Adult asthma report: responses to Consultees comments for ACD

Consultee	Comments	Assessment team response
ALTANA	In the assessment report, the reviewers estimated the mean annual cost per patient at £87. This, however, was based on the pack price of ciclesonide 80 µg (£0.238 per puff) as opposed to the pack price of ciclesonide 160 µg (£0.28 per puff), which results in a range of mean annual costs between £87 and £102, dependent on the dose used, as shown in the appendix to this response document.	The figures in the assessment report are correct.. At a dose of 400 µg/day (BDP equivalent) using the pack price of ciclesonide 160 µg (£0.28 per puff) the mean annual cost is £102.20 At a dose of 800 µg/day (BDP equivalent) using the pack price of ciclesonide 160 µg (£0.28 per puff) the mean annual cost is £204.40
AstraZeneca	We would also like to highlight that the modelling approach and base case results in the PenTAG model presented in Appendix 10 appear similar to the AstraZeneca approach, although no discussion of this is provided in the TAR. AstraZeneca suggests that the similarity between the two approaches and this external validity of the results of the AstraZeneca model is included in the TAR.	As is highlighted in the assessment report, the cost-utility model developed by PenTAG is of an entirely exploratory nature. The team therefore chose not to include the full methods and results of the final model in the main body of the assessment report. The exact reasons for either not providing a cost-utility model, or for choosing to only present the methods and results in an appendix varied for each of the five questions addressed. These reasons have also been outlined in the full assessment report. Furthermore, the assessment team has informed the Appraisal Committee that the purpose of providing the model in an appendix is not to inform the decision making process, and that this should only be informed by the costs presented in the main body of the report. Given the

		assessment team's cautious approach to presenting the model methods and results, it would be inappropriate for this to provide any external validity to the results of the model produced by AZ and no reference to any similarity of methods or results will be made within the TAR.
Trinity Chiesi	In Figure 26 (page 390), the assessment report states that the cheapest BDP product based on the annual cost of taking 400 µg BDP-CFC equivalent per day, excluding CFC-propelled products, is Clenil® Modulite®. However, in Figure 28 (page 393), the report claims that the cheapest BDP product based on the annual cost of taking 800 µg BDP-CFC equivalent per day, excluding CFC-propelled products, is Qvar®. It is difficult to understand how Qvar® can be considered cheaper than Clenil® Modulite® at this higher dose, as Table 56 on page 377 clearly shows Clenil® Modulite® to be of lower cost at each dose. We believe that there is an error in Figure 28 – it should state that Clenil® Modulite® is the cheapest BDP product.	The figures in the assessment report are correct. Any differences between the relative annual costs of Clenil® Modulite® and Qvar® at the starting low dose and maximum low dose are due to the assumptions regarding how the daily dose was achieved that were necessary to provide a mean annual cost for each of the products.
General Practice Airways Group	5.7.1 It is stated that "the mean adjusted exacerbation rate of the third trial (Volgemeier C et al European Respiratory Journal 26: 819-828 2005) was lower in the SALM:FP group than in the BUD;FF group. This led to one of the conclusions in the summary of this section that effectiveness of the one combination versus the other was variable across all endpoints. In fact in the Volgemeier study, the mean exacerbation rate per patient was lower in the BUD/FF group than in the FP/SALM group (0.24v 0.31 exacerbations per patient per year) in line with the other 2 comparative studies showing that adjustable therapy with BUD/FF is superior to SALM/FP in terms of exacerbations. The conclusion stated in the text is therefore incorrect	Reference to the third trial in the summary section is not necessarily to the study by Vogelmeier which was presented third in the sequence in the preceding results section. In the case in point the third trial is actually the Fitzgereald et al study which reported a statistically significant difference in exacerbation rates in favour of FP/SALM. The conclusion still remains correct in that two trials reported lower exacerbation rates for BUD/FF, and one reported lower rates for FP/SALM. We will revise the assessment report to make this clearer.
GSK	25 studies deemed as appropriate to addressing the comparisons in the scope in the GSK submission were subsequently not included in the Report. Seven	All of the 25 studies were excluded from the assessment report as they did not meet the

	studies excluded from the report for Question 1, five for Question 3a, nine for Question 3b, two for Question 4, and two for Question 5. A table of excluded studies and the reasons for exclusion would enhance the transparency of the report and allay any concerns of publication bias, as seven of these trials were unpublished studies but available on the GSK clinical trials register and detailed in the GSK submission.	inclusion criteria, as follows: • N=14 failed criteria because intervention was <5 weeks duration; or study reported as a conference abstract; or different inhaler delivery device between comparisons • N=7 unpublished GSK data presented only in abstract form from the GSK CTR, and summarized only briefly in GSK submission to NICE. We only included unpublished data where a full detailed trial report was supplied. • N=2 GSK erroneously claimed studies had been excluded, when they have in fact been included • N=2 studies published during the course of 2006 identified by our update search in October 2006. These are listed in Appendix 5 as being relevant for inclusion in any update.
GSK	**Consistency in evidence summaries** Clinical effectiveness & safety of FP vs BDP or BUD In a number of places the Report demonstrates that important differences in the clinical effectiveness of different steroids exist. The Report concludes (see page 81) that "In almost all cases the measured outcomes for lung function either favour treatment with FP over treatment with BDP, or indicate no	This is selective quotation of the evidence. In some trials there was a statistically significant benefit in terms of treatment effect for one of the comparators and in others no difference. The statement in the executive summary reflects the fact that differences were observed for some measures

	difference…but where differences were statistically significant the change in morning PEFR, evening PEFR and …FEV_1 … favour FP". Other conclusions in the Report such as "Changes in symptom scores and symptom-free days generally favour the use of FP over BDP.", "The incidence of nocturnal awakening was either reduced more by FP than by BDP, or showed no differences between the drugs.", "The use of rescue medication was reduced to the largest extent in FP-treated patients.", demonstrate that important differences in the clinical effectiveness of different steroids exist. However, these observations by the Assessment Group are not reflected in the Executive Summary which concludes that "When evaluated in pair-wise comparisons…no consistent significant differences or patterns among the outcomes were evident"	(eg) lung function, but no differences were observed for the number of symptoms, use of rescue medication, nocturnal awakenings or adverse event. To state that FP is superior to BDP on the basis of small significant differences that are observed in only a sub-set of the trials reviewed and only a limited number of the outcome measures is therefore potentially misleading. However, in light of the comments from both the Consultee's and the peer reviewers, the executive summary will be revised and expanded to discuss the any differences in outcomes between the ICS at both low and high dose.
GSK	Question 2 (ICS versus ICS high dose) Consistency in evidence summaries The Report concludes that the cortisol levels in the FP group were increased (page 166), however, seven of the eight trials included in the analysis found no statistically significant differences.[3-9]	The sentence that states that cortisol levels were increased refers to the 5 parallel group trials. Two of these (Barnes et al and Lorentzen et al) reported increases in cortisol for FP compared to decreases for BDP, with a statistically significant geometric mean ratio between treatments
GSK	Question 3a (ICS/Long Acting Beta2-Angonists (LABAs) versus increased dose ICS) - Pooling of incomparable studies The inclusion of the Busse et al. trial[10] in the meta-analyses of peak flow, symptom-free days (SFDs), rescue medication and adverse events (see pages 220-223) is inappropriate, as it is based on a patient population with controlled asthma reducing their ICS dose, whereas the Bergmann et al. trial[11] is of uncontrolled asthma patients increasing their dose of ICS. The main aim in reducing steroid dose in a controlled asthma population would be to maintain control and therefore, small or no differences/changes in clinical outcomes	The decision to pool studies quantitatively in a meta-analysis was carefully considered, and was based on factors such as comparability between studies in dose, length and severity. The assessment was based in part on the methods and data used by the Cochrane Airways Group in their systematic reviews of ICS and LABA. The Busse and Bergman trials were both combined in a meta-analysis in the Cochrane review of ICS +LABA

	would be expected. These two trials, therefore, need to be considered separately as they address different research questions in two entirely different populations.	versus increased dose of ICS by Greenstone *et al*, 2006. The respective results of the two studies can still be viewed from inspection of the forest plots. The direction of effect is similar for all but one of the pooled outcomes. In addition, the report notes that, for the Busse et al study, many of the outcomes were purported to be within clinically equivalent limits, with the caveat that the trial report for Busse *et al* failed to specify what these limits were.
GSK	GSK believes the use of cost-minimisation analysis is an inappropriate form of economic evaluation to compare ICSs, however, appreciates the difficulties of incorporating differences in efficacy into a model.	The assessment team recognizes the fact that a cost minimization analysis for ICS versus ICS is outside the reference case. However, in the absence of being able to combine all the relevant trial data for the five comparators under consideration and therefore incorporate differences in treatment effect into the model, a cost minimization approach was deemed to be the most useful. approach. The limitations of this approach have been discussed in the TAR, and are also consistent with the approach used in all of the submissions received from industry through the NICE Appraisal process, in which only the costs for a limited number of the comparators were presented for the questions of ICS versus ICS.
GSK	The comparison of costs is based on only one of the two SFC devices, namely the Accuhaler, which was used in the clinical trials reviewed. Given the clinical equivalence of these two devices 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 cost consequence comparisons were only undertaken where there was relevant clinical trial data available, in order to compare the differences in outcome between the two comparators with their associated costs.

	The analysis also excluded for no obvious reason, two unpublished GSK trials (SAM30013 and SAM40120), which were the only trials relevant to this question that used the Evohaler device. In the report, SFC (Accuhaler) is cheaper than FP or BUD alone in two out of the five trial/cost comparisons, however, if the Evohaler device cost is used, the evidence would show that there is a cheaper SFC device in all comparisons.	None of the trials of FP/S had used the Evohaler and the two unpublished GSK trials were not made available to the assessment team as full trial reports via the industry submission. As previously stated in these responses, we only included unpublished data where a full detailed trial report was supplied by industry.
GSK	In the main body of the Report the 'PenTAG' model is repeatedly referred to as 'exploratory' and the group do not report the results from this model in the main body of the report. The rationale for including this model in the Report and how the results of this modelling exercise should be interpreted by the Appraisal Committee are unclear.	The Appraisal Committee has been informed by the Assessment Team that the model outputs should not be taken in to considered in the decision making process.
GSK	Question 4 (ICS/LABA combinations vs ICS/LABA separates) Inconsistent dose cost comparisons High dose cost comparisons are undertaken for SFC but not for Symbicort i.e. made up to 800µg per day of BUD with Symbicort, and 1000µg per day with SFC.	A further cost-comparison of BUD/FF in a combination inhaler versus BUD and FF in separate inhalers at high dose will be undertaken. Preliminary analysis indicates that this will not change the overall results (ie) that combination therapy is consistently cheaper than the constituent drugs taken in separate inhalers.
GSK	Cost comparisons made are not transparent and may be inaccurate (p408 & 410) as the annual cost for SFC 50 and 125 Evohaler seems to be based on an incorrect cost per device. This is likely to be due to a misprint in the March 2006 BNF. With the correct SFC Evohaler costs, there is always a cheaper SFC option compared with both its components in separate inhalers and Symbicort at all doses	Due to the misprint in the March 2006 BNF for the Evohaler device, the costs reported by the assessment team for the Evohaler device are not correct . For the comparison of combination therapy versus combination therapy; Symbicort Turbohaler (BUD/FF) versus either Seretide Accuhaler or Seretide Evohaler (FP/S) the correct costs and the amendments to table 68 (page 408) are as follows:

GSK (continued)

Correct costs for the Evohaler device (table 68, page 408)

Annual cost of combination inhalers compared

Combination product	**Taken as**	**400µg* BUD per day**	**800µg* BUD per day**
Symbicort Turbohaler (BUD/FF)	2 puffs/day	231	462
		200µg FP per day	**500µg FP per day**
Seretide Accuhaler (FP and S combined)	2 blisters/day	379	446
Seretide Evohaler (FP and S combined)	4 puffs/day	237 (corrected cost £219)	479 (corrected cost £446)
* metered dose			

The implications of these corrected costings mean that at low dose level, the cheapest combination inhaler is FP/S as an aerosol pMDI (Seretide Evohaler® = £219 per year), but this is only slightly cheaper than BUD/F as a DPI (Symbicort Turbohaler® = £231 per year). At the higher dose level FP/S both as a DPI and an aerosol pMDI ((Seretide Accuhaler® and Seretide Evohaler® respectively) are the cheapest at both at £446 per annum, but this is only £16 cheaper than having the ICS 'equivalent' dose of BUF/F £446 Symbicort Turbohaler®.