

**Inhaled corticosteroids and long-acting beta₂-agonists for the treatment of chronic asthma in children under the age of 12 years:
Systematic review and economic analysis**

**Amended cost-off set comparisons and cost comparisons for the economic analysis section – Questions 3a, 4 and 5
(section 6.11.3 – 6.12)
All changes to the costs are highlighted in green**

0.1.1 Research Question 3: Increase ICS dose or add LABA to a lower ICS dose?

We have **not** performed a cost-comparison analysis of this research question because **we found no reliable evidence that would enable us to conclude, or reasonably assume, equivalence between ICS and ICS plus a LABA** (see section **Error! Reference source not found.**). Therefore below we set out the costs and cost differences between products and present the results of a speculative threshold analysis to examine the number of exacerbations that would need to be avoided for the more expensive product to achieve NHS cost-savings.

0.1.1.1 Exploratory cost-savings analysis of combination inhalers *versus* ICS monotherapy

Given the lack of any evidence on the relative effectiveness of combination inhalers compared with an increased dose ICS, but also the known differences in costs between different products, it is possible to calculate some threshold levels of effectiveness – in terms of exacerbations avoided – that would need to be achieved for the more expensive product to achieve NHS cost-savings. These are based upon an estimated mean cost of a hospital-managed exacerbation of £1056 (assumed range £500 to £2000) or the estimated cost of a GP-managed exacerbation of £24 (assumed range £20 to £40). (The estimation of these costs is shown in *Table 5* and *Table 6* at the end of this section.) In general therefore, averting one hospital-managed exacerbation is much more likely to generate cost-savings than averting a GP-managed exacerbation.

The calculations for these exploratory analyses are shown in *Table 1* to *Table 4*. *Table 1* and *Table 2* compare the cost of Seretide® and Symbicort® products with the weighted mean cost of an increased dose of each type of ICS drug.

Table 3 and *Table 4* compare the cost of Seretide® and Symbicort® products with an increased dose of the cheapest product for each ICS drug. Where the annual cost of either Seretide® or Symbicort® exceeds the cost of the increased dose ICS, we have calculated the annual number of either hospital-managed exacerbations or the annual number of GP-managed exacerbations that would have to be averted in order to compensate for the additional costs of the combination preventer medication.

Only the combination inhaler, Seretide Evohaler® (100µg/50µg FP/S per day) is slightly cheaper than the **weighted mean cost** of all types of ICS at increased dose except BDP 400µg/day (including CFC-propelled products). Compared with BDP-CFC products at 400µg/day, taking Seretide Evohaler® costs £52 extra per year. If the cost of a hospital-managed exacerbation lies somewhere between £500 and £2000, then in order to be cost-saving then Seretide Evohaler® would need to avert at least one hospital-managed exacerbation in between 10 and 39 people who are using these inhalers compared to BDP. However, treatment with this specific combination inhaler would annually need to avert between 1.3 and 2.6 GP-managed exacerbations per person to cover the extra drug treatment costs.

Both the combination inhalers, Seretide Accuhaler® and Symbicort Turbohaler® are more expensive than the weighted mean annual cost for all types of ICS at a two-fold increased dose.

Compared with the **lowest cost preparation** for each ICS drug, the combination inhalers are always more expensive than these ICS products at increased dose. The greatest cost difference is between taking Symbicort Turbohaler® (200µg/12µg per day = £201 per year) and BDP 400µg/day (as Becotide® 100µg = £20 per year). To compensate for these extra annual medication costs, the combination inhaler would annually need to avert at least one hospital-managed exacerbation in 3 to 11 people taking the drug. In contrast, between 4.5 and 9 GP-managed exacerbations per person would need to be averted annually to compensate for the extra cost of taking this combination inhaler, compared to increasing the dose of Becotide to 400µg/day.

However, since Becotide® and other CFC-propelled products will soon be withdrawn from sale in the UK, it is now probably more realistic to compare the cost of the combination inhalers with CFC-free ICS products. Compared with the cheapest CFC-free products of each ICS drug, the combination inhalers are between £6 and £145 more costly per year (see

Table 3 and Table 4). With a £6 extra annual cost of Seretide Evohaler® 100/50 per day over FP 200µg per day only a GP-managed exacerbation would have to be avoided every two to four years to cover the additional drug cost. In contrast, to cover the £145 extra annual cost of Symbicort® Turbohaler (200/12 per day) compared with increasing the dose of BDP (CFC-free) to 400µg per day, at least one hospital-managed exacerbation would have to be avoided per year for every 3 to 14 patients on the combination inhaler.

In summary, the extra annual cost to the NHS of combination inhalers, compared with an increased dose of the different ICS drugs as monotherapy varies enormously depending on the exact ICS product used. When the more expensive ICS preparations are considered (derived by use of the weighted mean cost of all ICS preparations) then only the combination inhaler Seretide Evohaler® is generally cheaper than an increased dose of ICS alone. However, for the cheapest ICS products the additional cost implied by using a combination inhaler (instead of increasing the ICS dose) will often be £100 or more per year. While this does not, perhaps, appear to be a large difference, this exploratory analysis shows that to achieve cost savings the combination inhaler would need to at least avert approximately four GP-managed exacerbations, or avert one hospital-managed exacerbation amongst 10 people on the drug for a year.

We appreciate that this basic ‘cost-savings’ or ‘cost-offset analysis’ does not take into account the other important benefits to individuals and their families of avoiding exacerbations, or having generally improved asthma control in between exacerbations. Nor does it capture the longer term cost impact of avoiding exacerbations on reducing the likelihood over time of treatment step-up. However, given the paucity of other reliable sources of effectiveness data we hope it is a useful illustration of how much more effective combination inhalers would need to be in order to be cost-saving compared with increasing ICS dose.

This illustration should also be read in the context of how likely these absolute differences in exacerbation rates could be for each of the different treatment options under consideration, given background exacerbation rates which may already be low. The results from the clinical effectiveness review highlighted there are currently no trials that have compared the effectiveness of increasing the dose of ICS alone to the addition of a LABA to a lower dose of ICS in a paediatric population. Therefore it is impossible to comment on the likely exacerbation rates associated with each of the treatment options, except to say that in adults these rates are typically fairly low.

TABLE 1 Exploratory cost-savings analysis: Annual exacerbations avoided to cover extra cost of FP/S compared with weighted mean cost of ICS

	Weighted mean annual cost of ICS	Seretide Evohaler 100/50 FP/S per day	Cost Difference per year	Cost of a hospital-managed exacerbation			Cost of a GP-managed exacerbation		
				£500	£1,056	£2,000	£20	£24	£40
BDP 400/day	£63	£115	£52	0.1	0.05	0.03	2.6	2.2	1.3
BUD 400/day	£120	£115	-£5	Seretide Evohaler cheaper than higher dose ICS					
FP 200/day (all CFC-free)	£133	£115	-£15	Seretide Evohaler cheaper than higher dose ICS					
BDP 400/day (excl. CFC-propelled)	£122	£115	-£7	Seretide Evohaler cheaper than higher dose ICS					
BUD 400/day (excl. CFC-propelled)	£134	£115	-£19	Seretide Evohaler cheaper than higher dose ICS					
		Seretide Accuhaler 100/50 FP/S per day							
BDP 400/day	£63	£190	£127	0.25	0.12	0.06	6.35	5.29	3.18
BUD 400/day	£120	£190	£70	0.14	0.07	0.04	3.50	2.92	1.75
FP 200/day (all CFC-free)	£133	£190	£57	0.11	0.05	0.03	2.85	2.38	1.43
BDP 400/day (excl. CFC-propelled)	£122	£190	£68	0.14	0.06	0.03	3.40	2.83	1.70
BUD 400/day (excl. CFC-propelled)	£134	£190	£56	0.11	0.05	0.03	2.80	2.33	1.40

TABLE 2 Exploratory cost-savings analysis: Annual exacerbations avoided to cover extra cost of BUD/FF compared with weighted mean cost of ICS

	Weighted mean annual cost of ICS	Symbicort Turbohaler 200/12 BUD/FF per day (100/6 inhaler)	Cost Difference per year	Cost of a hospital-managed exacerbation			Cost of a GP-managed exacerbation		
BDP 400/day	£63	£201	£138	0.28	0.13	0.07	6.90	5.75	3.45
BUD 400/day	£120	£201	£81	0.16	0.08	0.04	4.05	3.38	2.03
FP 200/day (all CFC-free)	£133	£201	£68	0.14	0.06	0.03	3.40	2.83	1.70
BDP 400/day (excl. CFC-propelled)	£122	£201	£79	0.16	0.07	0.04	3.95	3.29	1.98
BUD 400/day (excl. CFC-propelled)	£134	£201	£67	0.13	0.06	0.03	3.35	2.79	1.68

NB: costs for Symbicort Turbohaler are based on the inhaler 100/6. Symbicort 200/6 and 400/12 are not recommended in children under 12 years.

TABLE 3 Exploratory cost-savings analysis: Annual exacerbations avoided to cover extra cost of FP/S compared with cheapest ICS product for each drug

	Annual cost of cheapest ICS	Seretide Evohaler 100/50 FP/S per day	Cost Difference per year	Cost of a hospital-managed exacerbation			Cost of a GP-managed exacerbation		
				£500	£1,056	£2,000	£20	£24	£40
BDP 400/day	£20	£115	£95	0.19	0.09	0.05	4.75	3.96	2.38
BUD 400/day (all CFC-free)	£70	£115	£45	0.09	0.05	0.02	2.22	1.88	1.13
FP 200/day (all CFC-free)	£109	£115	£6	0.01	0.005	0.003	0.30	0.25	0.15
BDP 400/day (excl. CFC-propelled)	£56	£115	£59	0.12	0.06	0.03	2.95	2.46	1.48
		Seretide Accuhaler 100/50 FP/S per day							
BDP 400/day	£20	£190	£170	0.34	0.16	0.09	8.50	7.08	4.25
BUD 400/day (all CFC-free)	£70	£190	£120	0.24	0.11	0.06	6.00	5.00	3.00
FP 200/day (all CFC-free)	£109	£190	£81	0.16	0.08	0.04	4.05	3.38	2.03
BDP 400/day (excl. CFC-propelled)	£56	£190	£134	0.27	0.13	0.07	6.70	5.58	3.35

TABLE 4 Exploratory cost-savings analysis: Annual exacerbations avoided to cover extra cost of BUD/FF compared with cheapest ICS product for each drug

	Annual cost of cheapest ICS	Symbicort Turbohaler 200/12 BUD/FF per day	Cost Difference per year	Cost of a hospital-managed exacerbation			Cost of a GP-managed exacerbation		
				£500	£1,056	£2,000	£20	£24	£40
BDP 400/day	£20	£201	£181	0.36	0.17	0.09	9.05	7.54	4.53
BUD 400/day (all CFC-free)	£70	£201	£131	0.26	0.12	0.07	6.55	5.46	3.28
FP 200/day (all CFC-free)	£109	£201	£92	0.18	0.09	0.05	4.60	3.83	2.30
BDP 400/day (excl. CFC-propelled)	£56	£201	£145	0.29	0.14	0.07	7.25	6.04	3.63

NB: costs for Symbicort Tubohaler are based on the inhaler 100/6. Symbicort 200/6 and 400/12 are not recommended in children under 12 years.

TABLE 5 Estimated cost of a hospital-managed exacerbation for children with asthma

Resource type	Unit cost	Source			Cost
Oral steroids (prednisolone 2 × 25mg per day for 10 days, as per BTS/SIGN Guidelines)	17.27p per dose	BNF	20 doses		3.45
Child asthma patients discharged from A & E:					
% of those with exacerbations who are discharged			39% ^b		
Arriving by ambulance/paramedic services	£169	NSRC	39%	23% ^b	15.10
A & E Other high cost investigations	£100	NSRC	39%	11% ^b	4.30
A & E low cost investigations	£74	NSRC	39%	18% ^b	5.20
A & E No investigations	£62	NSRC	39%	71% ^b	17.22
Post discharge GP follow-up	£20	UCHSC	39%	64% ^b	4.97
Child asthma patients admitted from A & E:					
% of those with exacerbations who are admitted to hospital via A & E department			28% ^b		
Arriving by ambulance/paramedic services	£169	NSRC	28%	41% ^b	19.50
A & E Other high cost investigations	£151	NSRC	28%	18% ^b	7.65
A & E low cost investigations	£118	NSRC	28%	14% ^b	4.63
A & E No investigations	£112	NSRC	28%	68% ^b	21.46
Hospital episode for treating asthma (paediatric)	£721	NSRC	28%		202.75
ICU costs (3 bed-days in ICU, for 25% of those admitted via A & E)	£1910	NSRC	28%	3 ^b × 25% ^b	403.01
Child asthma patients admitted following GP referral:					
% admitted to hospital via GP referral			33% ^b		
GP appointment	£20	UCHSC	33%		6.60
Hospital episode for treating asthma (paediatric)	£721	NSRC	33%		237.77
ICU costs (mean = 1 bed-days in ICU, for 10% of those admitted via GP referral)	£1910	NSRC	33%	1 ^b × 10% ^b	63.01
All child asthma patients admitted to hospital:					
Post discharge GP follow-up	£20	UCHSC	61%	50% ^a	6.11
Post discharge hospital outpatient follow-up	£111	NSRC	61%	50% ^a	33.83
NHS cost per hospital-managed exacerbation					£1056.56
<p><i>BNF = British national Formulary No. 51 (March 2006).²²⁹ NSRC = National Schedule of Reference Costs 2005.²³⁰ UCHSC = Unit Costs of Health and Social Care 2005.²³¹</i></p> <p>^a authors' assumption</p> <p>^b administrative records of Royal Devon & Exeter NHS Trust and/or Southampton University Hospitals Trust</p>					

TABLE 6 Estimated cost of a GP-managed exacerbation for children with asthma

Resource type	Unit cost	Source			Cost
Oral steroids (prednisolone 2 × 25mg per day for 5 days, as per BTS/SIGN Guideline)	17.27p per dose	BNF	10 doses		1.73
% of consultations that are in surgery hours:			80% ^b		
In-hours GP visit (half see GP)	£20	UCHSC	80% ^b	50% ^b	8.00
In-hours GP visit (half see practice nurse)	£9	UCHSC	80% ^b	50% ^b	3.60
Out-of-hours GP telephone consultation (all out-of-hours)	£22	UCHSC	20% ^b	100% ^a	4.40
Out-of-hours GP visit (half of those calling out-of hours)	£59	UCHSC	20% ^b	50% ^a	5.90
NHS cost per GP-managed exacerbation					£23.63
<i>BNF = British National Formulary No. 51 (March 2006),²²⁹ UCHSC = Unit Costs of Health and Social Care 2005.²³¹</i> ^a authors' assumption ^b clinical expert opinion/estimate					

0.1.2 Research Question 4: Combination versus separate inhalers at Step 3?

The cost comparison results presented below are justified on the basis that **we found no consistent evidence of differential effectiveness in trials comparing the comparators of interest** (see section **Error! Reference source not found.**)

Table 7 and Table 26 below show, for both the currently available combination products (Seretide and Serevent), the combination ICS-with-LABA product is always cheaper than taking the same drugs in separate inhalers. For taking BUD with FF, using Symbicort via Turbohaler is always cheaper than taking Pulmicort via Turbohaler (at the same BUD dose) and taking FF separately. The estimated annual savings vary between £57 and £190 depending on the exact preparation of FF used and the daily dose of BUD required.

For taking FP with SAL, using Seretide via Accuhaler is always cheaper than taking Flixotide Accuhaler (at the same FP dose) and SAL separately. The estimated annual savings vary from £132 (if on 200µg FP per day) to £244 (if on 100µg FP per day). Similarly, using Seretide via Evohaler is always either **£189 or £274** cheaper than taking Flixotide via Evohaler (at the same FP dose) and taking SAL separately.

TABLE 7 Annual cost of combination versus separate inhalers: BUD with FF added

Combination or BUD	FF	Annual cost (£) by daily dose of BUD	
		200µg per day	400µg per day
Symbicort Turbohaler (combination product)		201	402
Separate inhalers: Pulmicort Turbohaler, plus:	Oxis 4.5µg (or 9µg)*	369	437
	Foradil 12µg	391	458
Difference in annual cost (separate less combination):			
Separate inhalers: Pulmicort Turbohaler, plus:	Oxis 4.5µg or 9µg	+169	+35
	Foradil 12µg	+190	+57

* Oxis® 4.5µg and 9µg are the same price per dose.

TABLE 8 Annual cost of combination vs separate inhalers: FP with SAL added

Preparation	Taken as	Annual cost (£) by daily dose of FP	
		100µg per day	200µg per day
As dry powder:			
Flixotide Accuhaler	2 blisters/day	78	155
Serevent Accuhaler (or aerosol inhaler)#	2 blisters/day*	356	356
Both (total):		434	511
Seretide Accuhaler (FP and S combined)	2 blisters/day*	190	379
Difference in annual cost:		+244	+132
As aerosol:			
Flixotide Evohaler	4 puffs/day	33	66
Serevent aerosol Inhaler	4 puffs/day*	356	356
Both (total):		389	422
Seretide Evohaler (FP and S combined)	4 puffs/day*	115	233
Difference in annual cost:		+274	+189

* Each blister contains 50µg of SAL, and each puff contains 25µg of SAL
 # Seretide Accuhaler and aerosol inhaler are the same price per µg.

Comparisons with SAL delivered as Serevent Diskhaler are not shown. However, two blisters of Serevent diskhaler per day costs £428 per year (£72 more than Serevent Accuhaler or Serevent inhaler), and therefore the difference in annual cost between separate and combination inhalers would be even greater.

0.1.3 Research Question 5: FP/S vs BUD/FF at Step 3?

The cost comparison results presented below are justified on the basis that **we found no consistent evidence of differential effectiveness in trials comparing the comparators of interest** (see section **Error! Reference source not found.**)

Table 9 below compares the cost of taking ICS with LABA in the two currently licensed combination inhalers, Seretide® and Symbicort®. In making the comparison between these products we have assumed that 200µg and 400µg of BUD is equivalent to 100µg and 200µg of FP, respectively.

Symbicort is more expensive than both of the Seretide preparations that are recommended for use in children. The estimated annual savings to the NHS of using Seretide instead of Symbicort may be between £11 and £172. However, these differences rely heavily on the assumed 2:1 dose-equivalence between BUD and FP, which is a rather crude rule of thumb (and not, for example, derived from a meta-analysis of trials of the relevant products in children). It should also be noted that the assumed equivalence of Symbicort to Seretide at half the ICS dose, is based on only four head-to-head trials in adults, and in all these trials the Seretide comparator product was Seretide Diskus (which is marketed as Accuhaler in the UK) and all the trials were in adults and of doses that would not be recommended in children (typically comparing 500µg/100µg FP/S per day with 800, 1600 or 400µg /12µg of BUD/FF per day).

TABLE 9 Comparison of the cost of currently available combination products

Combination product		200µg BUD	400µg BUD
		per day	per day
Symbicort Turbohaler (100µg:6µg of BUD:FF combined)	1 or 2 puffs/day	201	402
		100µg FP	200µg FP
		per day	per day
Seretide Accuhaler (100µg:50µg of FP:S combined)	1 or 2 blisters/day*	190	379
Seretide Evohaler (50µg:25µg of FP:S combined)	2 or 4 puffs/day*	115	233