an additional treatment step is required, switching to budesonide/formoterol in a single inhaler could improve asthma control without increasing costs, and may even provide cost savings.

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