19 June 2007

NICE HTA: Corticosteroids for the treatment of chronic asthma in children children under the age of 12 years– Appraisal Consultation Document (ACD)

Summary of comments

Many thanks for providing the ACD for the above appraisal. AstraZeneca welcomes this opportunity to comment and is generally supportive of the recommendations contained within the ACD. We do, however, have a number of comments, which we hope will be useful. In summary, these comments are:

- **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.

- **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.

- **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.

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."

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.

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.[1] 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 ($p<0.001$).

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:

> "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."

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.

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.[2] 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.[3] 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.[4 5] 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.

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).[6] 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.[7 8] It is also worth noting that no final height data are available for FP.

AstraZeneca therefore suggests that Paragraph 4.1.5 is changed to:

> "4.1.5 <u>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."</u>

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."

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."

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."

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.

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[1] Guilbert TW, Morgan WJ, Zeiger RS, et al. 2006. Long-term inhaled corticosteroids in preschool children at high risk for asthma. New England Journal of Medicine 354(19):1985-1997.

[2] Pedersen S. 2001. Do inhaled corticosteroids inhibit growth in children? American Journal of Respiratory and Critical Care Medicine. 164(4):521-35.

[3] Karlberg, J., L. Gelander, et al. 1993. Distinctions between short- and long-term human growth studies. Acta Ped 82: 631-34.

[4] Saha MT, Laippala P, Lenko HL. 1997. Growth of asthmatic children is slower during than before treatment with inhaled glucocorticoids.Acta Paediatrica. 18(2):138-42.

[5] Doull IJ, Campbell MJ, Holgate ST. 1998. Duration of growth suppressive effects of regular inhaled corticosteroids.Archives of Disease in Childhood. 78(2):172-3.

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[7] Larsen G, Liu AH, Chinchilli VM, Sorkness CA, Taussig LM, Martinez FD. 2006. Long-term inhaled corticosteroids in preschool children at high risk for asthma. New England Journal of Medicine. 354(19):1985-1997.

[8] Norjavaara E, Gerhardsson de Verdier M, Lindmark B. 2000. Reduced height in Swedish men with asthma at the age of conscription for military service. Journal of Pediatrics. 137(1):25-9.