Assessment Report for Appraisal of Corticosteroids for the treatment of Chronic Asthma in Children under 12 years

Executive Summary of GlaxoSmithKline (GSK) Comments for Consideration by the Appraisal Committee

Overall, GSK recognises the complexity of reviewing such a large evidence base. GSK would like to make a number of comments, which we hope will be useful to the Appraisal Committee in drafting their guidance. More detail on these comments can be found in a separate document, which we hope will be reviewed by the Assessment Group. In summary, these comments are:

1. Importance of child growth and the relative impact of inhaled corticosteroids (ICSs) has not received due prominence, with relevant studies excluded and a lack of synthesis or summary of the evidence.
2. Evidence of the relative effectiveness of Seretide™[i] (SFC) compared with increased dose fluticasone propionate (FP) was not considered.
3. Importance of adherence is acknowledged but the appropriate evidence base showing the benefit of combination inhalers not reviewed.
4. Modelling the cost effectiveness of ICSs in asthma is not straightforward, however, a cost-offset analysis is not an appropriate economic evaluation for decision-making.
5. A GSK approach translated symptom-free days (SFDs) into Quality Adjusted Life Years (QALYs) in line with the Reference case and showed SFC to be cost effective compared with doubling the dose of ICS.
6. Cost comparisons are not transparent and may be inaccurate due to a possible error in the SFC Evohaler®[i] cost and a typographical error.

Clinical effectiveness review

Question 1 (ICS vs ICS low dose)

Importance of growth to clinical effectiveness has not received due prominence

- A synthesis or appropriate summary of the relative impact of fluticasone propionate (FP) compared with either beclometasone dipropionate (BDP) or budesonide (BUD) on child growth was not undertaken.
- Reviews of the literature[1;2] and the three trials reviewed show that FP affects child growth significantly less than BDP or BUD.[3-6] The overall conclusions of this evidence base are not reflected in the evidence summary in the Report.
- Importantly three trials were excluded (see Table 1), two of which compared FP with BDP[7;8] and one compared FP with BUD.[9] All three studies found that the rate of growth was lower with BDP and BUD compared with FP, which is consistent with the other studies reviewed in the Report.
- Overall, the balance of the evidence suggests that FP has less effect on growth velocity at licensed doses than BDP. FP may therefore be a preferred option in children when used within licensed doses, particularly where there are concerns about a child's growth.

Question 3a & b (ICS/Long Acting Beta2 Agonist (LABA) vs ICS)

[i] Seretide™ and Evohaler® are trade marks of the GlaxoSmithKline group of companies

Evidence not reviewed

- The Report states that there are no studies available that compared SFC with an increased dose of ICS, in an entirely paediatric population (p97). However, in the original GSK submission a trial is reported that compared SFC with both the same and an increased dose of ICS (SAM40012).
- In SAM40012 548 children aged 4–11 years who were symptomatic on ICS were randomised to either SFC (FP 200µg/day and 100µg/day salmeterol) or FP 200 or 400µg/day for 24 weeks.
- No statistically significant differences were found in the main analysis, however, the quality of life scores and post-hoc analyses of baseline symptom scores showed that the patients enrolled were mild rather than moderate asthmatics. As such, there was little scope to detect efficacy differences among the treatment groups in this study.
- This point is supported by further post-hoc analyses on subjects with morning peak flow <85 percent predicted and percentage of SFDs less than 20 percent at baseline, showed statistically significant differences between SFC and FP 200 in percentage of rescue-free days weeks 1-24 ($p \leq 0.023$) and change from baseline in morning peak flow weeks 1-24 ($p \leq 0.033$).[10]
- This evidence suggests that for patients uncontrolled on ICS, switching to SFC is at least as effective as remaining on an equivalent dose of ICS or switching to an increased dose of ICS. There is a trend towards improving lung function and increasing the number of rescue-free days. Therefore, SFC may have benefits by delivering similar efficacy at a lower steroid dose than ICS alone.

Question 4 (ICS/LABA combinations vs ICS+LABA separates)

Importance of adherence to clinical effectiveness has not received due prominence

- Adherence with asthma medication is poor in children.[11;12]
- Double dummy double blind randomised controlled trials alone are not an appropriate study design to assess adherence, as patients in both arms of the trial receive the same number of inhalers. As the only trials comparing SFC with FP plus salmeterol delivered in separate inhalers are of this design, observational evidence should be reviewed to assess whether combination inhalers improve adherence.
- In the absence of observational research carried out in children, the large observational studies mainly in adult populations were not considered within the Report. This evidence shows that patients taking ICS plus LABA in separate inhalers are less likely to adhere to their medication than those taking combination inhalers.[13-17]
- It seems reasonable to assume that combination inhalers could therefore improve adherence in children, which may lead to better patient outcomes,[18;19] and ensure that patients take a LABA with an ICS, which is consistent with the guidance from both the MHRA/CHM (Medicines and Healthcare products Regulatory Authority / Commissioner on Human Medicines) guidance and BTS/SIGN (British Thoracic Society / Scottish Intercollegiate Guidelines Network) Asthma Guideline.[20;21]

Cost effectiveness review

Question 3a & b (ICS/LABA vs ICS)

Cost-savings analysis inconsistent with Reference case

- The cost-savings analysis in the Report (p171) is inconsistent with the Reference case as health effects were not valued using QALYs.
- GSK has a number of concerns about the cost-savings analysis and would agree that it is exploratory analysis and should not be used for decision-making purposes.

GSK estimates of cost effectiveness of SFC are a more appropriate & reasonable basis for decision-making

- The GSK estimates are a more reasonable and appropriate basis for decision-making, as the approach meets the requirements of the Reference case in estimating QALYs gained.
- SFDs take account of exacerbations, but perhaps are less able to capture the severity of chronic asthma. SFDs reflect the experience of <u>all</u> asthma patients and their quality of life,[22] and the aims of asthma management, namely the control of symptoms.[21;23]
- Exacerbations are an important endpoint but increasingly rare,[24] therefore, modelling on exacerbation data alone results in cost effectiveness results that apply to an uncontrolled and/or severe asthma population alone and are likely to have limited relevance to the broader asthmatic population. Indeed, exacerbations represent only one manifestation of the chronic morbidity experienced by patients with severe asthma, and by considering this endpoint alone the importance of symptoms to patients are ignored.
- SFDs are also a recommended modelling endpoint for economic evaluation in asthma and used in a number of economic studies of ICSs,[25-27] and the only widely available endpoint enabling multiple comparisons. (see Appendix for GSK's response to other Assessment Group criticisms)
- With a cost per QALY of £15,739, the GSK analysis shows that it is cost effective to add a LABA in the form of SFC Evohaler rather than increase the dose of ICS. The Assessment Group concluded that these model results were "reasonable" (p199).

Question 3, 4, 5

Incorrect SFC Evohaler costs

- Cost comparisons made are not transparent and may be inaccurate as the annual cost for SFC 50 Evohaler seems to be based on an incorrect cost per device. This is likely to be due to a misprint in the March 2006 BNF.
- The correct annual savings associated with SFC compared with ICS plus LABA in separate inhalers AND Symbicort[ii] are larger than those estimated in the Report (see Table 2).
- In addition, there is a typographical error in the Executive summary of the Report incorrectly summarising that SFC is more expensive than Symbicort (see page xix), whereas the Reports finds that Symbicort is more expensive than SFC.

[ii] Symbicort® is the trade mark of AstraZeneca AB

Table 1: Excluded studies that compare the effects of FP vs BDP and BUD on growth

Trial	Dose of *Flixotide*	Dose of BDP/BUD	Sample size	Population	Endpoints	Outcomes	Study design	Citation
Low dose								
FLIP51	200µg /day	400µg/day 800µg/day	17 Crossover	7-14 years	Cortisol levels Growth rates measured by knemometry PEF SFDs SFN	FP did not suppress growth as measured by knemometry, however BDP did. Adjusted mean knemometric growth rate (mm/week) was 0.22 higher in the FP group (p=0.003).	R, db, xo 15 days	Wolthers OD, Hansen M, Anders J *et al*. Knemometry, urine cortisol excretion and measures of the insulin-like growth factor axis and collagen turnover in children treated with inhaled glucocorticoids. Ped Res 1997; 41 (1): 44-50. Wolthers OD, Pedersen S. Arch Dis Child 1993; 68 (5): 673-676.
unknown	100µg/day	200µg/day 400µg/day	13	'Children'	Growth rates measured by knemometry	The author concluded that the short term growth suppression with BDP not seen with FP	R, db, xo 12 weeks	Mackenzie C.A., Growth in asthmatic children-clinical experience with inhaled fluticasone propionate, European Respiratory Journal 1991; 4(Suppl. 14).
FMS40001	200µg/day	400µg/day	233 114 FP 119 BUD	6-9 years	Growth velocity determined by stadiometric height measurement. Lung function, asthma symptoms, and use of relief medication.	FP has significantly less impact on childhood growth velocity than a therapeutically equivalent dose of BUD. Adjusted mean growth velocity was significantly higher in the FP than the BUD group (5.5cm/yr vs 4.6cm/yr, p<0.001)	R, db, pg 12 months	Ferguson AC, Van Bever HP, Teper AM, Lasytsya O, Goldfrad CH, Whitehead PJ. A comparison of the relative growth velocities with budesonide and fluticasone propionate in children with asthma. Respir Med 2007; 101: 118-129. Ferguson AC, Van Bever HP, Teper AM, Lasytsya OI, Whitehead PJ. Significantly reduced growth velocity over 1 year with budesonide 200mug bd compared to fluticasone propionate 100mug bd in children with asthma. Am. J. Respir. Crit. Care Med. 2003;167(7 SUPPL.):A269.

Key: DB = double blind; DD = double dummy; MC = multicentre; PG = parallel group; R = randomised; XO = crossover

Table 2: Comparison of SFC costs (corrected SFC Evohaler costs)

Preparation	Annual cost (£)	SFC 50 Evohaler annual cost (100µg/day)		Differences (SFC – Comparator)	
Question 3		TAR	Corrected	TAR	Corrected
BDP 400	£63	£119	£115	+£56	+£52
BUD 400	£120	£119	£115	-£1	-£5
FP 200	£133	£119	£115	-£14	-£15
BDP (excl CFC)	£122	£119	£115	-£3	-£7
BUD (excl. CFC)	£134	£119	£115	-£15	-£19
Question 4					
FP + Sal (aerosol) (100µg/day)	£389	£119	£115	-£270	-£274
FP + Sal (aerosol) (200µg/day)	£422	£119	£115	-£185	-£189
Question 5					
Symbicort 100/6 (200µgBUD/day)	£201	£119	£115	-£82	-£86
Symbicort 100/6 (400µgBUD/day)	£402	£237	£230	-£165	-£172

Appendix

Response to comments on GSK economic model

1) Choice of endpoint (p134)

- The SFD endpoint was selected as it is a recommended modelling endpoint for economic evaluation in asthma and used in a number of economic studies of ICSs.[26-28] SFDs directly reflect the experience of all patients with asthma.
- SFDs are also the most commonly and consistently reported endpoint, which allowed the inclusion of all relevant comparators (consistent with NICE methods guidance) and the analysis is based on a systematic synthesis of evidence.
- The model did include an attempt to include the effects of treatments on the outcomes such as exacerbations and night-time symptoms indirectly through the utility estimates derived from the GOAL[29] study, those patients in the 'with symptoms' group included those suffering exacerbations in a particular week.
- Indeed, symptom scores used to calculate SFDs often capture symptoms experienced over the previous 24 hours including night-time awakenings. For example, in the GOAL study for a patient to be symptom-free they would have to have had no symptoms (such as wheeze, shortness of breath, cough or chest tightness) at all during the previous 24 hours.

2) Transparency of model cost estimates (p137)

- To clarify, the cost estimates did not include routine visits as these would be the same in both groups; hence the low estimated cost for the symptom-free state.
- Sufficient details were provided of the regression model and unit costs (see page 39 in GSK submission), to allow the analysis to be reproduced given a similar data set. It should also be noted that the estimates were applied to all treatments.

3) Transparency of model utility estimates (p137)

- Unfortunately the methodology used to derive these values has not yet been published but an unpublished report has been sent to NICE to provide details.
- As few utility estimates for asthma patients exist the values used represent the best estimates for the clinical population being considered.
- The relatively high utility value for the symptom-free state may not be unreasonable for a healthy population whose asthma symptoms are controlled.

4) Limitations of evidence base, generalisability & extrapolation of model data (p137)

- The model was populated using the data from all applicable trials identified in a systematic review.
- The data and form of extrapolation used in the model are described in the report in sufficient detail to allow decision-makers to reach appropriate conclusions regarding the validity of the analysis.
- The uncertainties associated with generalising and extrapolating from trial data are features of nearly all cost-effectiveness analyses, the question is whether they are useful when compared with the alternatives.
- The use of GOAL data for a paediatric population was indicated in the absence of a more suitable alternative. Indeed, the Report confirms that no such alternative data sources exist (p171).
- As the Assessment Group conclude, the overall results of the GSK model are "reasonable" (see page 199). Therefore, GSK would strongly suggest that the model estimates of the cost effectiveness of SFC, using SFDs data, are an appropriate and reasonable reflection of the cost effectiveness of SFC. The results of the GSK analysis show that compared with increasing the dose of FP to FP400, SFC Evohaler is cost effective with cost per QALY of £15,739.

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