Adjustable maintenance dosing with budesonide/formoterol (Symbicort®) reduces treatment costs in asthma

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SUMMARY

Adjustable maintenance dosing permits patients to increase or decrease their medication, according to a management plan, in response to daily variations in asthma. Adjustable maintenance dosing with budesonide/formoterol in a single inhaler was compared with fixed dosing bid in eight randomised, open-label studies. Data on resource utilisation were collected prospectively in six of the studies. Duration of randomised treatment was 3 months (UK, Italy, Germany), 4 months (Belgium), 5 months (Canada) or 6 months (Sweden). Mean number of budesonide/formoterol inhalations/day was significantly lower for adjustable maintenance dosing vs. fixed dosing, which resulted in significantly lower drug and total costs with adjustable maintenance dosing vs. fixed-dosing group. In the 3- and 4-month studies, both regimens had similar effectiveness. In the Canadian and Swedish studies, a significantly lower percentage of adjustable maintenance dosing patients had asthma exacerbations compared with fixed dosing. Adjustable maintenance dosing reduced treatment costs, providing similar or better asthma control at a lower overall dose, compared with fixed dosing.

Keywords: Adjustable maintenance dosing; budesonide; formoterol; Symbicort®; cost; health economics

INTRODUCTION

Asthma is a widespread, chronic medical condition, and its prevalence is increasing (1). The burden of illness and associated morbidity are correspondingly high for the individual patient, society in general, and health-care systems.

Costs related to disease and its treatment are generally divided into direct and indirect costs. Direct costs include medical services (e.g. contact with health-care professionals), products (e.g. drugs) used by patients and non-medical assistance, such as food, accommodation and transportation, because of illness or health-care intervention. Indirect costs are those of lost or reduced productivity, resulting from morbidity or premature mortality because of a patient's medical condition and may also include informal caregiving. In Sweden in 1991, the annual direct cost of asthma was estimated at SEK 1.1 billion (€121 million) [exchange rates used for currency conversions were as follows: SEK 1, €0.11 (17 June 2003); US $1, €0.85 (17 June 2003); CAD $1, €0.64 (18 June 2003); £1, €1.42 (17 June 2003)], and the total annual cost (including indirect costs) at SEK 3 billion (€333 million) (2). In the USA in 1994, the total annual cost of asthma was estimated at US $10.7 billion (€9.1 billion), of which direct costs accounted for US $6.1 billion (€5.2 billion) (3). In Canada in 1990, the total cost of asthma was estimated to lie between Can $504 million (€323 million) and Can $648 million (€415 million) (4).

Exacerbations of asthma are associated with increased costs, particularly in secondary care. In a large, retrospective cohort study in the UK, costs of treating asthma during a 1-year period were 3.5 times higher for patients who had exacerbations than those who did not (5). This difference was mainly a result of a 17-fold increase in the cost of secondary care, such as hospitalisations; however, primary care costs, such as general practitioner and nurse visits, and medication costs were also increased (approximately doubled). Furthermore, asthma exacerbations have been shown to result in substantial reductions in patients' health-related quality of life (HRQL) (6).

International guidelines recommend a stepwise approach to the treatment of asthma (7), where maintenance treatment is adjusted appropriately in response to variation in asthma control. Traditional fixed-dose inhaled corticosteroid/long-acting β_2-agonist treatment is limited in its ability to maintain overall asthma control (8). During periods of well-controlled asthma, fixed-dose treatment may provide excessively high doses, unnecessarily increasing medication costs and potentially contributing to the increased risk of

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dose-related side effects. Conversely, during periods of asthma deterioration, fixed-dose treatment may under-dose the patient, increasing the risk of uncontrolled symptoms that may require medical intervention, such as health-care professional consultations, emergency treatment or hospitalisation, which are all associated with substantial costs.

As discussed elsewhere in this supplement (9,10), guided self-management plans are designed to help patients manage their disease by guiding them towards adjusting their maintenance dose in response to variations in their asthma control (11,12). Criteria for selecting those patients who are most suited to guided self-management have been proposed by Lahdensuo (11). Guided self-management has been shown to increase the number of successfully treated weeks, to reduce the required dose of inhaled corticosteroid (13) and to reduce the need for hospital admission (14,15). In addition, several studies have shown that guided self-management programmes can be cost-effective in asthma (16–18).

A series of randomised, multicentre studies in Europe and Canada have evaluated the efficacy and tolerability of budesonide/formoterol adjustable maintenance dosing in comparison with a traditional fixed-dosing regimen. Results from the first eight studies in this series have shown that budesonide/formoterol adjustable maintenance dosing provides effective asthma control, is well tolerated and leads to a lower overall dose compared with fixed dosing. More importantly, in two of the longer-term studies in Canada (5 months) and Sweden (6 months), a significantly lower proportion of patients on adjustable maintenance dosing had exacerbations compared with fixed dosing. In addition, a 7-month European multinational study demonstrated that budesonide/formoterol adjustable maintenance dosing significantly ($p < 0.05$) reduced the rate of exacerbations compared with fluticasone/salmeterol fixed dosing. Details of the methodologies (9) and clinical results (19) of all the studies are described elsewhere in this supplement. Using data obtained from these studies, this supplement examines the relative costs and effectiveness from a societal perspective (where possible) of adjustable maintenance dosing with budesonide/formoterol in a single inhaler (Symbicort®) compared with fixed dosing in patients with asthma.

METHODS

Data on health-care resource utilisation were collected prospectively alongside the clinical data during the study programme in Belgium (n = 1144), Italy (n = 2358), Germany (n = 4025), Sweden (n = 1153), Canada (n = 1229) and the UK (n = 1734) (all n values at enrolment). No resource utilisation data were collected in the small study in Switzerland (n = 142 enrolled) or in the European multinational study (n = 1044 enrolled). There were some differences in resource utilisation variables between studies. The main outcome variables included exacerbations/treatment failures, symptoms and, in Belgium, Germany and the UK, HRQL.

Unscheduled health-care contacts (excluding planned protocol study visits) and use of study and other asthma medication were recorded. In Germany, planned protocol visits were also taken into account. Medication costs were estimated either by multiplying the daily cost of medication by the number of days each patient reported taking medication (UK) or by multiplying the price per dose by the total number of inhalations during randomised treatment (Italy, Germany, Belgium, Sweden and Canada). The unit costs per medication dose in each country are listed in the Appendix. Short-acting β_2-agonist medication use was a very small component of costs in all countries and is not included as part of study medication costs. Health-care contact costs were estimated by multiplying the resource-use data by unit-cost data taken from published sources in each country, listed in the Appendix.

In those studies where indirect costs were estimated (Italy, Germany, Sweden, Canada and the UK), the number of days missed from work or school because of asthma was recorded. Days off work because of asthma (patients or persons caring for the patient) were valued using average gross income data (including payroll tax) (20). In the UK, the mean national wage rate (£85.28/day) was used as the value of a day's absence from work or study. In Canada, a lost workday was valued at the average industrial aggregate daily wage of Can $120.33 for a person in full-time employment and 50% of that for a person in part-time employment and at the Canadian Federal Employment Insurance benefit rate of Can $66.18 for an unemployed person (21). In Germany, a lost workday was valued at the average daily income for an employed person (€70.05). In Sweden, a day missed from work because of asthma was valued at the average wage of a Swedish employee (full-time worker SEK 1560, part-time worker SEK 936). This valuation included payroll taxes, taking into account the employment status of the patient and was based on SEK 195/h for an industrial worker, assuming that 8 h/day is full time and part time is 60% of full time. In the Canadian study, each missed school day was valued at Can $54.80, which was the Ontario minimum wage and was less than the value applied to a missed workday (21). In Germany, only patients aged 18 years or older were enrolled in the trial, and days missed from school (for the small number of patients likely to be still in full-time schooling) were recorded and valued as days missed from work. In Italy, missed school days were valued at €7.75 and missed workdays at €128.75 (22). In Sweden, the cost of missed schooldays was not calculated, but if an adult was staying at home to care for a child who was off school because of asthma, this was recorded as a missed workday.

Costs were calculated in the local currency for each country. In addition, this supplement also presents summary cost data in

Euros for all countries, using currency exchange rates as follows: SEK 1, €0.11 (17 June 2003); US $1, €0.85 (17 June 2003); Can $1, € 0.64 (18 June 2003); £1, €1.42 (17 June 2003).

Statistical methods

In the UK study, confidence intervals (CI) were generated using non-parametric bootstrap analysis. In the German study, differences in costs were analysed using a non-parametric test, the Wilcoxon two-sample test or the Kolmogorov–Smirnov test. In Canada, the difference in total daily costs between treatments was expressed using 95% CI. In Sweden, costs were analysed by analysis of variance. In Italy, analysis of variance and/or a Wilcoxon test was performed. In Belgium, differences in costs between groups were analysed using a non-parametric, Wilcoxon two-sample test.

In Canada, no adjustment was made for those patients who discontinued the study prematurely. As the withdrawal rate and time to discontinuation were similar between the treatment groups, this approach should not affect the results. In the Belgian and UK studies, data were collected while patients were enrolled and were divided by the number of days each patient was in the study if he or she discontinued early. The patient–year approach was used to adjust the patient discontinuations in the Italian and Swedish studies. Study medication data for discontinued patients in the German study were replaced using last-value-carried-forward methods.

RESULTS

Three-month studies

UK. The main outcome variable was the number of treatment failures (defined as at least one of – need for a course of oral corticosteroids lasting more than 5 days, hospitalisation because of asthma deterioration, emergency treatment, withdrawal due to lack of efficacy or a serious asthma exacerbation requiring the use of non-study asthma medication, excluding a short course of oral corticosteroids). Both adjustable and fixed dosing were effective and well tolerated (23).

The lower overall number of inhalations required in the budesonide/formoterol adjustable maintenance dosing group (Table 1) compared with the fixed-dosing group was responsible for a significant ($p < 0.001$) reduction in total direct costs (Table 2). The point estimates of clinic and emergency department visits were higher in the fixed-dosing group than in the adjustable maintenance dosing group, but differences between the groups were not statistically significant (the study was not powered to detect a difference). Indirect costs, associated with missed work or further education, were not significantly different between treatment groups (Table 2).

Italy. The main outcome measure was treatment failure [defined as at least one of – need for oral corticosteroids, hospitalisation, asthma-related serious adverse event (SAE), withdrawal due to lack of efficacy or need for change of asthma medication] (24). Adjustable maintenance dosing was effective and well tolerated.

Patients in the adjustable maintenance dosing group required significantly ($p < 0.001$) fewer inhalations of study medication per day than those in the fixed-dosing group (Table 1). This lower overall dose resulted in significantly ($p < 0.001$) lower total direct and total costs in the adjustable maintenance group, mainly due to significantly ($p < 0.001$) lower overall study medication costs (Table 2).

Germany. Outcome measures included symptoms and HRQL (measured by the Standardised Asthma Quality of Life Questionnaire) (25). Both dosing schedules were equally effective in improving asthma symptom control and HRQL (10,26).

Patients in the adjustable maintenance dosing group required significantly ($p < 0.001$) fewer inhalations of study medication than the fixed-dosing group (Table 1). This in turn resulted in significantly ($p < 0.001$) lower study medication, direct and total costs in the adjustable maintenance dosing group (Table 2).

Four-month study

Belgium. The main outcome variables were the total dose of inhaled budesonide/formoterol and the proportion of patients with severe asthma exacerbations [defined as at least

Table 1 In all studies, use of adjustable maintenance dosing with budesonide/formoterol in a single inhaler reduced the number of inhalations compared with fixed dosing

Country	*Number of patients enrolled*	*Duration of randomised treatment period (months)*	*Mean number of inhalations/day of study medication*	
			Adjustable maintenance dosing	*Fixed dosing*
UK	1734	3	3.2*	3.8
Italy	2358	3	3.0†	3.9
Germany	4025	3	2.6†	3.8
Belgium	1144	4	2.4†	3.9
Canada	1229	5	2.5†	3.9
Sweden	1153	6	2.4†	4.0

*$p < 0.05$; †$p < 0.001$ vs. fixed dosing.

Table 2 Mean costs per patient in all studies

Cost component	*Mean cost per patient over the randomised treatment period (standard deviation)*			
	Adjustable maintenance dosing		*Fixed dosing*	
UK (3 months)	£	€§	£	€§
Study medication	73 (37)	104 (53)	85 (29)	121 (41)
Total direct costs†	91* (55)	129 (78)	105 (44)	149 (62)
Indirect costs	15 (225)	21 (320)	11 (110)	16 (156)
Total costs, direct + indirect	107 (237)	152 (337)	116 (122)	165 (173)
Italy (3 months)	€		€	
Study medication	120* (51)		157 (40)	
Total direct costs†	124* (70)		160 (54)	
Indirect costs	91 (611)		119 (763)	
Total costs, direct + indirect	215* (623)		280 (768)	
Germany (3 months)	€		€	
Study medication	162* (75)		234 (71)	
Total direct costs†	317* (518)		397 (584)	
Indirect costs	129 (665)		131 (672)	
Total costs, direct + indirect	446* (964)		528 (991)	
Belgium (4 months)	€		€	
Study medication	125* (40)		206 (46)	
Total direct costs†	159* (115)		243 (126)	
Indirect costs	Not determined		Not determined	
Total costs (direct + indirect)	Not determined		Not determined	
Canada (5 months)	**Can$**	**€§**	**Can$**	**€§**
Study medication	261 (104)	168 (67)	408 (104)	262 (67)
Total direct costs†	285 (132)	183 (85)	434 (122)	278 (78)
Indirect costs	25 (130)	16 (83)	17 (89)	11 (57)
Total costs (direct + indirect)	309 (209)	198 (134)	450 (162)	289 (104)
Sweden‡ (6 months)	**SEK**	**€§**	**SEK**	**€§**
Study medication	2008* (691)	221 (76)	3301 (501)	363 (55)
Total direct costs†	2413* (2713)	265 (298)	3669 (1706)	404 (188)
Indirect costs	818 (5559)	90 (611)	454 (2031)	50 (223)
Total costs (direct + indirect)	3231* (7105)	355 (782)	4124 (2816)	454 (310)

*$p < 0.001$ vs. fixed dosing; †Includes study medication costs; ‡All costs evaluated were considered to be asthma related; §Exchange rates used for currency conversions as follows: SEK 1, €0.11 (17 June 2003); Can $1, €0.64 (18 June 2003); £1, €1.42 (17 June 2003). Totals may not add because of rounding.

one of – requirement for treatment with oral or systemic corticosteroids as judged by the investigator, morning peak expiratory flow <70% of baseline value on two consecutive days, hospitalisation due to asthma exacerbation, step-down requirements not fulfilled after 14 days of treatment with budesonide/formoterol (two inhalations four-times daily) or death from asthma] (27). The number of patients with at least one severe exacerbation was 37 (7.5%) in the fixed-dosing group and 38 (7.7%) in the adjustable maintenance dosing group and was not statistically significantly different between the groups. However, the percentage of patients who required oral or systemic corticosteroids was significantly lower in the adjustable maintenance dosing group than in the fixed-dosing group (1.0% compared with 3.5%; $p = 0.016$). Both treatments were well tolerated.

Patients in the adjustable maintenance dosing group required significantly ($p < 0.001$) fewer inhalations of study medication than the fixed-dosing group (Table 1). Consequently, drug costs as well as total healthcare costs were significantly ($p < 0.001$) lower in the adjustable maintenance dosing group compared with the fixed-dosing group (Table 2). Individual differences between the groups for other cost components were small.

Five-month study

Canada. The main outcome variable was the occurrence of exacerbations (defined as at least one of – requiring oral corticosteroids or an additional ICS, emergency department treatment, SAE or study withdrawal because of the need for an additional maintenance therapy for asthma) (21). Significantly fewer patients in the adjustable maintenance dosing group experienced an exacerbation compared with the fixed-dosing group (4.0% compared with 8.9%; $p = 0.002$), and both treatments were well tolerated (21).

As observed in the shorter-term studies, the mean daily number of inhalations of study medication was significantly ($p < 0.001$) lower in the adjustable maintenance dosing group than in the fixed-dosing group (Table 1). This difference

resulted in a 36% reduction in study medication costs and significantly lower total costs [difference in cost per patient over 5 months: Can –$141 (95% CI: –162, –116)] in the adjustable maintenance dosing group compared with the fixed-dosing group (Table 2) (21). Adjustable maintenance dosing provided more effective asthma control and lower total costs than fixed dosing and can thus be considered a cost-effective strategy.

Six-month study

Sweden. The main outcome variable was the proportion of patients having one or more exacerbations (defined as at least one of – requiring oral corticosteroids for worsening of asthma, treatment at a medical care unit due to worsening of asthma, an asthma-related SAE or withdrawal due to a need to use non-study asthma medication) (28). Adjustable maintenance dosing was significantly more effective than fixed dosing. Exacerbations occurred in only 6.2% of patients on adjustable maintenance dosing, compared with 9.5% of patients in the fixed-dosing group ($p < 0.05$). The two regimens were equally well tolerated (28).

As seen in the other studies, the adjustable maintenance dosing group required significantly ($p < 0.001$) fewer inhalations of study medication per day than the fixed-dosing group (Table 1) (28). Study medication costs were significantly ($p < 0.001$) lower in the adjustable maintenance dosing group, which resulted in significantly ($p < 0.001$) lower total direct and total costs (Table 2) (28,29). Differences in other costs were not statistically significant (28,29).

As in the 5-month Canadian study, adjustable maintenance dosing in this 6-month study was both more effective and less costly than fixed dosing.

DISCUSSION

These studies consistently showed that adjustable maintenance dosing with budesonide/formoterol achieved effective asthma control at a significantly ($p < 0.05$) lower overall dose compared with fixed dosing. These lower overall doses resulted in both a lower cost for study medication and lower total costs in the adjustable maintenance dosing group compared with the fixed-dosing group in the six studies reported here. Differences in other cost components, such as short-acting β_2-agonist use, hospital care, ambulatory care and indirect costs (21,28), were generally small, indicating that both regimens were effective. Short-acting β_2-agonist use accounted for only a small proportion of direct costs (ranging from 0.1% in Italy to 5.6% in the UK).

These results are particularly noteworthy because they were obtained in several different healthcare systems in Europe and in Canada. These data indicate that the lower cost observed with adjustable maintenance dosing is an important, robust finding that applies widely in different healthcare environments. More detailed cost-effective analysis for individual studies will be reported elsewhere.

As would be expected, total costs varied between the different countries. Such between-country variation is a common feature of health economic analyses and reflects differences in variables such as healthcare system structures, treatment traditions, average salary levels, costs and prices. Furthermore, as discussed elsewhere (9), there are some methodological differences between the studies, e.g. in the details of the adjustable maintenance dosing plans and in the patient populations recruited. A consideration of relative costs, i.e. the percentage difference in total direct costs between the adjustable maintenance dosing and fixed-dosing groups in each country, provides an interesting analysis, and these results are shown in Figure 1.

The UK study showed the smallest between-group percentage difference in total direct costs (Figure 1). This observation reflects the finding that the UK study also showed the smallest between-group difference in the number of inhalations (Table 1). This difference would, in turn, have affected the cost of study medication. As study medication was consistently the major cost component in all studies (Table 2), the difference in the number of inhalations is likely to be a major driver of the difference in total direct costs.

The longer studies in Belgium, Sweden and Canada reported the largest between-group percentage difference in total direct costs (Figure 1). This is an interesting finding and indicates that cost benefits may be enhanced over long-term therapy, reflecting the increased efficacy of longer studies. The Swedish and Canadian studies both showed that adjustable maintenance dosing was more effective, as demonstrated by a lower percentage of patients having exacerbations in addition to being less costly, than fixed dosing. The shorter studies, in contrast, reported similar efficacy for the two treatment groups. A reduction in the number of exacerbations would be expected to result in a corresponding reduction in costs, as asthma exacerbations

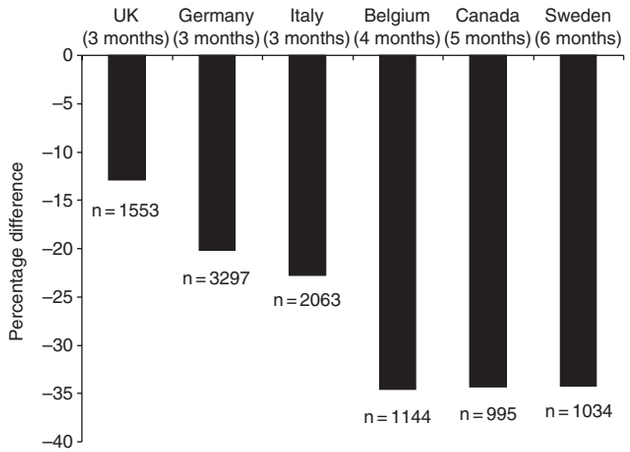

Figure 1 Percentage difference in total direct costs between adjustable maintenance dosing and fixed dosing groups in each country. (n, number of randomised patients)

are costly to treat (5), which explains in part why the longer studies showed a greater cost benefit for adjustable maintenance dosing relative to fixed dosing. It is possible that studies longer than 6 months would have the potential to show still greater cost benefits. Further research is required to test this hypothesis.

These findings have important potential implications for asthma management guidelines and policy. Adjustable maintenance dosing with budesonide/formoterol in a single inhaler has been shown to reduce medication and treatment costs in asthma compared with fixed dosing in six different countries. The cost savings from appropriate use of adjustable maintenance dosing could be substantial. Thus, it could encourage more efficient use of scarce healthcare resources than fixed dosing, either allowing more asthma patients to be treated for the same cost or freeing resources to be used elsewhere in the healthcare system.

In conclusion, adjustable maintenance dosing with budesonide/formoterol reduces treatment costs (direct and indirect), providing similar or better asthma control at a lower overall dose, compared with fixed dosing.

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APPENDIX

Unit costs for medication and health care resources in each country

Cost component	*Unit cost*	*Source/comments*
Study medication, 80 μg	£0.28/dose	British National Formulary 2001*
Study medication, 160 μg	£0.32/dose	British National Formulary 2001*
ICU admissions	£1193.00	NHS Reference Costs 2001†
Hospital admissions	£246.00	PSSRU per inpatient day: thoracic medicine‡
A and E visits	£61.00	PSSRU 2001‡
Specialist visits	£88.00	PSSRU: outpatient attendance: thoracic medicine‡
GP visit	£26.00	PSSRU: average length clinic consultation including direct costs and qualifications‡
Nurse contacts	£10.00	PSSRU: practice nurse per consultation‡
GP home visits	£59.00	PSSRU: including direct and qualification costs‡
Nurse home visits	£18.00	PSSRU: practice nurse per home visit‡
Physiotherapy sessions	£16.00	PSSRU: community physiotherapy per clinic visit‡
Spirometry	£0.00	Assumed no extra cost
APFT	£0.00	Assumed no extra cost
Chest X-ray	£13.00	NHS Reference Costs 2001: band A radiography†
CT scan	£56.00	NHS Reference Costs 2001: CT†
GP phone call	£22.00	PSSRU 2001‡
ECG	£13.25	Hospital source 2000§
Abdomen X-ray	£13.00	NHS Reference Costs 2001: band A radiography†
Blood test	£5.00	Estimate based on Royal London Trust Tariff 1999¶
Mouth swabs	£6.50	Etimate based on Royal London Trust Tariff 1999¶
Day off work	£85.28	ILO Bureau of statistics**

*Joint Formulary Committee. British National Formulary. 42 ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain 2001; †Department of Health: NHS reference costs 2001 (www.doh.gov.uk/nhsexec/refcosts.htm); ‡Price D, Haughney J, Duerden M, Nicholls C, Mosely C. The cost-effectiveness of chlorofluorocarbon-free beclometasone dipropionate in the treatment of chronic asthma: a cost model based upon a one year pragmatic, randomised clinical study. *Pharmacoeconomics* 2002; 20: 653–64; §General district hospital (anonymous source) 2000; ¶Royal London Price Tariff 1999, Royal London NHS Trust 2000; **International Labour Organization Bureau of Statistics (http://www.ilo.org/stat/). PSSRU, personal social services research unit; NHS, national health service; APFT, advanced pulmonary function test; GP, general practitioner; ECG, electrocardiogram; CT scan, computed tomography scan; A and E, accident and emergency; ICU, intensive care unit.

Italy

Cost component	*Unit costs*	*Source*
Study medication: 80 μg	€0.456/dose	Informatore Farmaceutico 2003*
Study medication: 160 μg	€0.576/dose	
Relief medication (Ventolin®)	€0.023/dose	Informatore Farmaceutico 2003*
Hospital care (general and intensive)	€237.57/day (general) €671.39/day (intensive)	Lucioni et al. 2002†
Emergency room visits	€20.66/visit	Decreto Ministeriale, 22 Luglio 1996‡
Physician visits	€11.83/visit	Lucioni et al. 2002†
Nurse visits	€4.77/visit	Lucioni et al. 2002†
Phone call to physician	€4.25	Lucioni et al. 2002†
Pharmacy visits	€1.63	Lucioni et al. 2002†
Day absent from work	€128.75	Lucioni et al. 2001§
Day absent from school	€7.75	Lucioni et al. 2001§

*L'informatore Farmaceutico Mediciniali. ISBN 8821427188. Masson ed., Mese-Anno di Pubblicazione, 2003, 928; †Lucioni C, Mangrella M, Mazzi S, Negrini C, Vaghi A. Impiego di un'associazione fissa formoterolo e budesonide nel trattamento del paziente asmatico, *Pharmacoeconomics Italian Research Articles* 2002; 4: 15–23; ‡Ministero della Sanità. Prestazioni di assistenza specialistica ambulatoriale erogabili nell'ambito del Sistema Sanitario Nazionale e relative tariffe. Decreto Ministeriale 22 Luglio 1996, Supplemento ordinario della Gazzetta Ufficiale n. 216, 14 settembre 1996; §Lucioni C, Costa B, Sessa A. I costi dell'influenza in Italia. *Farmacoeconomia e percorsi terapeutici* 2001; 2: 11–8.

Germany

Cost component	*Unit cost*	*Source*
Study medication (Symbicort®)	€0.67/dose (160/4.5 μg Turbuhaler)	Rote liste 2001‡
Relief medication (Aerodur)	€0.12/dose (500 μg Turbuhaler)	Rote Liste 2001‡
Hospital care	€309/24 h interval in hospital	EBM 2001§
Visit to doctor	€39.30*	EBM 2001§
Home visit by doctor	€34.19†	EBM 2001§
Emergency visit to doctor	€46.46	EBM 2001§
Telephone contact with doctor	€3.27	EBM 2001§
Telephone contact with medical staff	€1.12	EBM 2001§
Day absent from work	€70.05/24 h	Statistisches Jahrbuch 2001¶

*Costs are based on the assumption that spirography was conducted once by approximately 50% of physicians, and twice by the other 50%; †Costs for a home visit do not include spirography; ‡Rote Liste – Arzneimittelverzeichnis für Deutschland. ECV *Editio Cantor Verlag* 2001, Aulendorf; §Einheitlicher Bewertungsmassstab (EBM). Cologne: Deutscher Aerzte Verlag, 2001; ¶Statistisches Jahrbuch 2001 – Für die Bundesrepublik Deutschland. Wiesbaden: Statistisches Bundesamt 2001, 604 ff.

Belgium

Cost component	*Unit cost*	*Source*
Study medication, Symbicort® 160/4.5 μg (120 dose pack)	€0.50/dose	INAMI-RIZIV†
Short-acting β_2-agonist, mean cost per dose	€0.03/dose	INAMI-RIZIV†
Hospitalisation ICU, per day	€250*	INAMI-RIZIV†
Hospitalisation general ward, per day	€250*	INAMI-RIZIV†
Emergency room visit	€26.20	INAMI-RIZIV†
Specialist visit	€26.20	INAMI-RIZIV†
GP visit	€17.00	INAMI-RIZIV†
Nurse visit	€2.34	INAMI-RIZIV†
House call physician	€20.86	INAMI-RIZIV†
House call nurse	€3.41	INAMI-RIZIV†
Phone call, physician/nurse	€0.25	INAMI-RIZIV†
Physiotherapist	€15.57	INAMI-RIZIV†
Spirometry	€35.19	INAMI-RIZIV†
Advanced lung function (spirometry + diffusing capacity)	€75.40	INAMI-RIZIV†
Chest X-ray	€13.09	INAMI-RIZIV†
CT Scan	€113.43	INAMI-RIZIV†

*This price is the room charge; depending on extra charges due to the medical treatment, this price will go up; †Institut National d'assurance maladie invalidité (National Institute of Insurance Disease Invalidity) (http://inami.fgov.be/). GP, general practitioner; CT scan, computed tomography scan; ICU, intensive care unit.

Canada

Cost component	*Cost per unit*	*Source/comments*
Study medication, 80 μg	Can $0.50/dose	10% pharmacy mark-up and dispensing fee (assumes script filled in retail pharmacy, $6.47 for every 30-day supply) added in overall cost calculation
Study medication, 160 μg	Can $0.65/dose	10% pharmacy mark-up and dispensing fee (assumes script filled in retail pharmacy, $6.47 for every 30-day supply) added in overall cost calculation
Other asthma medications (taken during exacerbations and as reliever)	As applicable	Ontario drug benefit formulary, ed.; 37: 2002. 10% pharmacy mark-up and dispensing fee added in overall cost calculation.
Telephone contact with physician	Can $17.30	A001 – Minor assessment, Schedule of Benefits for Physician Services, April 2002. http://www.gov.on.ca/health/english/program/ohip/sob/physserv/a_consul.pdf
Telephone contact with nurse	Can $8.18	Ontario Nursing Association, registered nurses in hospitals as of April 2002, $32.71/h. Costing based on assumption of a 15-min phone call
Physician visit	Can $17.30	Ontario Ministry of Health 2002*

Nurse visit	Can $8.18	Ontario Nursing Association, registered nurses in hospitals as of April 2002, $32.71/h. Costing based on assumption of a 15-min visit
Lung-function test	Can $16.80	Ontario Ministry of Health Schedule of Benefits for Physician Services, April 2002. Includes professional and technical components http://www.gov.on.ca/moh/english/program/ohip/sob/facility/facpul.html
Ambulance	Can $240.00	Ontario ministry of health and long-term care. http://www.health.gov.on.ca/english/public/pub/ohip/amb.html
Emergency room visit	Can $258.30	Physician Fee – H102 – Comprehensive Assessment and Care ($31.75) Ontario Ministry of Health Schedule of Benefits for Physician Services, April 2002. Hospital ER ($226.55) http://www.gov.on.ca/moh/english/program/ohip/sob/physserv/a_consul.pdf
Hospital per night, general ward	Can $498.52	Awadh Behbehani et al. 1999†. Reported costs inflated to 2002 dollars using Bank of Canada calculator http://www.bank-banque-canada.ca/en/inflation_calc.htm
Hospital per night, ICU	Can $1908.69	
Absent from work, full-time employed	Can $120.33/day	National average daily wage, 1997‡
Assisted person absent from work	Can $120.33/day	National average daily wage, 1997‡
Absent from work, part-time employed	Can $60.17/day	20-h per week (half of full-time wage‡)
Absent from work, unemployed	Can $66.18/day	Canadian Federal Employment Insurance Benefits 1998 (55% of full-time wage)
Absent from work, homemaker	Can $54.80/day	Ontario minimum wage 1998 (included as paid helpers may be required to replace their time)
Absent from work, retired	Can $54.80/day	Ontario minimum wage 1998 (included as paid helpers may be required to replace their time)
Absent from work, student	Can $54.80/day	Ontario minimum wage 1998

*Ontario Ministry of Health. Ontario Drug Benefit Formulary/Comparative Drug Index, no. 37. Toronto: Queen's Printer for Ontario; 2002; †Awadh Behbehani N, Grunfeld A, FitzGerald JM. Health care costs associated with acute asthma: a prospective economic analysis. *Can Respir J* 1999; 6: 521–25; ‡Department of Human Resources Development Canada Employment Insurance Legislation. Ottawa: Government of Canada, 1997. ICU, intensive care unit.

Sweden

Cost component	*Cost per unit*	*Source/comments*
Study medication, 80/4.5 μg	Not for sale	Not applicable
Study medication, 160/4.5 μg	SEK 5.20	Apoteket AB*
Short-acting bronchodilator, per dose	SEK 0.72	Apoteket AB*
Other reliever medication	As applicable	Apoteket AB*
Telephone contact with physician	SEK 114	Andersson et al. 2001†
Telephone contact with nurse	SEK 35	Andersson et al. 2001†
Unscheduled physician visit	SEK 805	Andersson and Kartman 1995‡
Unscheduled nurse visit	SEK 351	Andersson and Kartman 1995‡
Emergency room visit	SEK 2846	Andersson et al. 2001†
Hospital per night	SEK 3724	Andersson et al. 2001†
Absent from work, full-time employed	SEK 1560	Based on SEK 195/h for industrial worker and assuming full time is 8 h/day§
Absent from work, part-time employed	SEK 936	Part time is 60% of full time§
Assisted person absent from school	SEK 1560	Valued as a missed workday

*Apoteket AB (Swedish national pharmacy) (http://www.apoteket.se); †Andersson F, Kjellman M, Forsberg G, Moller C, Arheden L. Comparison of the cost-effectiveness of budesonide and sodium cromoglicate in the management of childhood asthma in everyday clinical practice. *Ann Allergy Asthma Immunol* 2001; 86: 537–44; ‡Andersson F, Kartman B. The cost of angina pectoris in Sweden. *Pharmacoeconomics* 1995; 8: 233–44; §Statistiska centralbyrån (National Statistics Office of Sweden) (http://www.scb.se).