Appraisal Consultation Document (ACD) for the Appraisal of Corticosteroids for the treatment of Chronic Asthma in Adults & Children aged 12 years & over

GlaxoSmithKline (GSK) Comments for Consideration by the Appraisal Committee

Overall, GSK welcomes the preliminary recommendations made by the Appraisal Committee in the appraisal of inhaled corticosteroids (ICS) for chronic asthma in adults and children aged 12 and over. GSK would like to comment on a number of key aspects of the draft guidance. GSK's response has been put together with consideration to the following questions:

1. Whether all of the relevant evidence has been taken into account?
2. Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?
3. Whether the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

Recommendation 1.1 & 1.3: ICS versus ICS (low & high dose)

- Underpinning the recommendations made in sections 1.1 and 1.3 is the assumed clinical equivalence of ICSs at both the low and high doses. Indeed, the ACD concludes that there are few statistically significant differences between the ICSs (4.1.3) and that there was little evidence to reject the hypothesis that there is no difference in clinical effectiveness between them (4.1.4). However, these conclusions are inconsistent with the Appraisal Committee's summary (4.1.11) that there was "…little conclusive evidence of equivalence and more often there was inconclusive evidence concerning differential effectiveness.". This suggests that the hypothesis of no difference should be rejected.
- The assumption that fluticasone propionate (FP) is clinically equivalent even at half the daily dose of other ICSs is also inconsistent with systematic reviews undertaken by both the Cochrane Collaboration and by GSK. The Cochrane systematic review undertaken by Adams et al. concluded that at half the daily dose, fluticasone propionate (FP) produced a significantly greater improvement in lung function (both forced expiratory volume in one second (FEV_1) and morning peak expiratory flow (PEF)) compared with beclometasone dipropionate (BDP) or budesonide (BUD).[1] Given that one of the main aims of asthma therapy is the achievement of best possible lung function, acknowledging the relative efficacy advantage of FP over BDP assists patient education and guides clinical choice of ICS.
- In terms of safety, the majority of randomised controlled trial (RCT) evidence shows that at high doses (≥BDP 800µg/day or equivalent), FP has less effect on markers of adrenal suppression and no effect on bone mineral density (BMD) compared with BDP.[2-5]
- GSK would therefore urge that the clinical data is summarised consistently to reflect the above evidence, and in particular that FP is at least as clinically effective as BDP and BUD at half the daily dose, but may be superior in improving lung function. GSK therefore suggests that the wording for both of the recommendations made at 1.1 and 1.3 change from "…the least costly product

that is suitable for the person is recommended." to "the least costly product taking into account the relative efficacy and safety is recommended".

Recommendation 1.2: Use of ICS plus long acting beta-2 agonist (LABA) versus ICS alone

- In previous comments to the Assessment Group GSK highlighted the inappropriate exclusion and inclusion of studies in the assessment of efficacy of Seretide™[i] (SFC) compared with an increased dose of ICS. On balance, however, the conclusions on clinical effectiveness in the ACD are reasonable in that the addition of a LABA in the form of a combination inhaler is statistically significantly superior to increasing the dose of ICS alone across a range of outcomes (see 4.1.5).
- The Appraisal Committee cite the cost effectiveness evidence arising from the Gaining Optimal Asthma control (GOAL) trial[6] but reference the Assessment Group's conclusion that the generalisability of this trial may be limited (4.2.1). However, there are no reasons to believe that GOAL is not generalisable to the UK. Indeed, the baseline demographics of the trial population are representative of asthma patients in the UK[7;8] and thus are likely to achieve similar outcomes. In addition, the proportion of patients enrolled in the trial from the UK (n=294) exceeds an equal share given the number of countries (n=44) involved. Consequently, GSK suggests that the following sentence is added to the end of 4.2.1: "Despite this there is no reason to believe that GOAL is not relevant to the UK population".
- In addition to the GOAL economic analysis the recommendation in 1.2 is supported by cost effectiveness information provided by GSK, and recently published in a peer-reviewed journal,[9] that shows that for patients uncontrolled on either BDP 400 or 800µg/day or equivalent, the cost per Quality Adjusted Life Years (QALYs) for SFC compared with increasing the doses of FP or BDP are below the £20,000 threshold.
- Whilst GSK acknowledges the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) asthma guideline recommendation[10] of adding in a LABA rather than increasing the dose of ICS, GSK believes it would have been helpful to decision-makers if the Appraisal Committee had also highlighted that adding in a LABA is a cost effective approach.

Cost comparisons of SFC with ICS alone

- The Assessment Group's comparison of costs that is referenced in 4.2.7 is based on only one of the two SFC devices, namely the Accuhaler®[ii], which was used in the clinical trials reviewed. Given the clinical equivalence of the Accuhaler and Evohaler®[iii] devices[11;12] 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 reported in 4.2.7 also excluded two unpublished GSK trials (SAM30013 and SAM40120), which were the only trials relevant to this question that were conducted using the Evohaler device. The Assessment Group excluded these trials on the basis that they were not published and the study reports were not provided by GSK. However, GSK provided study reports for other studies as

[i] Seretide™ is a trade mark of the GlaxoSmithKline group of companies
[ii] Accuhaler® is a trade mark of the GlaxoSmithKline group of companies
[iii] Evohaler® is a trade mark of the GlaxoSmithKline group of companies

requested by the Assessment Group so it is not clear why the study reports for these two trials were not requested, although details of these studies were included in the GSK submission, listed in the data outline, and a summary available on the GSK clinical trial register website.[13] As a result of this omission the cost-consequence analysis only reflects the cost of the Accuhaler device.

- In the cost-consequence analysis alluded to in 4.2.7, 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 all trial comparisons. Information to illustrate this is shown in Table 1.
- GSK would request that it is made clear in this section that the cost differences are estimated using the Accuhaler device only, and that an additional sentence is included to state that "When the Evohaler device cost is included it is cheaper than either FP or BUD alone in all comparisons".

Recommendation 1.2: ICS plus LABA combination inhalers versus ICS/LABA in separate inhalers & each other

- GSK welcomes the Appraisal Committee's recommendation in section 1.2 that for patients requiring ICS plus LABA combination devices are an 'option', as combination inhalers improve adherence and ensure ICS and LABA are taken together in line with the Medicines and Healthcare products Regulatory Agency (MHRA) and Commission on Human Medicines (CHM) guidance.[14]
- Although the Appraisal Committee acknowledge the importance of adherence, GSK believes it would be helpful if the observational evidence base that supports this recommendation had also been reviewed and summarised in the guidance. This evidence was reviewed and summarised in GSK's submission (see section 3.10.5) and response to the Assessment Report (see page 2).

Cost comparisons of SFC with ICS/LABA

- Due to a misprint in the British National Formulary (March 2006), the incorrect cost for SFC was used in the Assessment Group's cost comparisons of SFC with ICS plus LABA in separate inhalers. After GSK highlighted this incorrect cost in comments on the Assessment Report, the Assessment Group revised the analysis. GSK requests that the Appraisal Committee's summary of the evidence includes this revised analysis. For example, in section 4.2.8, the last sentence "Only at a very high dose and using another device (Evohaler), the separate inhalers can be the cheaper option." is incorrect. As Table 2 shows, both SFC devices are always cheaper than it's components in separate inhalers at all doses.
- Also in GSK's response to the Assessment Report and submission document, cost comparisons of SFC with BDP plus salmeterol in separate inhalers were provided, however, this evidence was not considered by the Assessment Group. As Table 3 shows, using a weighted average cost approach identical to that of the Assessment Group, SFC is cheaper than BDP plus salmeterol in all circumstances except at infrequently used high doses using the Evohaler device only. Given that salmeterol and BDP are used frequently together in separate inhalers in the NHS, GSK believes it would add value to also include information on these relative comparators.
- In addition, GSK has concerns about the conclusion in the guidance that "…there is no combination inhaler that is cheapest in all circumstances…" (4.2.9), and would suggest that this be reworded to "…with current costs there is always a cheaper Seretide device in all circumstances". This is consistent with the cost

comparisons provided by both the Assessment Group and GSK, and reproduced in Table 4.

Recommendation 1.4: press-and-breathe pressurised Metered Dose Inhalers (pMDIs)

- GSK acknowledges the recommendation for pMDIs (1.4), as it is consistent with the recommendations within technology appraisal guidance no.38[15] and supported by the evidence assessed in the health technology assessment report for that appraisal.[16;17]
- GSK suggests that inhalers should only be prescribed after a patient has received training in the use of the device and has demonstrated satisfactory technique in line with the BTS/SIGN guideline.[10] If this can not be demonstrated the option of using a spacer could be considered. The use of a spacer should be reserved for patients who do not have the ability to use a pMDI on its own effectively. However, this treatment approach would not be necessary or suitable for all adult patients.
- Consequently, GSK suggests that the wording in section 1.4 be changed to "Whenever possible, taking into account sections 1.1 to 1.3, the use of press-and-breathe pressurised metered-dose inhaler (pMDI) is recommended in the first instance, with use of a spacer if appropriate. Thereafter, a therapeutically equivalent Dry Powder Inhaler (DPI) should be considered".

Table 1: Cost comparison of SFC vs increased dose ICS alone

Study	FP or BUD	Cost	Difference
Bergmann	FP1000µg/day	£481	
	SFC 250 Accuhaler	£446	-£35
	SFC 125 Evohaler	£446	-£35
Busse	FP500µg/day	£287	
	SFC 100 Accuhaler	£379	+£92
	SFC 50 Evohaler	£219	-£68
Jenkins	BUD1600µg/day	£540	
	SFC 250 Accuhaler	£446	-£94
	SFC 125 Evohaler	£446	-£94
Johansson	BUD800µg/day	£270	
	SFC 100 Accuhaler	£379	+£109
	SFC 50 Evohaler	£219	-£51
Zhong	BUD800µg/day	£270	
	SFC 100 Accuhaler	£379	+£109
	SFC 50 Evohaler	£219	-£51
SAM30013	FP500µg/day	£263	
	SFC 50 Evohaler	£219	-£44
SAM40120	FP500µg/day	£263	
	SFC 50 Evohaler	£219	-£44

Notes:
SFC – Seretide; BUD – budesonide; FP – fluticasone propionate
Grey shading denotes cost differences with device not used in trial and not estimated in Assessment Report

Table 2: Cost comparison of SFC vs components in separate inhalers

Preparation	Annual cost (£) by daily dose of FP		
	200µg/day	500µg/day	1000µg/day
As aerosol:			
FP + Sal (total)	£465	£615	£796
SFC Accuhaler	£379	£446	£498
Difference	-£85	-£169	-£298
FP + Sal (total)	£422	£615	£796
SFC Evohaler	£219	£446	£760
Difference	-£203	-£169	-£36

Notes:
SFC – Seretide; Sal – salmeterol xinafoate; FP – fluticasone propionate

Table 3: Cost comparison of SFC vs BDP + Sal in separate inhalers

	Annual Cost (£) by daily dose of BDP equivalent				
	400µg/day	800µg/day	1000µg/day	1600µg/day	2000µg/day
SFC (Accuhaler)	£379	£446		£498	
SFC (Evohaler)	£219	£446		£760	
Sal+BDP (weighted average)	£460	£541	£508	£694	£632
Cost differences:					
SFC (Accuhaler) vs Sal+BDP	-£81	-£95	-£62	-£196	-£134
SFC (Evohaler) vs	-£241	-£95	-£62	+£66	+£128

Sal+BDP					

Notes:
SFC – Seretide; BDP – beclometasone dipropionate; FP – fluticasone propionate

Table 4: Cost comparison of SFC vs Symbicort

	Annual cost (£) by daily dose of BUD	
Combination product	400µg/day BUD or 200µg/day FP	800µg/day BUD or 500µg/day FP
Symbicort Turbohaler (BUD/FF)	£231	£462
SFC Evohaler	£219	£446
SFC Accuhaler	£379	£446
Differences:		
Symbicort vs Evohaler	-£12	-£16
Symbicort vs Accuhaler	+£148	-£16

Notes:
SFC – Seretide; BUD – budesonide; FP – fluticasone propionate; FF – formoterol fumarate

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