Assessment Report for Appraisal of Corticosteroids for the treatment of Chronic Asthma in Adults & Children aged 12 years & over

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. There are a number of inconsistent summaries of the evidence in the Report so the data should be relied upon rather than the summaries. A number of relevant studies were excluded with no obvious reason (see comments to Assessment Group).
2. The incremental benefit of Seretide™[i] (SFC) compared with increased dose inhaled corticosteroids (ICS) is underestimated as incomparable studies are pooled and an unpublished study is excluded from the Report.
3. Importance of adherence is acknowledged but the appropriate evidence base showing the benefit of combination inhalers is not reviewed.
4. Modelling the cost effectiveness of ICSs in asthma is not straightforward, however, the Assessment Group has not reviewed the importance of symptoms to patients in their exploratory analysis thus rendering it an invalid and unreliable approach 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 is 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.

Clinical effectiveness review

Question 1 & 2 (ICS vs ICS)

Mismatch between data in report and conclusions drawn

- The assessment of the clinical benefits of fluticasone propionate (FP) over beclometasone dipropionate (BDP) and budesonide (BUD) are under-estimated due to inconsistencies in summaries of the evidence (see Comments to Assessment Group). GSK would suggest that the appraisal committee rely on the data rather than the summaries and conclusions of the Report.

Question 3a (ICS/Long Acting Beta2-Angonists (LABAs) vs increased dose ICS)

Studies inappropriately pooled & excluded

- The clinical effectiveness of SFC compared with increased dose ICS alone is under-estimated in the Report in three ways.
  - Firstly, the findings are based on a synthesis of data from two studies (p220-3). One of the studies (Busse et al.[1]) is in patients with controlled asthma reducing their dose of ICS. It is inappropriate to include this study in the

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

meta-analysis because the patient population is incomparable to studies of uncontrolled asthma patients and should be analysed separately.
    - Secondly, the data synthesis excluded an unpublished trial (SAM30013) without an obvious reason. If data from this trial of 237 patients were included in the meta-analysis, the incremental benefit of SFC on outcomes such as symptom-free days (SFDs) would be doubled from that found in the Report.
    - Lastly, onset of action data was not assessed. Nine trials show SFC improves lung function from the first week of treatment compared with FP alone.[2-10]
- Overall, the evidence for this question suggests that for patients uncontrolled on ICSs at a range of doses, a more rapid and significantly better level of control is achieved by switching to SFC at an equivalent ICS dose than by increasing the dose of ICS; with improvements in morning peak flow and SFDs.

Question 4 (ICS/LABA combinations vs separates)

Combination inhalers ensure LABA & ICS taken together in line with MHRA/CHM (Medicines and Healthcare products Regulatory Authority / Commissioner on Human Medicines) guidance

- As noted in the Report (see page 428), an advantage of combination inhalers over ICS plus LABAs in separate inhalers is that they ensure that the LABA is taken with an ICS, which is in line with the licence for LABAs in the UK and with both the prescribing guidance of the MHRA/CHM,[11] which were updated in November 2005 in response to concerns over the safety of LABA monotherapy[ii], as well as the BTS/SIGN (British Thoracic Society / Scottish Intercollegiate Guidelines Network) Asthma Guideline.[12]

Importance of adherence to clinical effectiveness has not received due prominence

- It is important to recognise that the Assessment Group has not reviewed evidence on the adherence benefits of combination inhalers.
- The Report concludes that there were few differences in clinical effectiveness between combination inhalers and their components in separate inhalers (pxix). However, these trials were not designed to detect differences, but only to show equivalence.
- These trials were also double blind double dummy in design with all patients receiving the same number of inhalers in each arm and so adherence levels, and therefore patient outcomes, would not be expected to differ.
- With these limitations of the evidence base in mind, observational studies are a more appropriate source of data to capture the benefits of combination inhalers in real-life clinical practice.
- Six large observational studies show that combination inhalers are associated with improved adherence compared with its components in separate inhalers.[13-18] The risk of moderate or severe exacerbations,[14] and the use of reliever medication were significantly lower in patients taking combination inhalers in some of these studies.[13;16;18] Combination inhalers are also associated with reduced oral steroid use and lower hospitalisation rates.[19;20]

Cost effectiveness review

[ii] MHRA are currently conducting a review of LABA safety – see www.mhra.gov.uk

Question 1 & 2 (ICS vs ICS)

Cost minimisation is not appropriate

- Cost minimisation is not an appropriate approach for assessing the cost effectiveness of steroids alone, as the assumption that all ICSs are equivalent is an inconsistent summary of the evidence (see comments the Assessment Group). However, GSK can appreciate the difficulties of incorporating the differences in efficacy into a model.

Question 3a (ICS/LABA vs increased dose ICS)

Main economic analysis inconsistent with Reference Case

- The Assessment Group's main approach to modelling the cost effectiveness of SFC is not consistent with the Reference Case,[21] as it does not value health effects in terms of Quality Adjusted Life Years (QALYs).

Exploratory analysis is invalid & unreliable for decision-making purposes

- GSK has a number of concerns about the Assessment Group's exploratory analysis and would agree is not valid or reliable for decision-making purposes, as there is unacceptable uncertainty in a number of areas:
    - Model is not transparent in its design or estimation of treatment effect.
    - Effectiveness estimate (exacerbation) is biased and unreliable, as exacerbation definitions vary across trials, these are rare events and adverse event data were used.
    - Utility data relate to severe asthma patients.
    - Quality is not assessed using checklist to assess manufacturer models.

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

- Modelling the cost effectiveness of ICSs in asthma is not straightforward, but GSK believes that the GSK estimates of the cost effectiveness of SFC are a more appropriate and reasonable basis for decision-making and should be taken into account. Indeed, the results of the same model were appraised in the children under 12 Report as "reasonable" (p199).
- The Assessment Group commented that the GSK model was based on SFDs, which, they suggest, does not capture all the important aspects of asthma control e.g. exacerbations (p360). However, SFDs have been a recommended modelling endpoint for economic evaluation in asthma and used in a number of economic studies of ICSs.[22-24] (see Appendix for GSK's response to other Assessment Group criticisms)
- Also SFDs do take into account exacerbations, although are less able to capture the severity of chronic asthma. SFDs were the only widely available endpoint enabling multiple comparisons and are perhaps most relevant to patients, their quality of life, and the aims of asthma management, namely the control of symptoms (see page 416).
- Exacerbations are an important endpoint but increasingly rare,[25] 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.

- The economic analysis of the GOAL trial[5] is based on both exacerbation and symptom data, and the resulting cost per QALYs range from £7,600 to £11,000 for SFC compared with ICS alone.[26]
- This supports the results from the GSK analysis based on the breadth of the evidence, which demonstrate that it is cost effective to add a LABA for patients uncontrolled on inhaled steroids at any point within step 2 of the BTS/SIGN Guideline rather than increasing the dose of inhaled steroids.
- The results of the GSK model show that compared with increasing the dose of FP to FP400/500 & FP1000, SFC is cost effective with cost per QALYs all below £20,000. Against BDP800-1000, the cost per QALYs for SFC are below £20,000. Against BDP1600/2000 the cost per QALYs are above £20,000 but below £30,000.

Comparison of costs is of limited relevance & inaccurate

- The Assessment Group's comparison of costs is based on only one of the two SFC devices, namely the Accuhaler®[iii], which was used in the clinical trials reviewed. Given the clinical equivalence of these two devices[2;9] their costs can be used interchangeably in cost comparisons. As both devices are used in the UK, an assessment of both device costs should be included.
- The analysis also excluded for no obvious reason, two unpublished GSK trials (SAM30013 and SAM40120), which were the only trials relevant to this question that used the Evohaler device.
- In the report, SFC (Accuhaler) is cheaper than FP or BUD alone in two out of the five trial/cost comparisons, however, if the Evohaler device cost is used, the evidence would show that there is a cheaper SFC device in <u>all</u> comparisons.

Question 4 (ICS/LABA combinations vs separates)

GSK cost analysis of SFC vs BDP plus salmeterol in separate inhalers

- The report concluded that the savings associated with SFC over components in separate inhalers may not hold if compared with BDP/salmeterol in separate inhalers (p406). However, using similar costing methods to the Report the GSK submission shows that there is <u>always</u> a cheaper SFC option compared with BDP/salmeterol in separate inhalers (see Table 1).

Question 4 & 5

Use of an incorrect SFC price has led to incorrect conclusions

- Cost comparisons made are not transparent and may be inaccurate (p408 & 410) as the annual cost for SFC 50 and 125 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.
- With the correct SFC Evohaler costs, there is <u>always</u> a cheaper SFC option compared with <u>both</u> its components in separate inhalers (see Table 2) and Symbicort®[iv] at <u>all</u> doses (see Table 3).

[iii] Accuhaler® is a trade mark of the GlaxoSmithKline group of companies
[iv] Symbicort® is the trade mark of AstraZeneca AB

Table 1: Cost comparison of SFC vs BDP + Sal in separate inhalers

SFC Treatment Code	Annual Cost (£) by daily dose of BDP equivalent		
	400µg/day	800 / 1000 µg/day	1600 / 2000 µg/day
SFC (average)	£288.55	£445.61	£701.28
SFC (Accuhaler)	£379.86	£445.61	£496.74
SFC (Evohaler)	£219.15	£445.61	£759.72
Sal+BDP (weighted average)	£460.22	£540.57 / £507.70	£693.98 / £631.88
Cost differences:			
SFC (average) vs SX+BDP	-£171.67	-£94.96 / -£62.09	+£7.3 / +£69.4
SFC (Accuhaler) vs SX+BDP	-£80.36	-£94.96 / -£62.09	-£197.24 / -£135.14
SFC (Evohaler) vs SX+BDP	-£241.07	-£94.96 / -£62.09	+£65.74 / +£127.84

Table 2: Cost comparison of SFC vs components in separate inhalers (corrected SFC Evohaler costs)

Preparation	Annual cost (£) by daily dose of FP					
As aerosol:	200µg/day		500µg/day		1000µg/day	
	Report	Corrected	Report	Corrected	Report	Corrected
FP + Sal (total)	£422	£422	£615	£615	£796	£796
SFC Evohaler	£237	£219	£479	£446	£815	£760
Difference	+£185	+£203	+£135	+£169	-£19	+£36

Table 3: Cost comparison of SFC vs Symbicort (corrected SFC Evohaler costs)

	Annual cost (£) by daily dose of BUD			
Combination product	400µg/day BUD or 200µg/day FP		800µg/day BUD or 500µg/day FP	
	Report	Corrected	Report	Corrected
Symbicort Turbohaler (BUD/FF)	£231	£231	£462	£462
SFC Evohaler	£237	£219	£479	£446
Differences	-£6	+£12	-£17	+£16

Appendix

Response to comments on GSK economic model

1) Choice of endpoint (p360)

- The SFD endpoint was selected as it is a recommended modelling endpoint for economic evaluation in asthma and used in several ICS economic studies.[22-24]
- SFDs directly reflect the experience of all patients with asthma. 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 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.
- 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.

2) Transparency of cost estimates (p361).

- To clarify, the cost estimates did not include routine visits as these would be the same in both arms of the study; hence the low estimated cost for the symptom-free state.
- Sufficient details were provided of the regression model and unit costs (see p60 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 (p361).

- 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 (p361)

- 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, including the exploratory analysis presented in appendix 10, the question is whether they are useful when compared with the alternatives.
- As the Assessment Group concludes, the overall results of the GSK model are "reasonable" (p199).
- In addition, the economic analysis of the GOAL trial[5] was based on both exacerbation and symptom control data in line with GINA[27] and BTS/SIGN[12] guideline definitions of asthma control, and found that the improvement in control with SFC is associated with cost per QALY figures that compare favourably with other uses of scarce health care resources (£7,600-£11,000 per

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