NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Inhaled corticosteroids for the treatment of chronic asthma in children aged younger than 12 years

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Comment from	Comment	Response
AstraZeneca	**Growth during ICS therapy**. We agree with the importance of a discussion on child growth and the relative impact of inhaled corticosteroids (ICSs), but we believe some of the text in the ACD may potentially mislead end users as to the conclusion of the appraisal committee. Please see detailed comments below.	Comments noted. See responses below.
AstraZeneca	Growth during ICS therapy: low-dose ICS (equivalent to 200-400µg BDP per day) Paragraph 4.1.3 (Page 11) discusses the study data for the comparison of low-dose ICS and states, "Other randomised controlled trials were identified in consultees' submissions but were excluded from the Assessments Group's systematic review. In general, these studies supported the conclusions of the studies included in the Assessment Report, although a number identified a statistically significant difference favouring the use of fluticasone propionate for growth outcomes when compared with budesonide and beclometasone dipropionate."	The evidence section draws on the evidence that was considered by the Committee and not necessarily just that from the assessment report. This section has been amended to reflect that the difference was not identified in the low dose studies included in the assessment report. See FAD section 4.1.4.

Comment from	Comment	Response
AstraZeneca	AstraZeneca believes this discussion of the additional studies not included in the systematic review does not reflect the discussion in the Technology Assessment Report (TAR) itself. At low dose ICS, the TAR systematic review includes five studies that examined adrenal markers - Bisgaard 1988; Gustafsson 1993; Rao 1999; Agertoft 1997; and Altintas 2005. Of these, four of the trials concluded no significant difference between trial arms. The exception was Rao 1999, which favoured fluticasone propionate (FP). However, as discussed in the TAR there are methodological issues with this study that cast doubt on the conclusion of the study.	
AstraZeneca	An additional study that the Institute may wish to consider is a large study of 285 steroid naïve children treated with a daily dose of 200µg FP over several years. Whilst this study is placebo controlled and so was not included in the TAR systematic review, this study found a significant growth suppressive effect of FP vs. placebo; in the FP group the mean increase in height was 1.1 cm less at 24 months ($p<0.001$).	Comments noted. The focus of the appraisal is on the difference in effect between inhaled corticosteroids (ICS), and not the difference between ICS and placebo. Therefore the issue is not whether all ICS have a suppressive effect on growth, but whether any one ICS can be considered to have less of a suppressive effect than the others. No change made to the FAD.
AstraZeneca	Given the contradictory nature of some of the available evidence, AstraZeneca feel it is inappropriate to highlight the conclusions of individual studies in Paragraph 4.1.3. We suggest that the statement “although a number identified a statistically significant difference favouring the use of fluticasone propionate for growth outcomes when compared with budesonide and beclometasone dipropionate” is removed so that the paragraph reflects the discussion in the TAR and the balance of all the available evidence. This means the paragraph now reads:	The studies included in this section were available to the Committee in consultee submissions and included in the overview. Removing the studies would mean the section would not reflect the inconsistencies seen in the evidence. This paragraph has been amended to reflect that the effect on growth was not seen in any studies in the assessment report. See FAD section 4.1.4

Comment from	Comment	Response
AstraZeneca	"4.1.3 Reporting of the study data was incomplete in some studies and inconsistent across the different studies. Because of the differences between the studies, they could not be meta-analysed. None of the studies reported any statistically significant differences between treatments in the outcome measures of lung function, symptoms, use of rescue medication, exacerbations and adverse events. Other randomised controlled trials were identified in consultees' submissions but were excluded from the Assessments Group's systematic review. In general, these studies supported the conclusions of the studies included in the Assessment Report."	
AstraZeneca	Growth during ICS therapy: high-dose ICS (equivalent to 400-800µg BDP per day) Paragraph 4.1.5 (Page 12) discusses the study data for the comparison of high-dose ICS and states, "…two studies identified a statistically significant difference in growth rates favouring fluticasone propionate compared with budesonide; and one study identified a statistically significant difference in cortisol excretion favouring beclometasone dipropionate when compared with budesonide." AstraZeneca believes that the summary in the ACD comparing the study of beclometasone dipropionate (BDP) with budesonide (BUD) incorrectly concludes that the difference in cortisol excretion favours BDP. We believe the study referred to here is Pedersen and Fuglsang 1988 (reference 206 in the TAR). This study found a significant difference ($p<0.01$) in cortisol excretion favouring BUD when compared with BDP. AstraZeneca suggests that the summary in the ACD is changed to reflect this; in addition we suggest the summary in section 5.2.3.4 of the TAR (page 94) is also changed to reflect this. We appreciate that stakeholders have already been given the opportunity to review the TAR and apologise that this error was not highlighted at this time.	This has been amended in the FAD. See FAD section 4.1.6.

Comment from	Comment	Response
AstraZeneca	We would also like to highlight that growth rate in normal children is very variable over short periods of time, and so short-term studies are of limited value in predicting the effects of long-term treatment with inhaled steroids. In addition, it has been found that the correlation between one-, two- and three-year velocity values are only partly correlated with one another or final height. Also any discrepancy between the results of short-term and intermediate-term studies may be explained by the finding in several trials that any significant effect of inhaled steroids on growth is most marked at the beginning of treatment. The conflicting results of studies underline the importance of long-term studies using final adult height as an endpoint. This issue is also discussed on page 22 of the TAR.	The Committee concluded that the data from short term studies were not sufficiently consistent for any differential effect on growth to be an overriding factor in decision making. The FAD also acknowledges the long term data "that the long-term evidence for an impact on growth and final height was inconclusive" See FAD section 4.3.9.
AstraZeneca	As highlighted within our original submission, a long-term prospective study assessing final adult height in children receiving inhaled BUD has been performed (reference 81 in our submission). Whilst this study is placebo controlled and therefore not included in the TAR systematic review, it provides extremely useful evidence for long-term effect on growth that may add to the current discussion. The study compared the adult height of children receiving inhaled BUD at a mean daily dose of 412µg for 3 to 13 years with the adult height of asthmatic children not receiving any ICS and healthy siblings of patients in the BUD group. The study concluded that adult height in children treated with inhaled BUD is normal with all three groups of children reaching their target adult height. Neither the duration of BUD treatment, nor the cumulative dose of BUD affected final adult height. In addition, these final height data are supported by retrospective and epidemiological studies in Sweden, where BUD has been the most widely used inhaled steroid. It is also worth noting that no final height data are available for FP.	The FAD section 4.3.9 mentions both the short term evidence included in the submissions and assessment report and the long term evidence that the Committee heard about from clinical specialists. The Committee concluded that the evidence was not sufficient for this to be an overriding factor when formulating the guidance recommendations.

Comment from	Comment	Response
AstraZeneca	AstraZeneca therefore suggests that Paragraph 4.1.5 is changed to: "4.1.5 No statistically significant differences between ICSs were identified for measures of lung function, symptoms, use of rescue medication, exacerbations or adverse effects. Individual trials reported statistically significant differences in morning peak expiratory flow rate (PEFR), growth rates, and cortisol excretion."	The suggested change does not indicate which treatment arm the statistically significant differences favour, without this information the document is less informative. No changes made to the FAD.

Comment from	Comment	Response
AstraZeneca	Similarly paragraph 4.3.8 (Page 24) discusses the evidence considered by the Institute on the adverse events profile and states "The Committee noted that some studies had demonstrated that, in the short term, fluticasone propionate may be associated with less impact on growth than other ICSs." Again AstraZeneca would like to highlight that this is not consistent with the discussion above. In addition, later in the paragraph it states, "The Committee concluded it was not appropriate to distinguish between the different ICSs on the basis of adverse events." AstraZeneca agrees with this summary of the evidence and is concerned that Paragraph 4.3.8 is not consistent with this summary or indeed our discussion above. Given the contradictory nature of some of the available evidence, we feel it is inappropriate to highlight the conclusions of individual studies and believe that the paragraph may potentially cause confusion for the end user. We suggest that the sentence "The Committee noted that some studies had demonstrated that, in the short term, fluticasone propionate may be associated with less impact on growth than other ICSs" in paragraph 4.3.8 is simply removed to avoid any confusion. This would result in the paragraph 4.3.8 now reading: "4.3.8 The Committee considered the adverse event profiles of the different ICSs. It was aware that parents were often concerned about possible adverse events associated with ICSs, including growth and adrenal suppression. The Committee heard from clinical specialists that such adverse events were more frequently associated with higher than licensed doses and that the long-term evidence for an impact on growth and final height was inconclusive. The Committee heard from clinical specialists that in clinical practice the possible differences in the impact on growth were not sufficient for this to be an overriding factor in considering which product to use. The Committee concluded it was not appropriate to distinguish between the different ICSs on the basis of adverse events."	The paragraph indicates that **some** studies identify a short term effect on growth which favours the use of fluticasone. This reflects the evidence included in section 4.1.4, and 4.1.6. A further sentence has been included to state that the Committee did not consider that this effect was consistent across studies. See FAD section 4.3.9. The suggested amendment removes the reference to the consideration of the evidence base included in the assessment report and submissions. It would not therefore reflect what the Committee considered. No changes made to the FAD.

Comment from	Comment	Response
AstraZeneca	**Flexible dosing.** Paragraph 3.5 (Page 9) states "The Symbicort inhaler can be used either as a fixed or an adjustable dose allowing a patient to change the dose according to their symptoms." AstraZeneca agrees that it is important to highlight the additional therapeutic benefits to patients of the different combination inhalers and support the inclusion of this statement. In addition, we suggest that for consistency a similar statement should also appear in the final appraisal determination (FAD) for the Adults and children over 12 years HTA.	Comments noted. See responses below
AstraZeneca	**Economic assessment.** Further to our point above, AstraZeneca believes it is important that where the cost-minimisation examples are stated, there is clarity regarding the dosing regimen used in the comparison. Pease see further details on this below.	
AstraZeneca	Economic assessment Paragraph 4.2.17 (Page 21) discusses the annual costs associated with the different combination inhalers. Different dosing regimens are available and AstraZeneca suggests that to avoid confusion for end-users, clarity is provided regarding the comparator dosing regimen. AstraZeneca suggests the paragraph is changed to: "4.2.17 Finally, the Assessment Group compared the annual costs associated with the different fixed dose combined inhalers. For 200 micrograms per day beclometasone dipropionate equivalent, the cost of Symbicort fixed dose was £201, compared with £190 and £115 for Seretide Accuhaler and Evohaler, respectively. The corresponding figures for 400 micrograms per day beclometasone dipropionate equivalent were £402, £379 and £233 per year. The Assessment Group concluded that, assuming equal efficacy, Seretide is currently less expensive than Symbicort fixed dose, although this is based on a relatively crude assumption of clinical equivalence at a dose ratio of 1:2."	The sentence in the FAD has been amended to state "Finally the assessment group compared the annual costs associated with providing a fixed dose of inhaled corticosteroid with the different combined inhalers". See FAD section 4.2.17.

Comment from	Comment	Response
AstraZeneca	Similarly in Paragraph 4.3.12 we suggest that it is made clear that Symbicort flexible dosing can be less expensive than fixed dosing. We suggest the paragraph is changed to: "4.3.12 The Committee was aware that there were two combinations of ICS and LABA available in single inhalers and that these were available in a variety of devices. It noted that comparisons of costs carried out by the manufacturers and the Assessment Group concluded that the combination of fluticasone propionate/salmeterol was currently the least costly fixed dose combination treatment. The Committee recognised that this was the only combination available as a pMDI inhaler and so was the only one that could be used with a spacer. However, it was aware that there could be benefits to the other combination; budesonide/formoterol fumarate because dosing could be more flexible. Taking into consideration the different profiles of the products and the need to maximise adherence with medication, the Committee concluded that it would not be appropriate to specify a particular combination product or device. However, if more than one combination device was considered appropriate for an individual child, the least costly product should be used."	This sentence has been amended to state "It noted that comparisons of costs carried out by the manufacturers and the Assessment Group concluded that for a fixed dose of ICS the combination of fluticasone propionate/salmeterol was currently…". See FAD section 4.3.14.
AstraZeneca	As stated above, AstraZeneca also suggest for consistency that a similar discussion around the added benefit of Symbicort flexible dosing is included in the FAD for the Adults and children over 12 years HTA.	Please see responses to the consultation on the adult's corticosteroids for asthma FAD.

Comment from	Comment	Response
GlaxoSmithKline (GSK)	*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™ (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).	The text of the FAD has been amended to reflect both the SAM30012 study and the AstraZeneca study by Pohunek as these were both sources of evidence seen by the Committee. See FAD section 4.1.11.
GSK	*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. 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.	The Committee has considered the safety issues around providing ICS and LABA as separate and combined inhalers. See FAD section 4.3.12.

Comment from	Comment	Response
GSK	Combination inhalers are a particularly important factor in improving adherence with asthma medication, which is poor in children. Although the Appraisal 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, and could have been considered to support this recommendation.	A statement about the use of double-blind double-dummy designs and adherence has been added to FAD. See section 4.1.13
GSK	*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 and by GSK show that there is little uncertainty about these dosing ratios. Indeed, the Cochrane systematic review undertaken by Adams et al. 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". 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. 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.	The assessment report notes that the dose equivalence is relatively crude but widely accepted. Other consultees also raise issues around dose equivalence. Therefore the Committee considered it necessary to discuss this issue. The Committee came to the same conclusion as GlaxoSmithKline that it was appropriate to consider the comparative evidence where fluticasone propionate was given at half dose to beclometasone dipropionate or budesonide. The data in the evidence section summarises only the evidence from the assessment report where fluticasone is given at half dose. The evidence in the FAD is therefore consistent with the Committee conclusion in this paragraph.

Comment from	Comment	Response
GSK	*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. GSK suggests that explicit reference is made to recent MHRA guidance advising that licensed doses of ICSs should not be exceeded in paediatrics. 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.	The Committee normally does not make recommendations about the use of ICS outside of their licensed indications. It is stated in the recommendations that they are made within the marketing authorisation (guide to the methods of technology appraisal 6.1.6). Such a comparison would better fit the decision problem of a clinical guideline for the treatment of asthma. The Committee has formulated recommendations that follow an initial consideration of whether a specific treatment option is appropriate for a patient. This initial consideration is not the subject of the Committee's recommendations.
GSK	*Recommendation 1.1: Effect of ICS on growth* In previous comments, GSK highlighted the exclusion of three trials 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.	The Committee heard from clinical specialists that higher doses of ICS were associated with a greater impact on growth than lower doses. The evidence from short term studies is referred to in this consideration section. See FAD section 4.3.9.

Comment from	Comment	Response
GSK	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.	Comments noted. No actions requested.
GSK	Two recent trials not reviewed by the Assessment Group show that ICSs reduce growth rates over long periods of time. 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.	Comments noted. See FAD section 4.3.9
GSK	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".	The economic analyses of ICS alone by the assessment group and the manufacturers are all based on cost minimisation which assumes equal efficacy and adverse events. No changes made to the FAD.
GSK	*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® 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.	This has been amended in the FAD. See FAD section 3.7

Comment from	Comment	Response
GSK	*Recommendation 1.2: Use of ICS plus LABA versus ICS alone* Whilst GSK acknowledges the BTS/SIGN asthma guideline recommendation 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.	Such a comparison would better fit the decision problem of a clinical guideline for the treatment of asthma. The Committee has formulated recommendations that follow an initial consideration of whether a specific treatment option is appropriate for a patient. This initial consideration is not the subject of the Committee's recommendations.
GSK	*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).	Such a comparison would better fit the decision problem of a clinical guideline for the treatment of asthma. The Committee has formulated recommendations that follow an initial consideration of whether a specific treatment option is appropriate for a patient. This initial consideration is not the subject of the Committee's recommendations.
GSK	The cost effectiveness analysis presented in GSK's submission, which has recently been published in a peer review journal, 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.	Such a comparison would better fit the decision problem of a clinical guideline for the treatment of asthma. The Committee has formulated recommendations that follow an initial consideration of whether a specific treatment option is appropriate for a patient. This initial consideration is not the subject of the Committee's recommendations.

Comment from	Comment	Response
GSK	*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. 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.	This reflects a concern of the clinical specialists at the Committee meeting. See FAD section 4.3.12.
GSK	*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 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. Trials of flexible dosing in paediatrics 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.	Adjusted maintenance dosing was included in submissions from consultees and therefore needed to be considered by the Committee. See FAD section 4.3.14.
Asthma and Allergy Research Group	Section 2.3: Approx 30% of kids have concomitant allergic rhinitis, and as per ARIA guidelines it is important to consider treating the unified airway with either intranasal steroids, antihistamines or antileuoktrienes, as well as allergen avoidance -treating the upper airway can reduce asthma exacerbations	Comments noted. The FAD has been amended to include allergy testing in FAD section 2.2

Comment from	Comment	Response
Asthma and Allergy Research Group	Section 2.8: At step 3 adding LTRA may help treat concomitant allergic rhinitis [which occurs in 30% of kids] as well as exhibiting complimentary non steroidal anti-inflammatory therapy for the lower airway, and thus allow inhaled steroid dose reduction.	Comments noted. Leuktriene receptor antagonists were outside the scope of this appraisal.
Asthma and Allergy Research Group	Section 3.6: The point needs to be made here that lung absorption of fluticasone is dependent on the device in terms of fine particle dose -so that for example the lung bioavailability [and hence adrenal suppression] is approx 5 fold higher with fluticasone via pMDI plus large volume spacer vs dry powder inhaler [as accuhaler] -i.e. 400ug daily via pMDI plus spacer has the equivalent systemic bioavailability as 2000ug via dry powder. For FP there is complete 1st pass inactivation by the liver for the swallowed fraction such that its systemic bioavailability comes entirely from the lung .This is not the case with BDP where there is incomplete first pass inactivation in the liver, for the swallowed dose -i.e. 60% for BDP v 99% for FP -so that adding a spacer to BDP pMDI may reduce oral bioavailability but at the same time increase lung bioavailability -the net effect may therefore be neutral . The other point is that lung absorption of FP but not BUD is dependent on airway calibre such that patients with impaired FEV1% will have reduced systemic exposure.	Section 3.6 is meant to give basic details of adverse events. Readers are referred to more comprehensive information in the summary of product characteristics. A note has been included in FAD section 3.6 to state that adverse effects may differ depending on the drug and delivery system.
British Paediatric Respiratory Society	Section 1.1 This recommendation is in line with the SIGN National Guidelines. The BPRS trusts, however, that in some uncommon situations inhaled corticosteroids may be used outside their marketing authorisation (but perhaps only by respiratory paediatric specialists). The other consideration is that with 18 different inhaled corticosteroid preparations in almost as many devices, comparison of costs by individual clinicians is virtually impossible.	The Committee recognised that inhaled corticosteroids may be used outside of their marketing authorisation (see FAD section 4.3.5). However, the Institute is only able to make recommendations within the marketing authorisations (guide to the methods of technology appraisal 6.1.6)
British Paediatric Respiratory Society	Section 1.2: This is in line with the SIGN National Guidelines on the Management of Asthma.	Comment noted. No action required.

Comment from	Comment	Response
British Paediatric Respiratory Society	Section 2: Many members of the BPRS feel that it is important not to group together children under and above the age of 5 years. Those who wheeze above the age of 5 years are highly likely to benefit from inhaled corticosteroid (ICS) treatment. Those under 5 years of age may well not do so as the diagnosis of asthma may not be correct. Indeed, even where the diagnosis is correct the severity of the disease can vary hugely and therefore many of the statements in Section 2 are simplistic and difficult to relate to a particular clinical setting.	Section 2 provides background information to the disease treatment area. It is not meant to reflect a comprehensive guide to the treatment of management in different age groups. No changes made to section 2 of the FAD.
British Paediatric Respiratory Society	Section 2.2 Which lung function test is NICE suggesting and why is it preferable to demonstrate reversibility on several occasions?	This has been amended in the FAD (section 2.2)
British Paediatric Respiratory Society	Section 2.3 Children develop symptoms not after but *during* viral infections. The vast majority of children develop some respiratory symptoms in relation to cigarette smoke.	This has been amended in the FAD (section 2.3)
British Paediatric Respiratory Society	Section 2.4 Many children with asthma have lung function within the normal range and therefore not all children, as they become adults, have a greater decline in lung function than the general population.	This has been amended in the FAD (section 2.4)
British Paediatric Respiratory Society	Section 2.5 Asthma does occur in those under 5 years of age but one certainly wouldn't recommend achieving the best possible lung function in that age as we have no instruments tried and tested to do so. Given that over 90% of children with asthma are managed in primary care, what are the recommendations about annual reviews for children over 5 years of age?	This sentence has been amended to include the word school age. See FAD section 2.5. The scope of the appraisal and the evidence collected does not enable NICE to make recommendations about annual reviews. No changes made to the FAD.

Comment from	Comment	Response
British Paediatric Respiratory Society	Section 2.8 There is no ICS dose threshold for commencing add-on therapy because no suitable studies have been undertaken. The SIGN Guidelines in children are without any clear evidence base. A leukotriene receptor antagonist could be considered at any age. The evidence for this therapy even in the preschool age is poor. Members of the BPRS are concerned that NICE recommend for children younger than 2 years who do not respond to ICS, referral should be made to a respiratory paediatrician. Recurrent wheezing episodes in children in the first 2 years of life are extremely common and these frequently do not respond to ICS. Such a recommendation would lead to a vast increase in the cost of care and parental anxiety.	Section 2.8 provides background information and is meant to reflect current BTS/SIGN guidelines and not a NICE recommendation. This section has been amended to include the word consideration.
British Paediatric Respiratory Society	Section 2.9 The evidence for *Step 4* is even less good than that for *Step 3*. The same is true for *Step 5*.	Comment noted. See FAD section 4.3.8
British Paediatric Respiratory Society	Section 2.10: It is inappropriate to extrapolate from adult studies about compliance in paediatric patients. BPRS members would entirely agree that this is a huge issue and is likely to be of much greater relevance than the basic cost differential between the 18 different ICS preparations. There are paediatric studies which have assessed inhaler technique. Studies using adults should not be included in this appraisal document.	Section 2.10 is based on studies from the assessment report, and is meant only as background information rather than a comprehensive account of the issues in asthma management. No changes made to the FAD.
British Paediatric Respiratory Society	Section 2.11: The use of the most appropriate inhaler device for an individual child is perhaps the most important issue in paediatric asthma management. It is not necessarily the healthcare professional's decision, it is a combined decision between that professional and the family. Guidance from NICE, SIGN or anywhere else needs to emphasise this. Doing so, however, probably negates any pharmaco-economic evaluation as it is impossible to fully incorporate this into an overall guideline	The scope of the appraisal was inhaled corticosteroids rather than the device in which they were delivered. However, the Committee recognised the importance of choosing the most appropriate device, hence the recommendations to use the cheapest where there was more than one appropriate device (see FAD section 1.1, 1.2, 4.3.4)

Comment from	Comment	Response
British Paediatric Respiratory Society	Section 3.1 The availability of two CFC-free beclometasone preparations for use in children is likely to occur at a later stage than for adults. CFC-free issues in paediatric asthma are different to those in adult asthma.	Comments noted. No actions requested.
British Paediatric Respiratory Society	Section 3.2-3.4 These sections show the complexity of the licensing situation. They reflect the huge differential between adults and children demanded by the regulatory authorities and deemed necessary by the pharmaceutical industry. One can only hope that the development of the Medicines for Children Research Network will make a significant difference to this in the future.	Comments noted. No actions requested.
British Paediatric Respiratory Society	Section 3.5: There seems an inconsistency in the statement about combination therapy 'Only the lowest dose strength inhalers are recommended for children and these are not recommended for individuals with severe asthma'. It is particularly in children with severe asthma that combination therapy is recommended. The statement that 'The Seretide Evohaler device is the only combined inhaler currently available that can be used with a spacer' is superfluous as the Symbicort inhaler is a dry powder inhaler and spacer devices cannot be used with such inhalers.	The statement about lowest dose strength inhalers reflects the Summaries of Product Characteristics for Seretide and Symbicort. No changes made to the FAD The statement about the use of a spacer with Evohaler has been amended to state " The Seretide Evohaler device is the only combined inhaler currently available as a pMDI and therefore which can be used with a spacer" (FAD section 3.5)
British Paediatric Respiratory Society	Section 3.6 This information is taken directly from adult patients and is not relevant in paediatrics. There should be clear statements here about the evidence of systemic adverse effects in children.	This section provides a brief description of the possible side effects of ICS. Clinicians are referred to the summary of product characteristics for comprehensive information. No changes made to the FAD.

Comment from	Comment	Response
British Paediatric Respiratory Society	Section 3.7 The range of annual costs of beclometasone dipropionate, budesonide and fluticasone are remarkably similar supporting earlier comments that the most relevant cost in the management of children with asthma is using the most appropriate inhaler device and encouraging adherence to therapy.	The Committee agrees with the Consultee that the price ranges are similar. However, for each drug within the range there is a lot of variation. Therefore the Committee did not recommend a specific drug, rather they recommended the cheapest where there was more than one appropriate product available (see FAD section 4.3.9).
British Paediatric Respiratory Society	Section 4: BPRS members feel it is very difficult to make comments on the comparison of individual high dose, low dose or combination therapy corticosteroid treatments without being involved in the process. It is not always clear from the Appraisal why certain studies were excluded and others were not. BPRS members agree that there is a dearth of good clinical studies comparing one regime with another but it must be remembered that, in terms of efficacy, it is extremely difficult to show clinically significant differences in such studies and there continues to be wide-ranging discussion about what outcome measures are important. The fact that outcome measures in many studies show no difference does not mean to say that there is no relevant difference between regimes. It may well be that the wrong outcome measures have been used.	The Committee was mindful of the weaknesses in the evidence base. However, it is necessary for the Committee to make a decision based on the evidence before it, and having considered this it decided that it was not appropriate to recommend the use of one corticosteroid over another.
British Paediatric Respiratory Society	Section 4.2 This economic assessment section is critically dependant on evaluation of outcome measures. Given that we have little evidence that we understand these in paediatric asthma, it is difficult to draw any conclusions from this section.	The Committee was mindful of the weaknesses in the evidence base. However, it is necessary for the Committee to make a decision based on the evidence before it, and having considered this it decided that it was not appropriate to recommend the use of one corticosteroid over another, but that where there was more than one appropriate product the cheapest should be used.

Comment from	Comment	Response
British Paediatric Respiratory Society	Section 4.2.14: This section suggests that switching from beclometasone diproprionate to Seretide Evohaler increases the cost by £52, only one hospital-managed exacerbation would need to be averted for every 20 patients using the combined inhalers suggesting this may be a relatively cost-effective switch.	The Committee recommended the addition of a LABA using a combined device as a treatment option where it was considered appropriate.
British Paediatric Respiratory Society	Section 4.2.16: The costs of combination therapy in the same or different inhaler devices is non-interpretable without information relating to whether patients are more likely to adhere to treatment if the medication is given in one, rather than two, inhalers.	Comment noted. This paragraph summarises the approach taken by the assessment group. The Committee recognised that adherence was important when considering inhaled corticosteroids. See FAD section 4.3.4.
British Paediatric Respiratory Society	Section 4.3.3: It appears that only 3 clinical specialists were interviewed but all three stressed the importance of distinguishing between preschool and school-aged children with asthma.	Two clinical specialists and one patient expert attended the Committee meeting and provided responses to questions from Committee members. The Committee heard from them that the management of preschool children may differ from that of school aged children and that this may be reflected in updates of the BTS/SIGN guidelines. No actions requested.
British Paediatric Respiratory Society	Section 4.3.4: The evidence for NICE guidance on the use of inhaler devices in children under 5 years of age is extremely limited. An example of this is that the recommendation about the use of Turbohalers in 3-5 years of age, for instance, has no evidence base.	The current appraisal did not appraise the use of inhaler devices, but it heard from clinical specialists that a number of the issues in the NICE guidance on inhaler devices were still relevant to clinical practice. The guidance in this FAD has not made any recommendations about the use of any particular devices in an age group.

Comment from	Comment	Response
British Paediatric Respiratory Society	Section 4.3.7 The Committee concluded that it would be appropriate to draw on the evidence from the older age group (5-12 years) when considering treatment for the preschool age group and also to take into consideration evidence that has been available in the ICS appraisal for adults and children over the age of 12 years of age' BPRS members would universally disagree with this statement. The whole point about Medicines for Children and children of different age groups is that they are not comparable nor are they comparable with adults.	The Committee considered that as ICS can be prescribed to this age group, they should be reflected in the guidance. However, they note the uncertainties in diagnosis and management for this age group and the weaknesses of the evidence base. Research recommendations are made in relation to this age group.
British Paediatric Respiratory Society	Section 4.3.8: This brief paragraph discussed adverse events. It was very cursory but this issue is the greatest concern that parents have about the use of inhaled corticosteroids. Even if long-term growth in studies undertaken so far show no difference between the inhaled ICS, short-term growth differences may be important both clinically for professionals and emotionally for parents.	The FAD section 4.3.9 recognises the concern from patients about the use of inhaled corticosteroids. However, the Committee heard from clinical specialists that the potentially different adverse event profiles were not considered sufficient in clinical practice for NICE to consider recommending the use of one inhaled corticosteroid over another.
British Paediatric Respiratory Society	Section 4.3.10 There is no evidence at present to support the Committee in its statement that rather than increase the dose of inhaled steroids, adding an LABA is the more appropriate option.	FAD section 4.3.11 does not state that the addition of a LABA is a more appropriate option, only that it may be an option as reflected in the BTS/SIGN guidelines. Such a comparison would better fit the decision problem of a clinical guideline for the treatment of asthma. The Committee has formulated recommendations that follow an initial consideration of whether a specific treatment option is appropriate for a patient. This initial consideration is not the subject of the Committee's recommendations.

Comment from	Comment	Response
British Paediatric Respiratory Society	Section 4.3.11 There is no specific reason why combination therapy discourages patients from stepping down treatment. In clinical practice, combination therapy can be switched to ICS treatment alone without any issue. The NICE committee discussed 'fully compliant individuals'. The suspicion is that such people do not exist.	The Committee heard from clinical specialists that stepping down treatment could be an issue where combined devices were prescribed. The Committee recognised the importance of adherence to medication. The decision about which devices are appropriate should be based on therapeutic need and treatment adherence.
British Paediatric Respiratory Society	Section 4.3.12 The BPRS membership would agree that both combination therapies have their merits and each should be considered for each individual child.	Comments noted, no actions requested.
British Paediatric Respiratory Society	Section 6.1: The BPRS membership welcomes recommendations for further research. Post-marketing research on the use of combination inhalers, however, is almost exclusively confined to studies within the pharmaceutical industry. Such studies need to be encouraged through other sponsorship routes. Section 6.2: The BPRS is delighted about this recommendation but feels the age range needs to be limited to school-age and not below 5 years. Section 6.3: The BPRS is delighted at this recommendation.	Comments noted, no actions requested.
British Paediatric Respiratory Society	Given that we have so little information about inhaler device usage, technique and compliance with therapy, the BPRS wonders if this is a recommendation for further research that NICE would consider.	As the appraisal focuses on differences between ICS, rather than devices, research recommendations focus on the ICS rather than devices.

Comment from	Comment	Response
British Paediatric Respiratory Society	Finally, it is recognised that many medications prescribed for use in children are prescribed outside their licensed recommendations. Indeed, this was the reason for the original Medicines for Children Formulary published in 1999. Inadequate studies have been undertaken over the last few decades in children and the new Medicines for Children Research Network will go some way to rectifying this. However, when considering the prescription of children's medications the BPRS would recommend that NICE looks at medications already prescribed outside their license as ignoring these would ignore a significant percentage of accepted clinical practice within paediatrics.	The Committee would not normally make recommendations for medicines outside of their marketing authorisations (guide to the methods of technology appraisals 6.1.6). However, the Committee understood the difficulties faced by clinicians in relation to prescribing. See FAD section 4.3.5
DOH	"There are no problems with this appraisal, as far as we can see. It basically says that there is nothing to choose between them, other than cost. It supports the use of ICS-LABA combination inhalers where appropriate, so simplifies regime for some. There is no difference in side effects, including growth suppression with different products."	Noted. No actions requested.
General Practice Airways Group (GPIAG)	Before answering your specific questions we would like to point out one inaccuracy in the document text: Under point 2.8 the document states that "*for children younger than 2 years, Step 3 is referral to a respiratory paediatrician."* The BTS/SIGN Guidelines state "*consider referral to a respiratory paediatrician*". Many general practitioners, especially those with an interest in asthma, would be competent to add in a Step 3 treatment at this age and thus avoid unnecessary referral. It would be helpful if the wording of this guidance followed that of the guidelines.	This has been amended in the FAD. See FAD section 2.8.

Comment from	Comment	Response
GPIAG	**Do you consider that all the relevant evidence has been taken into account?** In general, yes. However, as stated in 4.3.8 many parents (and health professionals) are concerned with potential long term side effects (especially suppression of growth) of treatment with ICS. An appraisal of ICS treatment in children should really include long term studies of ICS and not just assess safety data from relatively short term randomized controlled trials between two different ICSs. This issue is summarised in a systematic review: Pedersen S. "Clinical Safety of inhaled corticosteroids for asthma in children: an update of long term trials." *Drug Safety* 2006;**29(7):**599-612	The assessment report included RCT evidence which as consultees state tends to be short term. Mindful of this the Committee heard from clinical specialists who provided information in regard to the longer term impact. See FAD section 4.3.9.
GPIAG	**Do you consider that 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?** The situation has been made more complex by the phasing out of CFC-containing beclometasone, but the ACD seems to have taken this into account appropriately. We have no other specific comments.	Comments noted. No changes required.
GPIAG	**Do you consider that the provisional recommendations of the appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?** In common with our previous comments regarding the assessment report we still have concerns that little acknowledgement appears to have been made that there is great heterogeneity in the response to ICS, especially in younger children. The recommendations have been made on the basis of group mean data and a statement would be welcomed regarding the limitations of this approach given the heterogeneity of response.	The FAD has been amended to reflect the heterogeneity of response in the under 5 year olds. See FAD section 4.3.7.

Comment from	Comment	Response
GPIAG	Para 4.3.8. The issue of comparative safety of various ICS has been addressed. However given the importance of this issue amongst parents and health professionals and notwithstanding the limitations of the evidence analysed it would be beneficial if the ACD could make a statement in the summary emphasizing the safety of ICS treatment in children	Appraisal documents provide a summary of adverse events as shown in the clinical trials and a short description of the adverse events described in the summary of product characteristics. No changes made to the FAD.
GPIAG	Para 4.3.11. We welcome the acknowledgement that use of a combination LABA/ICS minimises the chance that the ICS will be omitted by the patient. We were therefore disappointed that the endorsement for combination inhalers was diluted by the statement “Thus, in the future, delivery via separate inhalers in fully compliant individuals may become the preferred option.”	The Committee recognised the concerns with using separate inhalers. However, the Committee considers the cost effectiveness of a technology, and in future it may be that separate inhalers may become more cost effective than a combined inhaler and therefore for individuals where separate inhalers are considered appropriate they may become a preferred option. See FAD section 4.3.12, 4.3.13.

Comment from	Comment	Response
GPIAG	In adults, the Salmeterol multicenter asthma research trial (SMART) (Nelson HS, Weiss ST et al *Chest* 2006:129:15-26) in the USA has led to concerns expressed by the FDA in America and the MHRA in this country, that use of long-acting beta-2 agonists (LABA) without ICS increases the risk of asthma deaths. Evidence from SMART (USA study) and experience in this country suggests that many patients on ICS are non-compliant. Prescription of separate ICS and LABA inhalers increases the risk of non-compliance with the ICS compared to the combination as patients tend to preferentially use (or fill the prescription) for the LABA which they feel is working, at the expense of the ICS, which they are not so aware of benefiting from. For many people with asthma requiring an LABA plus ICS, the prescription of separate inhalers is therefore potentially dangerous. The recommendation from NICE should be worded more strongly that "*LABA/ICS should be prescribed in combination and only in exceptional circumstances (when the patient is fully compliant) should separate inhalers be prescribed*".	The Committee recognised the concerns with separate inhalers (See FAD section 4.3.12). The guidance states that the choice of a combined inhaler and separate inhalers should take into account therapeutic need and likelihood of treatment adherence(See FAD section 1.2).
Royal College of Nursing (RCN)	We acknowledge that the Appraisal Consultation Document is a working document, and consider it very comprehensive. The contents, however, seem to be modelled around existing guidelines, the British Thoracic Society (BTS) Guidelines and the Children's British National Formulary (BNF) rolled into one and may not inform clinical practice more than those documents already do. The NICE technology appraisals guidance are very informative, particularly informing those with limited clinical knowledge of the technology under consideration, in this case, inhaler devices and provide a quick summary of considerations when choosing these devices for children. Whilst this information is very useful for patients and carers, for the healthcare professionals a different approach is suggested, particularly for inclusion in the Quick Reference Guide version of the guidance.	NICE guidance as a result of a technology appraisal is not meant to provide a manual of clinical management of asthma. The guidance is focused on cost effective use of NHS resources and clinical information is included only to provide a background to the subject and coherence to the document.

Comment from	Comment	Response
RCN	We note that the ACD recommends the cheapest preparation. We accept the need to maximise resources, however, as nurses, we feel the psychological and social needs of children and families should be fully taken into account in deciding what is best for the patient. The ACD does not seem to have fully considered this. We would suggest more discussion around the value of patient education and empowerment should be included. Healthcare professionals rely heavily on parents / carers to administer treatment and so it is their health care beliefs that we need to consider. This is very much a nursing role and should be promoted.	While recommending the cheapest product the guidance qualifies that by saying it should be 'appropriate'. This includes factors such as therapeutic need and ability to use the device. The guidance does not detail best practice in the management of asthma or try and replace current published guidelines.
RCN	We note the advice from 'clinical specialists'. It would have been good to have had more advice from more healthcare professionals. Overall, guidance on the use of corticosteroids for treatment of asthma in children under twelve years is welcomed. However, we consider that the current document as it stands may not add to the body of knowledge on paediatric asthma management issues as the contents are already widely disseminated in other formats.	Comments noted. No actions requested.
NHS QIS	Whether you consider that all the relevant evidence has been taken into account. *Yes as far as I can tell, given the references to BTS/SIGN Guidelines.* Whether you consider that 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. *The summaries appear sensible* Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. *I find the provisional recommendations a suitable basis for guidance*	Comments noted. No actions requested.

Comment from	Comment	Response
Welsh Assembly Government	Thank you for giving the Welsh Assembly Government the opportunity to comment on the above consultation. We are content with the technical detail of the evidence supporting the consultation and have no further comments to make at this stage.	Comments noted. No actions requested.
Patient expert	Having read the attached ACD, I have no particular comments to make, other than the fact that I am satisfied that the provisional recommendations are sound. The basic premise seems to be that a choice of ICS should be available based on clinical need first and economic factors second, and this seems an appropriate response to the evidence available.	Comments noted. No actions requested.
Web Comment: Clinical specialist	Whilst this is a technology appraisal, it is highlighted that care is delivered in many settings and different healthcare professionals are engaged at different stages. It is essential that 2 aspects of care are considered which relate to this topic. Firstly is the prescribing clarity of these devises and concomitant equipment. Not only must the medicine and type of inhaler be prescribed (including strength) such that it is clear which one is required, but any spacer devices must also be clearly prescribed together with any mouth piece or mask required. Secondly, it is worth documenting that community pharmacists play a huge role in counselling children/carers on all aspects of the asthma control from how to use their inhalers, caring for their devices, avoiding side effects and dealing with exacerbations. A formal acknowledgement of this role from NICE would assist community pharmacists to maintain and develop this role for the benefit of patients.	Comments noted. A sentence acknowledging the involvement of community pharmacists has been added to section 2.5.

Comment from	Comment	Response
Web Comment: Clinical specialist	Reference is made to the fact that different strength products can be used to deliver the same doses and this can change the cost impact quite considerably. However no reference is made to what this might mean in clinical practice. If the cost impact is being looked at, it would seem sensible to discuss the clinical impact of using one versus two puffs of a delivery system to give the same dose or the use of "Once" versus "Twice" daily dosing schedules.	The scope of the appraisal was to compare the different ICS, rather than to compare different methods of delivering the same ICS. Such a comparison would better fit the decision problem of a clinical guideline for the treatment of asthma. To make the task of comparing the products manageable the assessment group assumed that effect is equivalent with equivalent doses and doesn't depend on the number of puffs or frequency of administration by which this dose is achieved. No changes to the FAD made.
Web Comment: Clinical specialist	4.3.4 Adherence to treatment is probably the most vital aspect to the treatment of asthma. Whilst the appraisal is highlighting differences in the active components of the medicines, more emphasis should be put on the choice of device to fit the patients' needs. This may require selecting products less desirable for other reasons (e.g. active agent, cost). This is especially true when a second inhaler is added to the regimen. Whilst some patients cope well with a selection of devices, it would be more appropriate to start the second medicine being delivered in the same device as the first this choice is likely to outweigh any small advantage the choice of active ingredient may give. 4.3.5 Clinical need should normally outweigh variances in marketing authorization. Whilst the guidance cannot be seen to contradict market authorization, it could be perceived as negligence not to use a more appropriate device and product, if it is in the patients' interest. 4.3.7 / 4.3.11. Use of combined products may be very desirable in terms of adherence. It should not be understated the problem this may cause in terms of weaning up or down, in terms of using optimal doses	The recommendations state that the least costly product that 'is suitable' be used and that the decision about which device to use should be made 'on an individual basis, taking into consideration therapeutic need and the likelihood of treatment adherence.' This reflects the importance the Committee attached to issues around maximizing adherence. No changes made to the FAD. Further consideration of combined inhalers versus the use of separate inhalers has been included in the FAD document. See FAD section 4.3.12, 4.3.13.