



Stepping down from high dose fluticasone/salmeterol to extrafine BDP/F in asthma is cost-effective

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KEYWORDS

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Summary

Background: GINA guideline recommends stepping down treatment of asthma patients where control is achieved.

The aim of this analysis was to estimate the costs and health outcomes associated with step down of controlled patients on high dose fluticasone/salmeterol (FP/S 1000/100 µg daily) to either medium dose FP/S (500/100 µg) dry powder or extrafine beclometasone/formoterol (BDP/F 400/24 µg) pMDI in three European countries.

Methods: A patient-level simulation Markov model was constructed to enable the simulation of three comparative arms (FP/S 1000/100, FP/S 500/100, BDP/F 400/24). Transition probabilities and healthcare resources consumption were derived from a multinational clinical trial comparing BDP/F 400/24 µg vs. FP/S 500/100 µg as step down therapy in asthma. Direct costs and health state utilities were sourced from public source and published literature. The analysis was conducted from a health system perspective, based on six months horizon. Probabilistic sensitivity analyses were conducted.

Results: The ICER (Incremental Cost-Effectiveness Ratio) associated with high dose dry powder FP/S 1000/100 µg vs. extrafine BDP/F 400/24 µg was above 70,000 GBP and 200,000 €/QALY (Quality Adjusted Life Years). An ICER of 29,000 GBP/QALY and above 30,000 €/QALY was associated with medium dose dry powder FP/S 500/100 µg vs. BDP/F 400/24 µg.

Conclusions: It was found that maintaining controlled patients on high dose FP/S is not cost-effective. Extrafine BDP/F 400/24 µg daily can be considered to be a cost-effective option

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in the countries analyzed to maintain control of asthmatic patients stepped down from high dose FP/S 1000/100 μg daily dry powder or suspension formulations.

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Introduction

There has been a rapid increase in the cost of healthcare, driven by new technologies and an ageing population. This is a challenge that all industrialized societies are facing [1]. European pharmaceutical expenditure has increased steeply in recent years, rising between 4% and 13% (approx.) year on year [2] and is now one of the largest cost components across a number of European countries [2–7].

As a result, almost all European countries have introduced cost containment measures aimed directly or indirectly at limiting the growth of healthcare expenditure [8].

Given that approximately 30 million adults in Europe have asthma [9], identifying cost-effective therapeutic strategies to treat adult asthma is important as the disease imposes a severe economic burden on society [10–13]. According to GINA (Global Initiative for Asthma) [14] asthma control is achieving and maintaining control of symptoms and normal daily activity, maintaining pulmonary function as close to normal as possible, preventing asthma exacerbations and avoiding adverse effects from asthma medication. The stepwise approach is to gain control, sustain control and then to “step down” treatment to the minimum amount of medication necessary to maintain asthma control, avoiding unnecessarily high drug exposures and the potential associated long-term side effects [14–16].

Ongoing monitoring is essential to assess that control is maintained for a prolonged period (at least 3 months) before “step down” is considered [14]. Although “step-down” is recommended [14,17], it has been previously reported that controlled asthma patients appear to be left overtreated on high dose ICS [18].

Few studies evaluated treatment step-down from a high dose to a lower dose ICS/LABA combination [15,19], and only one such study has assessed it with different drug formulations [15].

As discussed above, the growing economic pressures within healthcare systems mean that an efficient use of health-care resources is warranted, in which both health and economic outcomes of treatments are assessed [20].

The aim of this analysis was to estimate the costs and health outcomes associated with “step down” of patients controlled on high dose fluticasone/salmeterol (FP/S 1000/100 μg daily) to either extrafine beclomethasone/formoterol (BDP/F 400/24 μg) pMDI or medium dose FP/S (500/100 μg) dry powder in three western European countries.

Methods

Study design

A recent clinical trial [15] provides evidence confirming that lung function and asthma control can be maintained in patients stepped down from the highest recommended

dose of ICS/LABA combination therapy to extra-fine beclomethasone/formoterol treatment. In a prospective, multinational, randomized, open label, parallel group controlled trial, patients with controlled asthma treated daily with high dose (1000/100 μg) fluticasone/salmeterol (FP/S) Diskus were randomly assigned to 24 weeks of treatment with either FP/P Diskus 500/100 μg daily or BDP/F pMDI 400/24 μg daily.

Based on clinical outcomes and resource consumption data from the trial, a Markov decision model (Fig. 1) was constructed in TreeAge® Pro 2009 to analyze cost and cost-effectiveness of high dose FP/S 1000/100 μg , medium dose FP/S 500/100 μg and BDP/F 400/24 μg for three European countries (United Kingdom, Spain and the Netherlands). In a probabilistic patient-level health economics Markov model, the individual experience is represented by defining his/her possible health states and the probability of transitioning from one to the others in a given time unit. The permanence in any given state and/or the transition from one to another is associated with a set of clinical and economic outcomes. In the present model, the three GINA – defined [14] control levels were used to characterize patients health states in the clinical trial and for the simulation, namely Controlled, Partly Controlled and Uncontrolled; the time unit is four weeks, and the applied transition probabilities have been calculated to reflect the monthly rates of patients losing/gaining control, as observed in the FORTE trial.

Variability is a characteristic feature of asthma and achieving GINA defined asthma control maybe challenging in clinical practice. It has been reported that patients may adopt a lifestyle to ensure fewer symptoms at the expense of limiting daily activities [21]. Therefore, both partially controlled and controlled asthma may sometimes be acceptable health states in clinical practice, and they have been aggregated in the model.

Health conditions of the simulated patients were characterized by a set of individual parameters attributed at each state of the Markov model. These parameters were:

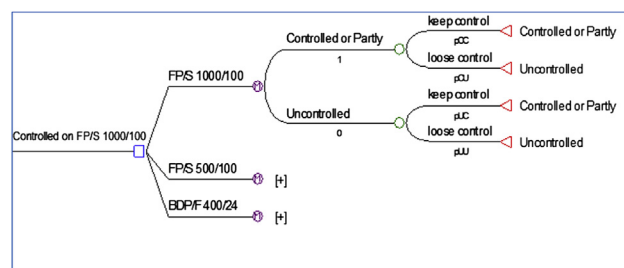


Figure 1 Graphic representation of Markov model structure. Two arms are collapsed for graphical convenience; their structure is identical to the fully represented arm.

- number of exacerbations in 4 weeks;
- days with daytime symptoms in 4 weeks;
- days with nocturnal symptoms in 4 weeks;
- days with use of rescue treatments in 4 weeks;
- average PEF (peak expiratory flow, measured as % of predicted).

These parameters were extracted from distributions fitted to the data recorded in the trial on the ITT population (Table 1). In the model, the determination of the occurrence of an event in each cycle depended on a binomial distribution for each parameter (except the PEF value, which is sampled from a normal distribution). For patients with a "yes" determination, the number of events was extracted from a gamma distribution.

Data from the 8-weeks run-in phase was used to build the FP/S 1000/100 µg arm of the model, while the 24-weeks data from patients randomized to BDP/F 400/24 µg or to FP/S 500/100 µg were used to feed the two respective arms. The database containing the asthma control status at each visit for each patient in the Intention To Treat (ITT) population was analyzed. Overall 378, 174 and 164 patients in treatment with FP/S 1000/100 µg, FP/S 500/100 µg and BDP/F 400/24 µg were considered, respectively. Since the run-in phase lasted only for 8 weeks, the last observed value was carried forward in the assumption of stable asthma control for the next 16 weeks in the FP/S 1000/100 µg arm of the model [15].

It was chosen to calculate outcomes in terms of additional QALY (Quality Adjusted Life Years). Utilities for each asthma control state were derived from a study by Briggs et al. [29].

The time frame of the model is the clinical trial period of 24 weeks, divided into 4-weeks cycles for the simulation, according to the visit schedule of the trial.

Economic analysis

The chosen perspective is the payers' perspective in all countries analyzed. The cost input parameters include medical costs and outpatient physician care (Table 2). Unit costs are reported in 2011 € (Spain and the Netherlands) and GBP (United Kingdom)

The outpatient care costs, i.e. office-based general practitioner consult, were based on literature [22–24].

Drug prices are based on local price databases collected between June and August 2011, including VAT and patients' copayments (where they exist).

Test treatment costs were calculated according to the pharmaceutical form and contents used in the trial. Drug prices were derived from formulary drugs, specific to each country.

As controlled asthma is generally monitored by general practitioners (GP), in the model it was assumed that patients attend the GP once per quarter, independently from the patient's state.

In the trial no exacerbation gave rise to emergency consultations or to hospitalizations. Consequently, additional consumption of these resources for patients experiencing exacerbations were not added. On the other hand, the trial population attended every 4 weeks a physician visit and it's reasonable to hypothesize that in real practice, where asthma control assessments are not so frequent, the patient is more likely to request health care in case of exacerbation, a consideration consistent with GINA guidelines, that recommend the attending of a health care visit within two weeks to one month after an exacerbation [14]. Based on this, the management of an exacerbation was linked to the cost of a general practitioner visit. The study protocol allowed the use of inhaled salbutamol as *on demand* medication; in the model the cost of rescue medications was estimated based on the mean number of days with salbutamol use, according to patient's state. Similarly, the control state-specific cost of concomitant medications was estimated based on the drug consumptions recorded at follow-up visits.

Simulation: base case and probabilistic sensitivity analysis

In all cost-effectiveness models, it is important to test for sensitivity to assumptions and uncertainties in the data [30]. The present probabilistic simulation is performed at patient-level, by drawing parameter values from their probability distribution for each simulated individual (conditioned on the asthma control state he/she is assigned to), which enables two levels of uncertainty to be taken into account:

Table 1 Frequencies and mean numbers of events recorded in the trial by asthma control state.

Parameter	CPC	U	TDF
%With at least 1 exacerbation in 4 weeks	1.57%	42.16%	Binomial
Mean (SD) exacerbations/4 weeks	1.91 (1.94)	1.35 (0.81)	Gamma
%With at least 1 day with daytime symptoms in 4 weeks	33.4%	73.0%	Binomial
Mean (SD) days with daytime symptoms/4 weeks	3.47 (3.70)	9.99 (7.73)	Gamma
%With at least 1 day with nocturnal symptom in 4 weeks	8.4%	62.0%	Binomial
%With at least 1 day with rescue treatment in 4 weeks	35.3%	81.0%	Binomial
Mean (SD) rescue treatment days/4 weeks	4.12 (6.08)	13.54 (10.95)	Gamma
Mean (SD) PEF (% of predicted) in 4 weeks	98.77 (20.07)	88.23 (17.03)	Normal

SD: Standard deviation; CPC: controlled/partly controlled; U: uncontrolled, TDF: type of distribution fitted to the data and used for model simulation.

Table 2 Cost inputs.

Country	Resource			Sources	
	Treatment acquisition (4 weeks)				
	High FP/S	Medium FP/S	BDP/F		
UK (£)	38.08	32.76	27.44	[25]	
Spain (€)	77.49	57.42	48.09	[26]	
Netherlands (€)	58.19	42.49	35.49	[27]	
GP consultation (unit)					
UK (£)	13.07			[22,28]	
Spain (€)	32.91			[24,28]	
Netherlands (€)	28.37			[25,28]	
Mean (SD) cost for concomitant and rescue medications (4 weeks)					
	Concomitant drugs		Rescue medications		
	CPC	U	CPC	U	
UK (£)	1.21 (8.38)	1.61 (6.62)	0.02 (0.06)	0.16 (0.17)	[25]
Spain (€)	1.33 (17.86)	1.79 (8.10)	0.04 (0.13)	0.34 (0.35)	[26]
Netherlands (€)	0.72 (5.03)	2.14 (8.74)	0.07 (0.19)	0.51 (0.53)	[27]

GP: General practitioner; SD: standard deviation; CPC: controlled-partly controlled; U: uncontrolled.

- The uncertainty on patient characteristics, which represents the effective heterogeneity among subjects;
- The intrinsic uncertainty of events (even when the rate of occurrence of a given event is perfectly known in a population, it is not possible to know if the event will actually occur in any individual belonging to that population).

A third order of uncertainty, related to the input data used for model parameters representing the cognitive uncertainty on values derived from experimental measurements, can be evaluated through the probabilistic sensitivity analysis (PSA) [30].

In simulating the presented model, distributions related to clinical outcomes and quality of life were sampled at the patient-level, while distributions accounting for were sampled at the cohort level, in the PSA external loop.

The single outcomes of the patient-level iterations (each one representing a simulated patient) provide the base-case results of the analysis, and reflect the inter-individual variability in outcomes. The PSA provides an evaluation of the uncertainty surrounding the mean (cohort-level) results which is due to the uncertainty on collected mean costs and resource consumption rates.

Base-case results were obtained with 10,000 iterations; the PSA with 1000 (external loop) $\times$ 1000 (internal loop) iterations.

Results

Estimated QALYs show very similar values across treatments and the increments of high and medium dose FP/S vs. BDP/F are very close to 0 (Table 3).

In contrast, the total costs varied significantly between treatments, mainly reflecting differences in drug acquisition costs, as concomitant medication and other direct medical costs were similar (Fig. 2).

Table 3 reports the mean incremental cost-effectiveness ratios calculated for high and medium dose FP/S vs. BDP/F.

An additional analysis was carried out for the UK to consider a different formulation of FP/S, consisting in a pressurized metered dose inhaler (pMDI) with packages containing 120 inhalation doses of 250/25 μ g (£59.48) and of 125/25 μ g (£35.00), respectively for the high and the medium requested dosages. The resulting ICERs for this analysis were 192,166 £/QALY and 29,826 £/QALY.

Results of the PSA for the UK, the Netherlands, and Spain are represented as scatter plots on the cost-utility plane, where the grade of dispersion of the cloud can provide a visual indication of the stability of the model, and as cost/effectiveness acceptability curves in Fig. 3.

Discussion

Decision makers responsible for optimizing health gains from finite resources are increasingly relying on an evidence-based approach involving a cost-effectiveness analysis. The measure most widely employed in such an analysis is the ICER [31].

Table 3 Simulation results.

	BDP/F 400/24	FP/S 1000/100	FP/S 500/100
Controlled state (days)	160	161	162
Δ vs. BDP/F	—	1.22	2.27
QALYs	0.3884	0.3890	0.3896
Δ vs. BDP/F	—	0.0006	0.0012
ICER vs. BDP/F			
UK (£/QALY)	—	72,441	29,826
Spain (€/QALY)	—	295,319	44,780
Netherlands (€/QALY)	—	227,801	33,364

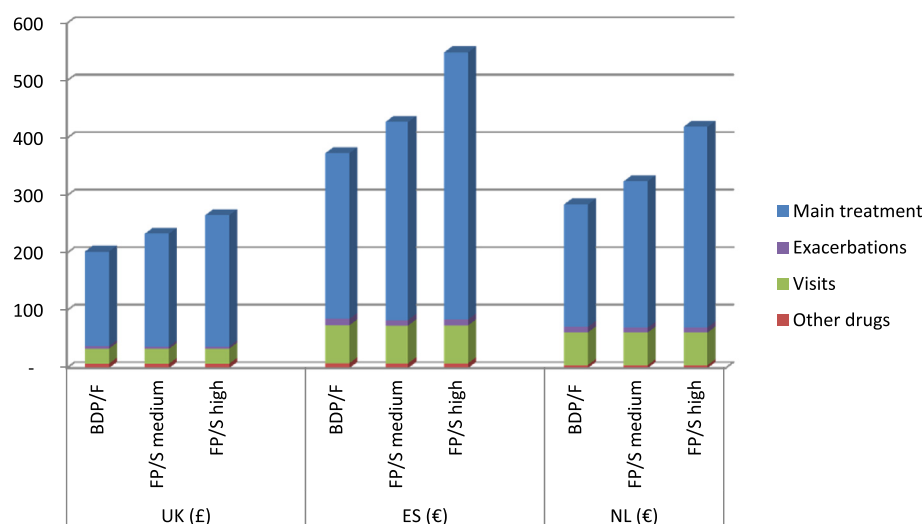


Figure 2 Simulation results: total cost by treatment and country.

In this economic analysis involving three European countries, acceptability at 30,000 € per QALY and 25,000 GBP per QALY gained [32] was considered. This was a conservative approach as it is known that, for example, the UK Health Technology Assessment body (NICE), would need special reasons to accept technologies with ratios over 25,000 to 35,000 GBP per QALY [33].

Costs and outcomes of high dose FP/S (1000/100 µg daily), extrafine BDP/F (400/24 µg) pMDI and medium dose FP/S (500/100 µg) dry powder were compared. In the UK, where there is a strong preference for pMDI devices, in contrast to most other countries in Europe, an extra cost-effectiveness analysis was done using medium dose FP/S

pMDI. The cost-effectiveness analyses showed that high dose FP/S and medium dose FP/S were not cost-effective options when compared to medium dose BDP/F (400/24 µg), with a less than 1% probability of being cost-effective, when the 25,000 GBP/QALY and 30,000 €/QALY thresholds are used.

Conversely, medium dose FP/S had a probability of being cost-effective above 50% only with a willingness to pay (WTP) threshold of 39,000 and 50,000 €/QALY in the Netherlands and Spain, or of 28,000 GBP/QALY. Corresponding WTP threshold figures for high dose FP/S were 162,000 and 210,000 €/QALY and of 78,000 GBP/QALY.

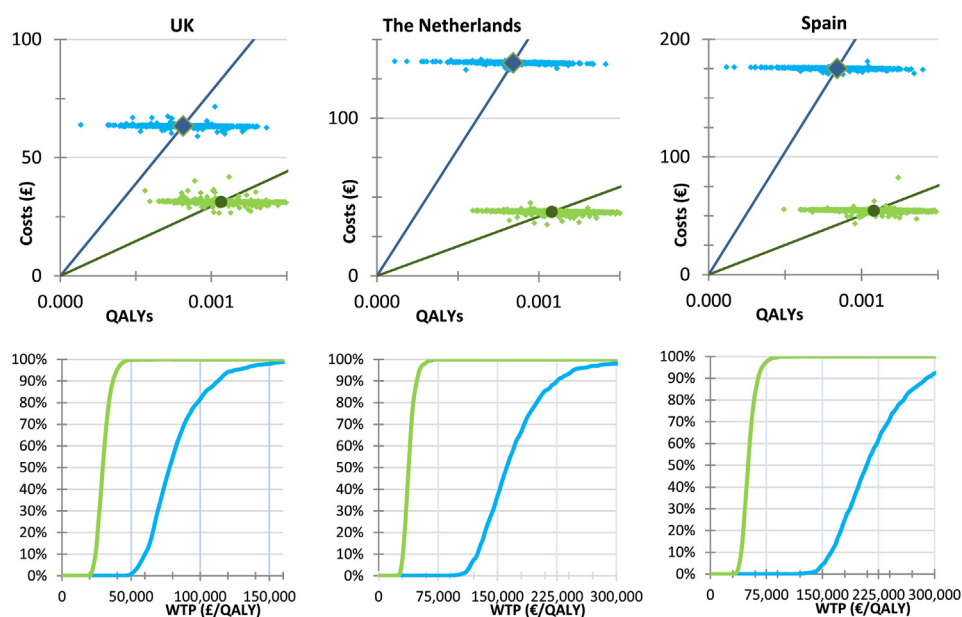


Figure 3 Scatterplots of the incremental costs and benefits (QALY) vs. BDP/F 400/24 µg on the cost-effectiveness plane (top) and cost-effectiveness acceptability curves (CEACs), in the UK, Netherlands, and Spain. Blue line and dots: FP/S 1000/100 µg vs. BDP/F 400/24 µg. Green line and dots: FP/S 500/100 µg vs. BDP/F 400/24 µg. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Whilst the incremental effectiveness was marginal between treatments, this was expected, as the analysis was based on an equivalence clinical trial involving controlled asthma patients.

Ideally, it would have been interesting to evaluate the cost/effectiveness of the minimal effective dose. Two main reasons prevented us to do so: firstly, as discussed in the publication of the clinical trial results, the study design prevented the researches from determining this dose level; and secondly, we could not uncouple the efficacy data used in the modeling from the doses which attained that level of efficacy.

In contrast, the incremental total costs between treatments (numerator) showed notable values.

The length of the clinical study period may be considered as a draw-back, because ideally the time horizon would be longer than six months for patients with this chronic disease. However, a limit to the time horizon of the economic analysis was applied to avoid further effectiveness assumptions for the medium term. Moreover, asthma is not a progressive disease and the study recruited patients over a 2-year period therefore including periods with known triggers of asthma symptoms such as allergens (spring) and viruses (winter).

In common with all economic models, a number of assumptions have been made. The multinational setting of the trial determined the need to modify the cost of drugs prescribed in other countries by imposing the relevant prices from each country concerned. The number of unscheduled visits to general practitioners is often difficult to determine and therefore the number of exacerbations was used as a proxy. The cost of hospitalization due to exacerbations was not included as no hospitalizations were reported during the trial [15]. This may underestimate a rare but relevant event, especially when looking at a longer time horizon. However, given that the study population was controlled asthma patients, where control was being maintained following step-down, the occurrence of hospitalization may have been observed during a longer time horizon.

Another possible criticism of this analysis is that health related quality of life was not assessed during the trial. Hence, the utility attached to each health state had to be derived from published literature [29]. This is often done and it is well accepted in health economics, but ideally it is advisable to collect health related quality of life data during the trial to obtain more reliable results.

Classical double dummy double blind RCTs tend to limit generalizability to usual clinical practice [34]. In the case of the randomized control trial upon which the model is based, the trial was an open label study, making it partly pragmatic in terms of trial design [35]. This encourages healthcare resource utilization more similar to actual clinical practice [34].

All in all, despite the limitations discussed, this study provides a useful analysis for decision makers and prescribers wanting to adopt cost-effective treatment options.

Furthermore, if possible, future clinical work should attempt to phenotype those patients who are likely to remain stable following step-down, permitting refined targeting of such a strategy. This would allow even greater cost-savings while maintaining asthma control for an even greater part of the population.

Conclusion

The present study shows that maintaining controlled patients on high dose FP/S is not cost-effective in the Netherlands, Spain and the UK. Furthermore, stepping patients down to medium dose FP/S was shown not to be cost-effective relative to stepping down to BDP/F. Extrafine BDP/F 400/24 µg daily can be considered to be an effective and cost-saving option in the countries analyzed to maintain control of asthmatic patients stepped down from high dose FP/S 1000/100 µg daily.

Given the stretched healthcare resources in the countries concerned and the current economic climate, step-down to extrafine BDP/F offers a proven, evidence-based therapeutic option that provides economic value to manage controlled patients on high dose FP/S that are in need of step down in accordance with clinical guidelines.

Authors contributions

PP, PS, NG, and AP participated in the design and conduct of the study and critically revised the manuscript. PL and OZ performed the economic analysis and drafted the manuscript. All authors read and approved the final manuscript.

Conflict of interest statement

Professor Paggiaro declares no conflict of interest; doctors Patel and Nicolini are employees of the sponsor company; doctors Pradelli and Zaniolo are employees of AdRes, which has received funding and research grants from Chiesi, GSK, Boehringer Ingelheim, among others; professor Papi declares no competing interests.

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