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

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 children aged under 12. GSK would like to comment on a number of key aspects of the draft guidance.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?

Whether all of the relevant evidence has been taken into account?

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

- In comments on the Assessment Report (see page 2), GSK highlighted the exclusion of an unpublished trial comparing Seretide™[i] (SFC) with both increased and same dose ICS (SAM40012). GSK welcomes the inclusion of the results from this trial in the ACD (see 3.1.7) but wishes to highlight the omission of the results from one arm of the study.
- In SAM40012, there were two fluticasone propionate (FP) alone treatment arms in the trial, as the 548 children aged 4–11 years were randomised to either SFC (FP 200µg/day and 100µg/day salmeterol) or FP 200 or 400 µg/day for 24 weeks. No mention is made of the results from the FP 200 µg/day arm of the trial in section 4.1.9 even though they were included in GSK's response to the Assessment Report (see page 2 and the GSK submission).

Recommendation 1.2: ICS plus LABA in combination inhalers versus separate inhalers

- 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.[1] GSK suggests that explicit reference is made in section 4.3.8 to the MHRA/CHM guidance, as it is an important benefit:risk consideration to emphasise the place of combination inhalers.
- Combination inhalers are a particularly important factor in improving adherence with asthma medication, which is poor in children.[2;3] Although the Appraisal

[i] Seretide™ is a trade mark of the GlaxoSmithKline group of companies

Committee acknowledge the importance of adherence in paediatrics, GSK believes it would be helpful if the double dummy double blind nature of the randomised controlled trials comparing combination inhalers with separate inhalers was highlighted in 4.1.10. Double dummy trials are not an appropriate study design to assess adherence, as patients in both arms of the trial receive the same number of inhalers. Instead, the large observational studies, although mainly in adult populations, show that combination inhalers are associated with higher levels of adherence,[4-8] and could have been considered to support this recommendation.

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?

Recommendation 1.1: ICS versus ICS dosing ratios

- In section 4.3.2 the Appraisal Committee note "uncertainty regarding equivalence" of FP at half the daily dose of budesonide (BUD) and beclometasone dipropionate (BDP) (4.3.2), however, findings from systematic reviews undertaken by both the Cochrane Collaboration[9] and by GSK show that there is little uncertainty about these dosing ratios.
- Indeed, the Cochrane systematic review undertaken by Adams et al.[9] concluded that "When FP was given to children or adults at approximately half the daily dose of either BDP or BUD, it appeared to be at least as effective as the other two drugs in improving airway opening".[9] Furthermore, the 1:2:2 dosing ratio of FP, BUD and BDP respectively is endorsed in the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) asthma guideline.[10]
- GSK suggests that the clinical data is summarised consistently to reflect the above evidence, and in particular that FP is at least as effective as BDP when used at half the dose in patients who require treatment with an ICS alone and there may be some additional benefits in lung function.

Recommendation 1.1: High dose ICS use

- GSK believes the Appraisal Committee has not sufficiently highlighted the risks of high dose ICS use in terms of side-effects associated with doses above 400µg/day BDP equivalent. This is a particular problem in paediatric asthma where there is considerable use of above licensed doses of steroids and in many instances without trials of add on LABA therapy.[11] GSK suggests that explicit reference is made to recent MHRA guidance advising that licensed doses of ICSs should not be exceeded in paediatrics.[12;13] Where higher than licensed doses of ICSs are required, GSK recommends that the child be under the care of a specialist in asthma management. In general, there should be regular monitoring of ICS dose and response particularly with regard to height and adrenal suppression.

Recommendation 1.1: Effect of ICS on growth

- In previous comments, GSK highlighted the exclusion of three trials[14-16] in the Assessment Report that compared the effect of FP on growth compared with either BDP or BUD. GSK welcomes the acknowledgement by the Appraisal Committee that these trials were excluded (4.1.3). However, as each of these

three trials was conducted using low doses of FP (200 µg per day), BDP (400 µg/day) and BUD (400 µg/day), and showed that FP had less effect on growth velocity compared with BUD and BDP, GSK would question the Appraisal Committee's assumption that the impact of ICSs on growth is more of an issue at high doses.

- GSK also pointed out in comments to the Assessment Group that the evidence on growth had not been appropriately synthesised or summarised. On balance, however, the conclusions in 4.1.3 are reasonable in that FP has less effect on growth velocity compared with BDP and BUD.
- Two recent trials not reviewed by the Assessment Group show that ICSs reduce growth rates over long periods of time.[17;18] This evidence indicates that ICSs may have a long term impact on growth and so should be considered when clinicians or a child's parents have concerns over growth. In these circumstances, FP may be preferred over other ICSs.
- GSK therefore suggests that the wording of the recommendation made at 1.1 changes from "…the least costly product that is suitable, within its marketing authorisation, for an individual child is recommended" to "the least costly product taking into account the relative efficacy and safety is recommended".

Recommendation 1.2: Costs of ICS plus LABA combination inhaler

- In the paediatric Assessment Report GSK commented on the incorrect costs estimated for the SFC Evohaler®[ii] device, as they were based on a misprinted cost in the March 2006 British National Formulary. GSK welcomes the use of the corrected costs in the ACD but would like to highlight one instance where an incorrect cost of £110 for SFC Evohaler is used (see section 3.7) instead of the correct cost of £115.

Whether the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

Recommendation 1.2: Use of ICS plus LABA versus ICS alone

- Whilst GSK acknowledges the 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 recommended within 1.2 that where it is appropriate to either increase the dose of ICS or add in a LABA, adding in a LABA should be an appropriate option. Indeed, this is stated as much in section 4.3.10.

Recommendation 1.2: Cost effectiveness of ICS plus LABA versus ICS alone

- GSK welcomes the Appraisal Committee's conclusion that adding a LABA was an appropriate option compared with increasing the dose of ICS (4.3.10). However, there is some concern that the cost-offset analysis is used for decision-making purposes. This analysis was described as 'exploratory' by the Assessment Group (p171 of the Assessment Report) and is inconsistent with the Reference case as health effects were not valued using Quality Adjusted Life Years (QALYs).

[ii] Evohaler® is a trade mark of the GlaxoSmithKline group of companies

- The cost effectiveness analysis presented in GSK's submission, which has recently been published in a peer review journal,[19] demonstrated that SFC is a cost – effective option and would support the recommendation of adding a LABA rather than increasing the dose of ICS alone.

Recommendation 1.2: Stepping down with ICS plus LABA combination inhalers versus ICS/LABA in separate inhalers

- Clinical experts to the Appraisal Committee cautioned that combination inhalers may discourage patients from stepping down treatment (see 4.3.11). However, GSK is concerned that this statement is not based on any evidence or the findings of the Assessment Group. GSK supports the BTS/SIGN asthma guideline recommendation that patients should be reviewed every three months and treatment stepped down once control is achieved.[10] GSK believes that this is possible with SFC. Indeed, with the SFC 50 Evohaler patients can step down from two puffs per day to one and so move to a lower dose if required, but it is also possible to move to FP alone using the same device, if they are controlled on the lowest dose of SFC.

Recommendation 1.2: ICS plus LABA combination inhalers versus each other

- In section 4.3.12 of the ACD, SFC was noted as the cheapest combination inhaler, and available as a pMDI, however, the Appraisal Committee then state that there could be benefits to using Symbicort[iii] as it can be used flexibly. In paediatrics the decision to adjust maintenance dosing is left with the child's parents who may not be able to assess accurately whether their child's asthma is adequately controlled or not.[20] Trials of flexible dosing in paediatrics[21] were not reviewed by the Assessment Group and therefore this dosing strategy is outwith the scope of this review. GSK therefore urges caution in highlighting the benefits of flexible dosing without a robust appraisal of the evidence.

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

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